PART I

CIS- AND TRANS-1,2-DIAMINOCYCLOHEXANES

PART II

A STUDY OF THE TERTIARY AMINE PRECURSORS OF PIRYLENE

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

1961

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ACKNOWLEDGMENT

It is with deepest appreciation that I acknowledge my indebtedness to Dr. E. R. Buchman, my research advisor, for his helpfulness and guidance during my stay at the Institute. I would like to thank Dr. G. S. Hammond for his helpful and critical discussions of much of the work that is reported in this thesis. The help rendered by Dr. Paul R. Shafer in not only taking the nuclear magnetic resonance spectra reported in this thesis, but also in interpreting the results, is greatly appreciated. Dr. J. D. Roberts offered much encouragement in the nuclear magnetic resonance spectral work and his discussions are appreciated.

The number of people to whom I am indebted is too great to list. I am especially grateful to Dr. I. A. Updike of Randolph-Macon College for his guidance in the early years of my training. To my parents, to all the people of the Institute, and to all the people in Pasadena who have given encouragement when it was most needed, I extend my deepest thanks.

Without financial assistance my studies could not have been possible. I would like to thank my parents, Mr. and Mrs. George Farrar, for financial aid, the California Institute of Technology for tuition scholarships (1957-58, 1959-60), teaching assistantships (1957-58, 1959-60) and for a Sloan summer grant (1958), the duPont Company for a summer grant (1959), and the Allied Chemical Corporation for a fellowship (1958-59).

ABSTRACT

PART I

cis- and trans-1, 2-Diaminocyclohexanes.

Work initiated in these laboratories by Reims and Buchman on the stereospecific conversion of cis- and trans-cyclohexane-1, 2-dicarboxylic acids to the corresponding diamines has been extended. cis- and trans-1, 2-Diaminocyclohexanes have been characterized by measurements of densities, refractive indices, acid constants and melting points and by preparations of both side-chain and cyclic derivatives.

PART II

A study of the tertiary amine precursors of pirylene.

The observation of Sargent, Buchman and Farquhar that the Hofmann degradation of N, N-dimethyl-α-bromomethylpyrrolidinium bromide does not give a single $C_7H_{13}N$ amine, but a mixture of isomeric tertiary amines has been confirmed. The components of the $C_7H_{13}N$ amine mixture have been identified as follows:

(1) 1-dimethylamino-4-pentyne

(2) 1-dimethylamino-2, 4-pentadiene

(3) 1-dimethylamino-3, 4-pentadiene

(4) 1-dimethylamino-3-pentyne

(5) 1-dimethylamino-1, 3-pentadiene.

Components (2), (4) and (5) have been isolated and characterized. Components (1) and (3) were detected by infrared spectroscopy.

A probable course of formation of the $C_7H_{13}N$ amine mixture from N,N-dimethyl-α-bromomethylpyrrolidinium bromide is discussed.

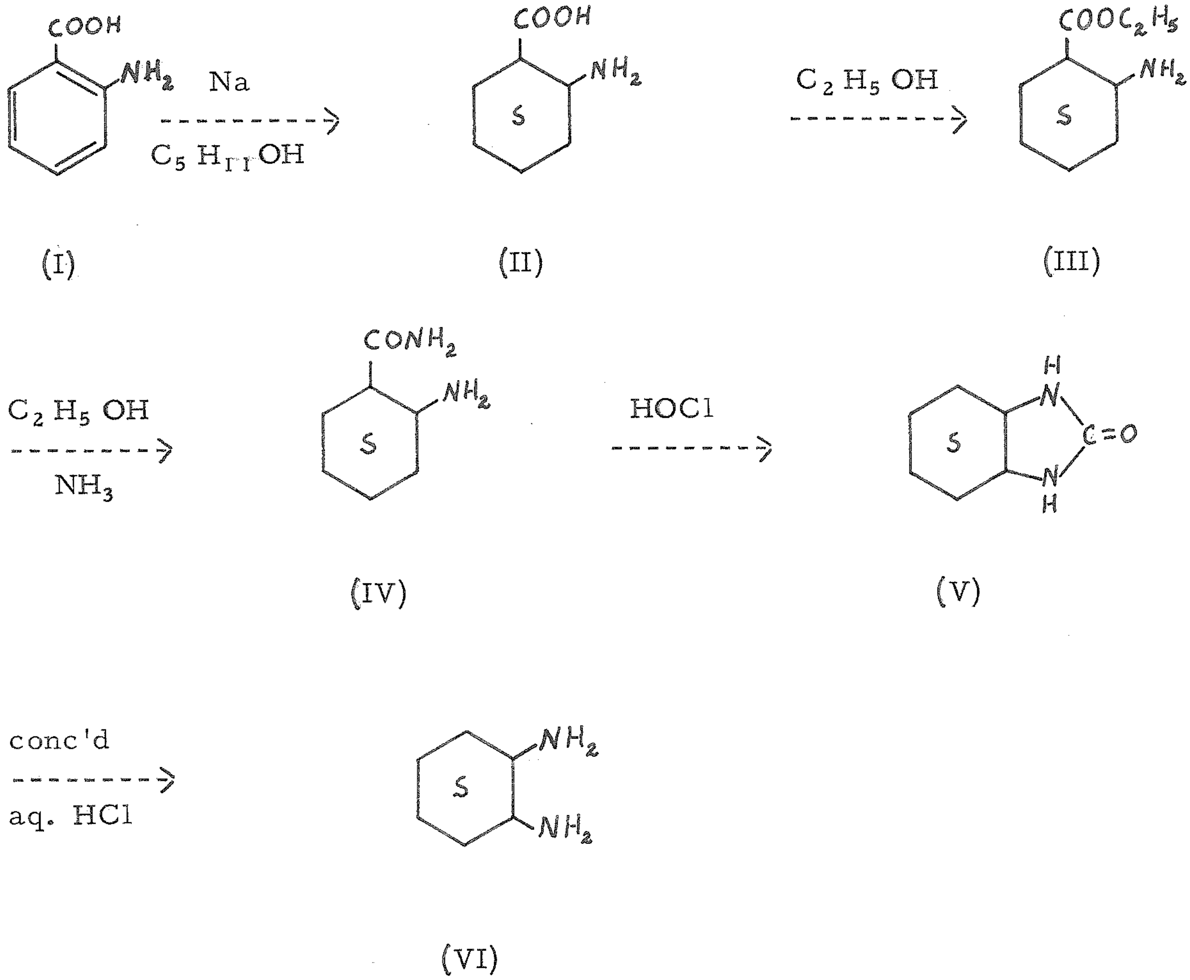
PART I

CIS- AND *TRANS*-1,2-DIAMINOCYCLOHEXANES

Introduction

The first reported preparation of 1, 2-diaminocyclohexane, (VI), was by Einhorn and Bull (1), in 1896. The preparation followed the steps shown on Scheme I and involved the formation of an amine from an amide by treatment of the latter with hypohalous acid, a reaction first observed by Hofmann (2).

Scheme I

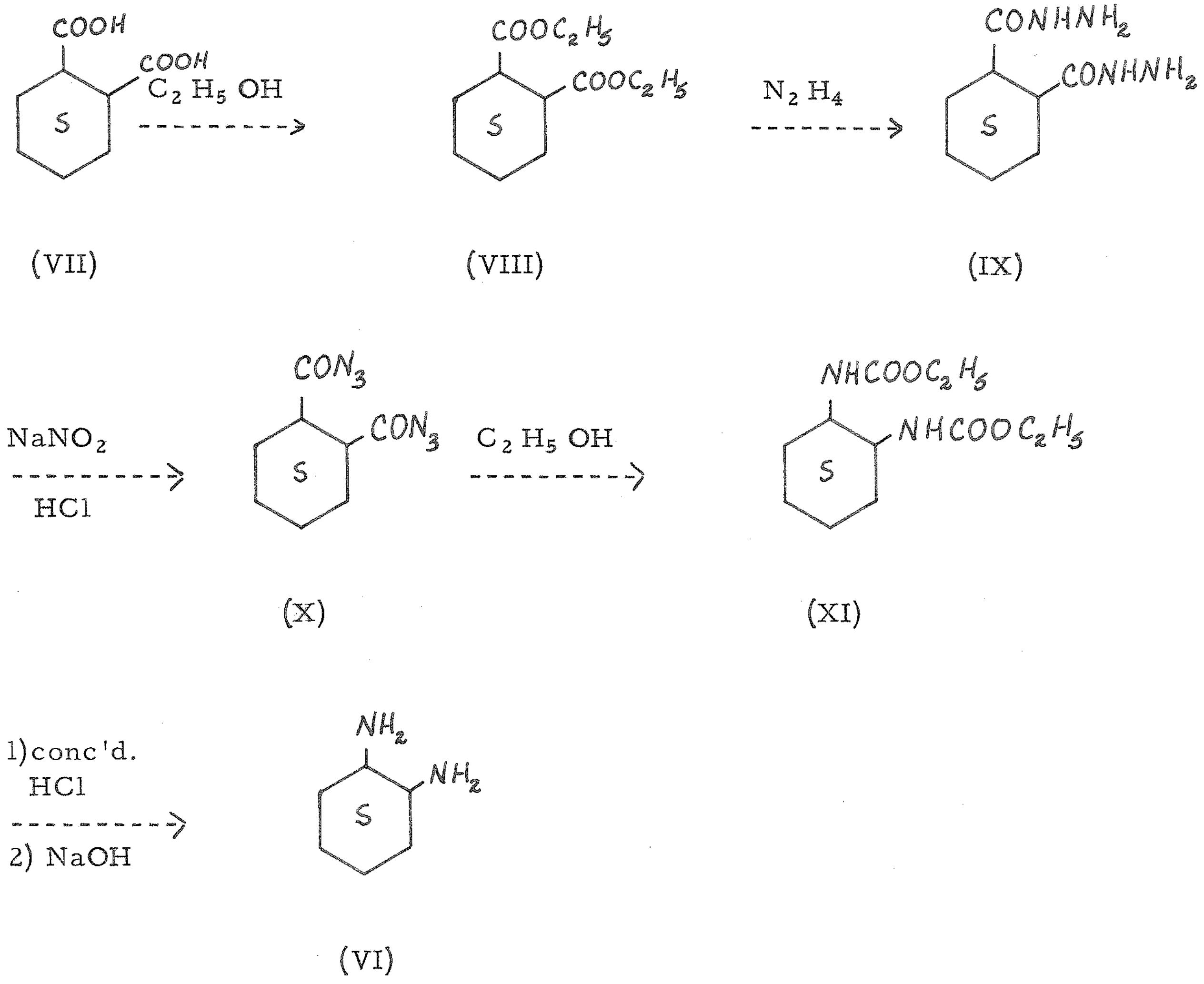


Einhorn and Bull (1) prepared many derivatives of their diamine. The dibenzene sulfonate derivative had a melting point (M.P.

155°) identical with that of the same derivative later prepared from the trans-diamine by Jaeger and van Dijk in 1936 (3). The work of this thesis also affords evidence that (VI) has the trans configuration.

Wieland and co-workers (4) reported the preparation of (VI) by the Curtius method (5) in 1926. Their preparation followed the steps shown on Scheme II.

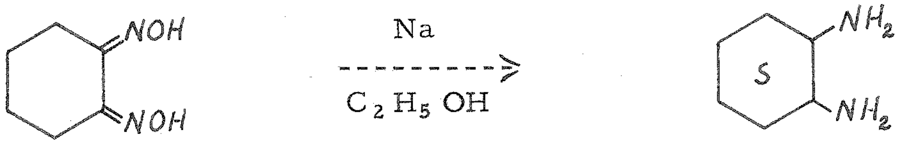
Scheme II



Beilstein tentatively listed the diamine of Wieland and co-workers (4) as the *cis*-isomer. Comparison of the melting points of the *cis*- and *trans*-diurethans obtained in the work reported in this thesis with the melting point of Wieland's compound, (XI), (M.P. 145°) indicates the *trans* configuration for the latter and also for the diamine, (VI).

In 1936, Jaeger and van Dijk (3) prepared 1, 2-diaminocyclohexane by reduction of the dioxime, (XII), of cyclohexane-1, 2-dione (Scheme III).

Scheme III



(XII) (VI)

The following year, Jaeger and Bijerk (6) resolved the diamine via the d-tartrate. Since 1, 2-diaminocyclohexane has two asymmetric centers, it is capable of exhibiting optical isomerism, as well as having two geometrical isomers, *cis* and *trans*. The *cis*-isomer has a center of symmetry and therefore, is *meso* and not capable of resolution. Jaeger and Bijerk's compound was clearly the *trans*-isomer, since it was resolved into its *d* and *l* antipodes.

In addition, the isolation of 1, 2-diaminocyclohexane has been reported (7) without accompanying data which permits an assignment of configuration. Prior to 1956, the preparation of *cis*-1, 2-diaminocyclohexane had not been described in the literature.* In 1956, Winternitz and Condamines (11a) reported the preparation of *cis*-1, 2-diaminocyclohexane by catalytic hydrogenation of benzimidazolone, followed by acid hydrolysis of the hydrogenated product. Yashunskiǐ (11b), in 1958, reported the preparation of *cis*-1, 2-diaminocyclohexane from *cis*-cyclohexane-1, 2-dicarboxylic acid by the Schmidt reaction. He was also able to successfully prepare *cis*-cyclohexane-1, 2-dihydrazide and convert the latter to the *cis*-diamine.

There has been frequent mention of derivatives of 1, 2-diaminocyclohexane in the literature. Notable among these derivatives are imidazolines which have therapeutic activity (12). Other than the recent work of Winternitz and Condamines (11a, 11c) and of Yashunskiǐ (11b), nothing has been published regarding the stereochemistry of such derivatives.**

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*Bailes and Calvin (8) reported the use of *cis*-1, 2-diaminocyclohexane in their studies of cobalt chelate compounds. The *cis*-diamine used in this work was prepared by W. G. Young and co-workers using the method developed by Reims (9). Since 1956, Honda and Schwarzenbach (10a) have employed *cis*- and *trans*-1, 2-diaminocyclohexanes in their studies of complex formation with acetylacetone. They obtained their diamines commercially from J. R. Geigy, Basel. Martell and co-workers (10b) also used both diamines in their studies of copper chelate compounds. They reported that their diamines were prepared by a stereospecific method, but they did not describe the method.

**Winternitz and Condamines prepared *cis*-hexahydrobenzimidazolone and *cis*-2-phenylhexahydrobenzimidazole (11a). A later publication by these authors (11c) described the preparation of *cis*- and *trans*-2-hexahydrobenzimidazolidinethione; the melting points of these isomeric compounds agreed with the values reported in this thesis for the same two compounds. Yashunskiǐ (11b) reported the preparation of *cis*-hexahydrobenzimidazolone.

cis- and _trans_-1,2-Diaminocyclohexanes.

It has been shown in these laboratories by Alf Reims (9) that _cis_- and _trans_-cyclohexane-1,2-dicarboxylic acids undergo the Schmidt reaction (13) without change of configuration, yielding the corresponding diamines. Though the yields are not high, the method is one of simplicity and starting materials are relatively inexpensive. The present problem was designed to expand the work of Reims, investigating more thoroughly the preparations and making a study of the characterizations of the isomers.

Scheme IV gives the series of reactions carried out to obtain the diamines.

The _cis_-diacid, (XIV), was obtained from hexahydrophthalic anhydride, (XIII), by hydrolysis in 99 % yield. The latter is available commercially. The dimethyl ester of (XIV) yielded the _trans_-diacid, (XVIII), on treatment with sodium methoxide and subsequent hydrolysis (88.7% yield).*

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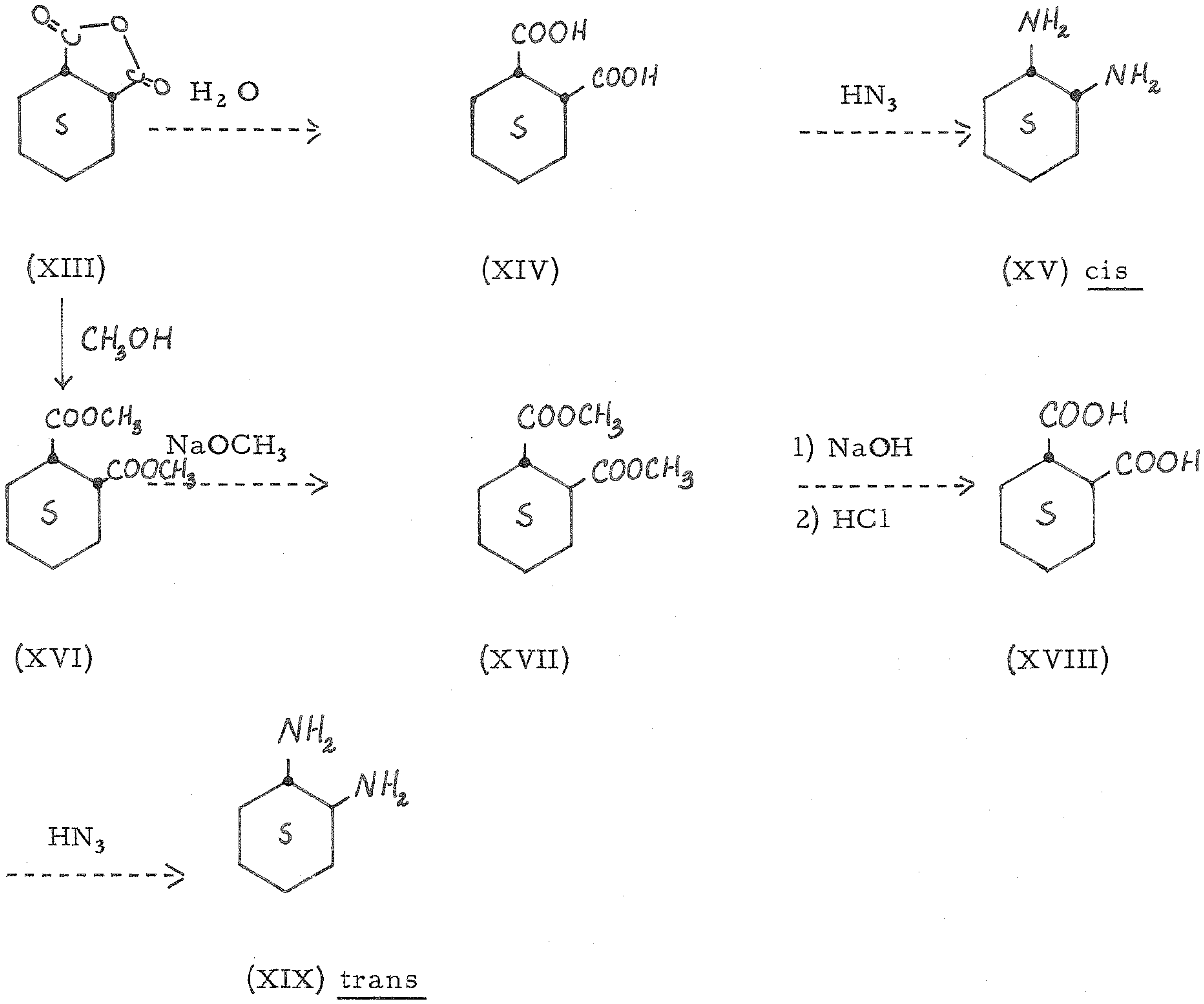
*Hückel and Goth (14) have studied the transformation of _cis_-cyclohexane-1,2-dicarboxylic acid to its _trans_-isomer by reaction of the methyl ester with sodium methoxide.

Scheme IV



The cis-diamine, (XV), was prepared from the diacid, (XIV), by adding a solution of hydrazoic acid in chloroform to the diacid in sulfuric acid, maintaining the temperature between 40-50°. The diamine was isolated by neutralizing the acid solution and distilling over the free base into 6N HCl. On evaporation of the acidified distillate, the crude diamine dihydrochloride was obtained in an average yield of 20.9%. The pure diamine was obtained by dissolving the dihydrochloride in water, neutralizing, extracting the base with ether and distilling the residue after removal of ether (average overall yield of diamine --- 10.7%).

From the trans-diacid, (XVIII), the trans-diamine, (XIX), was obtained in an average overall yield of 14.9% (crude yield of diamine dihydrochloride --- 23.8%).

The cis- and trans-diamines have been characterized by measurements of densities, refractive indices, acid constants and melting points and by preparations of both side-chain and cyclic derivatives.

Each diamine readily formed a dipicrate and a diurethan, showing the normal behavior of the two amino groups.

The cyclic derivatives are of more general interest. The preparation of 2-benzylhexahydrobenzimidazole is mentioned in the literature (12b)* and a study of its pharmacological properties has been mentioned (12c, 15), but the stereochemistry of this compound has not been reported. Preparation of both stereoisomers by reacting the diamines with phenylacetimino ethyl ether hydrochloride and comparison of the melting points of the products with the value given in the literature have shown that the compound previously described had the trans configuration. No mention of the cis-isomer, (XX), has been found in the literature.

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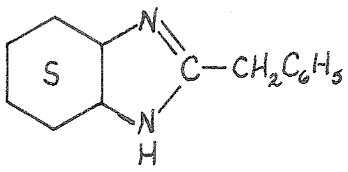
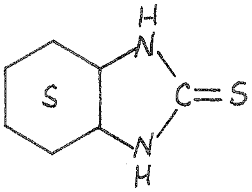
*The melting point of 118-119° given in this patent(12b) is identical with that of the derivative obtained from the trans-diamine in the present work.



(XX) *cis*

(XXI) *trans*

cis-Hexahydrobenzimidazolidinethione, (XXII), and its *trans*-isomer, (XXIII), were prepared by reacting the corresponding *cis*- and trans-diamines with carbon disulfide.*



(XXII) *cis*

(XXIII) *trans*

The reactions of benzil with the *cis*-diamine to form *cis*-2,3-diphenyl-5,6,7,8,9,10-hexahydroquinoxaline, (XXIV), and with the *trans*-diamine to form the corresponding *trans* derivative, (XXV), proceeded very smoothly.** Analysis of the two compounds combined with a study

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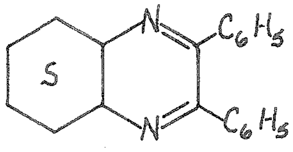
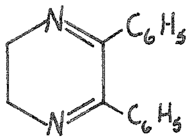
*Ettlinger (16) has presented infrared spectral evidence to demonstrate that, in compounds related to (XXII) and (XXIII), the thione-thiol tautomeric equilibrium lies on the side of the thione. Gillam and Stern (17) presented ultraviolet spectral evidence for the same conclusion. Therefore, (XXII) and (XXIII) are written in their thione forms.

**Einhorn and Bull (1) prepared this derivative. Their melting point of 167-169° agreed with the melting point of the derivative obtained from the *trans*-diamine in the present work.

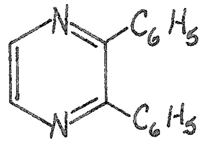
of their ultraviolet absorption spectra in comparison with the spectra of 2,3-diphenyl-5,6-dihydropyrazine, (XXVI), and 2,3-diphenylpyrazine, (XXVII), was used to establish their structures.



(XXIV) *cis*
(XXV) *trans*



(XXVI)



(XXVII)

A study of the infrared spectra of the *cis*- and *trans*-2-benzyl derivatives, (XX) and (XXI), revealed many differences, as did a comparison of the spectra of the *cis*- and *trans*-2-thione derivatives, (XXII) and (XXIII). However, no conclusive evidence could be obtained to attribute spectral differences to *cis* and *trans* configurations.

The acid constants of the *cis*- and *trans*-1,2-diaminocyclohexanes were measured (Table I).

Table I

	pK$_{a_1}$[+]	pK$_{a_2}$[+]
cis-1,2-diamine	(9.73; 9.80[=])	(6.03; 6.16[=])
trans-1,2-diamine	(9.61; 9.68[=])	(6.24; 6.33[=])

[+] Average values.

[=] Values determined from the 1,2-diamine dihydrochlorides.

Hewgill and Jefferies (18) have prepared *cis*- and *trans*-1,3-diaminocyclohexanes by the Schmidt reaction on the corresponding diacids. The acid constants for the 1,3-diamines as determined by these authors were notably different from the values obtained for the 1,2-diamines (Table II).

Table II

	pK_{a_1}	pK_{a_2}
cis-1,3-diamine	10.36	8.54
trans-1,3-diamine	10.30	8.29

Experimental

cis-Cyclohexane-1, 2-dicarboxylic acid, (XIV). To 202.7 g. (1.315 moles) of hexahydrophthalic anhydride (Matheson Coleman and Bell, practical grade) in a 2-liter flask was added one liter of water. The mixture was heated on a steam bath for 5 hours. The yield of cis-cyclohexane-1, 2-dicarboxylic acid was 99% (224.2 g.). It melted at 196-197°.*

trans-Cyclohexane-1, 2-dicarboxylic acid, (XVIII). To 219.3 g. (1.424 moles) of hexahydrophthalic anhydride (practical grade) were added 225 ml. of sulfuric acid (du Pont, C.P. reagent). The solution was refluxed for 4 hours. From 300 ml.** of the solution, the excess of methanol was distilled off and the residue was neutralized with 20 g. of sodium carbonate in 200 ml. of water. The dimethyl ester was extracted with ether, the extracts dried over anhydrous sodium sulfate, the ether distilled off and the ester distilled under reduced pressure (131-133°/26 mm.). The yield of dimethyl ester, (XVI), was 159.4 g. (74.6%). To 500 ml. of absolute methanol (refluxed over magnesium turnings and distilled) were added 7.45 g. of sodium.

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*All melting points reported are uncorrected.

**To 100 ml. of the esterification mixture was added sodium methoxide directly. After refluxing, treating with sodium hydroxide and again refluxing, the basic solution was neutralized with hydrochloric acid. The melting point (187-188°) of the white solid diacid obtained indicated a mixture of cis- and trans-diacids.

The 159.4 g. of dimethyl ester, (XVI), were added to the methanol solution and the mixture was refluxed for 4 hours. To the cooled mixture were added 120 g. (3.0 moles) of sodium hydroxide dissolved in 200 ml. of water. A white solid precipitated and the mixture was refluxed for 2 hours. The solid was washed with methanol, dissolved in 1 liter of water,and the resulting solution was acidified with 250 ml. of concentrated hydrochloric acid. A white solid precipitated and was removed by filtration. The yield of trans-diacid, (XVIII), was 121.5 g. (88.7% based on the diester). The diacid was recrystallized from hot acetic acid to remove a small amount of inorganic material. The recrystallized product was in the form of white platelets and melted at 223-225°.

cis-1,2-Diaminocyclohexane dihydrochloride. A 1-liter, three-necked flask was equipped with a dropping funnel, mechanical stirrer, gas outlet tube and thermometer. To the flask were added 14.96 g. (0.087 mole) of the cis-diacid, (XIV), and 40 ml. (0.75 mole) of sulfuric acid. The flask was immersed in an oil bath at a temperature of 40°. To the dropping funnel were added 129 ml. of a solution of hydrazoic acid in chloroform* (found by titration to contain 8.6 g. (0.198 mole) of hydrazoic acid). The hydrazoic acid-chloroform solution was added slowly

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*The hydrazoic acid solution was prepared according to the procedure described in "Organic Reactions" (13). In a typical preparation, 32 g. (0.50 mole) of sodium azide (Matheson Coleman and Bell) and 32 ml. of warm water were mixed in a 1-liter, 3-necked flask, equipped with stirrer, dropping funnel and gas outlet tube. To the paste were added 200 ml. of chloroform. The flask was immersed in a salt-ice bath and the stirrer was started. From the dropping funnel were added 13.7 ml. (0.25 mole) of sulfuric acid. After the addition was completed (2 hours), the contents of into the reaction flask; the temperature was maintained between 40-50°. The rate of evolution of gas was used as an indication of the rate of reaction. Stirring was continued for 1-2 hours after addition of the hydrazoic acid-chloroform solution was completed. The reaction mixture was poured onto ice and the chloroform (containing the excess hydrazoic acid) was distilled off on a steam bath. A solution of 100 g. (2.5 moles) of sodium hydroxide in a small amount of water was added slowly to the remaining acid solution. The sodium sulfate which precipitated was removed by filtration and the liberated diamine was distilled over into 75 ml. of 3N hydrochloric acid contained in a 1-liter flask. Fractions were collected until evaporation left a negligible residue. The amount of crude cis-1,2-diaminocyclohexane dihydrochloride obtained was 3.43 g. (21.2% yield).

Eight identical reactions were run in the manner described varying only the quantities of reactants. Neither heating the reaction mixture at 65° for 2-3 hours after addition of the hydrazoic acid-chloroform solution, nor adding chloroform to the diacid-sulfuric acid mixture before addition had any effect on the yields obtained. In a ninth reaction, an excess of diacid over the hydrazoic acid was used; the yield of crude diamine dihydrochloride being only 6.6%. A tenth reaction was run generating the hydrazoic acid in situ, the yield being only 7.0%. An

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the flask were filtered through a Büchner funnel, having a coarse sintered glass disk. The chloroform filtrate was dried over anhydrous sodium sulfate. After removing the drying agent, the equivalents of hydrazoic acid were determined by titrating a 1 ml. aliquot portion with standard sodium hydroxide solution to a phenolphthalein end-point.

eleventh reaction was carried out according to the procedure* used by Rutherford and Newman (19), using sodium azide in trifluoroacetic acid and trifluoroacetic anhydride to effect the reaction. In this case no product was isolated.

Table III (pp. 16-17) is a compilation of the data for the series of reactions carried out to obtain the cis-1, 2-diaminocyclohexane dihydrochloride. The yield could not be improved by varying the conditions of reaction.

trans-1, 2-Diaminocyclohexane dihydrochloride. In three reactions of trans-cyclohexane-1, 2-dicarboxylic acid with hydrazoic acid by the same procedure as described above, the average yield of crude trans-1, 2-diaminocyclohexane dihydrochloride was 23.8%.

Liberation of cis-1, 2-diaminocyclohexane, (XV), from its dihydrochloride. To 32.06 g. (0.183 mole) of cis-1, 2-diaminocyclohexane dihydrochloride was added just enough water to dissolve it. To this solution was added slowly 40 g. (1.0 mole) of sodium hydroxide dissolved in a small amount of water. The basic solution was continuously extracted with ether. The ether extracts were dried, the ether distilled off and the cis-diamine, (XV), distilled (112-113°/80 mm.). The weight of cis-diamine obtained was 10.74 g. (51% yield). The preceding is an average representation of the procedure used for obtaining the free diamine from its dihydrochloride. The overall yield of the cis-diamine from the cis-diacid was 10.7%.

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*These reaction conditions were found in a trial run with cyclohexane monocarboxylic acid to give a 61.4% yield of cyclohexylamine hydrochloride.

Table III

Wt. of starting diacid	Moles of HN_3 added	Time of addition of HN_3	Temp. during addition	Time of reaction after addition	Temp. during additional time	Theoretical yield of diamine di HCl	Wt. of diamine di HCl	% Yield
14.96 g. (0.087 mole)	0.198 mole	2 hrs. 20 min.	40-47°	7 hrs. 35 min.	67°	16.2 g.	3.43 g.	21.2
34.4 g. (0.2 mole)	0.585 mole	7 hrs. 5 min.	42-49°	3 hrs. 40 min.	65°	37.2 g.	6.65 g.	17.8
34.4 g. (0.2 mole)	0.537 mole	10 hrs. 25 min.	40-48°	1 hr. 5 min.	40°	37.2 g.	9.40 g.	25.3
86.0 g. (0.5 mole)	1.072 mole	7 hrs. 45 min.	35-44°	20 hrs. 55 min.	40°	93.0 g.	18.62 g.	20.0
43.0 g.* (0.25 mole)	0.316 mole	9 hrs. 45 min.	38-43°	10 hrs. 15 min.	40°	29.3 g.	1.94 g.	6.6
10.0 g.** (0.058 mole)	Moles of NaN_3 = 0.135 (8.64 g.)	Addition of NaN_3 = 1 hr. 5 min.	45-53°	1 hr. 20 min.	40°	10.8 g.	0.75 g.	7.0
17.2 g. (0.1 mole)	0.280 mole	5 hrs. 40 min.	40-48°	16 hrs. 5 min.	40°	18.6 g.	6.27 g.	33.7
20.6 g. (0.12 mole)	0.288 mole	6 hrs. 5 min.	40-45°	19 hrs.	40°	22.3 g.	4.65 g.	21.0
21.5 g.*** (0.125 mole)	0.300 mole	6 hrs. 25 min.	40-48°	3 hrs.	40°	23.25 g.	2.58 g.	11.1
21.5 g.**** (0.125 mole)	0.294 mole	5 hrs. 40 min.	40-47°	3 hrs. 40 min.	40°	23.25 g.	3.98 g.	17.1
0.96 g.***** (5.6 millimoles)	1.44 g. NaN_3 (22.5 millimoles)	-	0-5°	-	-	-	-	0

*An excess of diacid was used.

**The hydrazoic acid was generated *in situ*. This technique has been used successfully in some cases (see Reference (13), p. 328).

***The reaction mixture was refluxed (9 hrs. 30 min.) after pouring onto ice and the chloroform had been removed.

****The reaction mixture was refluxed after pouring onto ice.

*****The reaction of sodium azide with the diacid was carried out in the presence of trifluoroacetic acid and trifluoro acetic anhydride. No product was isolated.

Physical properties of cis-1,2-diaminocyclohexane, (XV), (distilled over sodium).*

Melting point: -1.2° to 0°

Refractive index ($n_D^{25°}$)**: 1.4920

Density ($d_4^{22°}$): 0.9625

Analysis***: Calculated for $C_6H_{14}N_2$: C, 63.11%; H, 12.36%. Found: C, 62.63%; H, 12.24%.

A dipicrate was made by adding an ethereal picric acid solution to the diamine in ether solution. It was recrystallized from hot water containing a small amount of N,N-dimethylformamide. The dipicrate did not melt up to 250°.

Analysis: Calculated for $C_{18}H_{20}N_8O_{14}$: C, 37.77%; H, 3.52%. Found: C, 37.70%; H, 3.59%.

A diurethan was prepared by adding ethyl chlorocarbonate to a cooled solution of the cis-diamine in pyridine. It was recrystallized from hot isopropyl ether in the form of fluffy white crystals melting at 72-74°.

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*Even though the pycnometer used was of a very small bore, the density measurement may not be very accurate, because the diamine absorbed carbon dioxide extremely rapidly. This might also have affected the refractive index measurement.

**Refractive indices were taken with a Carl Zeiss, Jena, Germany, refractometer, having a constant temperature bath.

***All analyses were made by Elek Microanalytical Laboratories, Los Angeles.

Analysis: Calculated for $C_{12}H_{22}N_2O_4$: C, 55.79%; H, 8.59%. Found: C, 55.80%; H, 8.53%.

A dibenzene sulfonate derivative was prepared by adding benzene sulfonyl chloride to an aqueous sodium hydroxide solution of the cis-diamine. The derivative recrystallized from hot ethanol in the form of platelets melting at 169.5-171°.

Liberation of trans-1, 2-diaminocyclohexane from its dihydrochloride. The procedure for liberating the trans-diamine, (XIX), from its dihydrochloride was identical with that described for the cis-diamine. It distilled at 110-112°/80 mm. The average yield from the dihydrochloride was 62.6%, giving an average overall yield from the trans-diacid of 14.9%.

Physical properties of trans-1, 2-diaminocyclohexane, (XIX), (distilled over sodium).*

Melting point: 18.8° to 20.4°

Refractive index ($n_D^{25°}$): 1.4868

Density ($d_4^{22.3°}$): 0.9473

Analysis: Calculated for $C_6H_{14}N_2$: C, 63.11%; H, 12.36%. Found: C, 62.82%; H, 12.19%.

A dipicrate was prepared and recrystallized from hot water containing a small amount of N,N-dimethylformamide. It did not melt to 250°.

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*The trans-diamine absorbed carbon dioxide, though not as rapidly as did the cis-diamine. The density and refractive index measurements characterize the two stereoisomers, though they may not be accurate values. Einhorn and Bull (1) noted that their diamine absorbed carbon dioxide.

Analysis: Calculated for $C_{18}H_{20}N_8O_{14}$: C, 37.77%; H, 3.52%. Found: C, 37.98%; H, 3.84%.

A diurethan was prepared and recrystallized from hot ethanol-water (50:50) mixture in the form of long white needles melting at 144.5-145.5°.

Analysis: Calculated for $C_{12}H_{22}N_2O_4$: C, 55.79%; H, 8.59%. Found: C, 55.91%; H, 8.56%.

Acid constants of (XV) and (XIX). A standard sodium hydroxide solution (0.1358N) and a standard hydrochloric acid solution (0.1065N) were prepared according to the procedures of Pierce and Haenisch (20). The *cis*-diamine, (XV), was titrated in aqueous solution with the standard hydrochloric acid solution. A Beckman pH meter, having a calomel electrode and a glass electrode was used to measure the pH values. A curve was plotted of the titration values and the pK values were read from the plot (the first pK value was the pH of the solution when one-quarter equivalent of acid had been added and the second pK value was the pH of the solution when three-quarters equivalent of acid had been added). The *trans*-diamine, (XIX), was treated similarly. Table I (p. 10) gives the data. Each pK value is the average of three titrations.

The diamine dihydrochlorides* were prepared by treating their respective diamines in ether solution with an ether solution of hydrogen chloride. The dihydrochlorides were recrystallized from ethanol-ethyl

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*The *cis*-diamine dihydrochloride was very hygroscopic, while the *trans*-isomer was not hygroscopic.

acetate mixture. Aqueous solutions of the dihydrochlorides were titrated with the standard sodium hydroxide solution and the pK values were obtained as described for the diamines. The data are given on Table I (p. 10) as average values for three titrations.

The pK values of ethylene diamine and its dihydrochloride were checked by this procedure. The same consistency for the free base ($pK_{a_1} = 9.78$; $pK_{a_2} = 6.85$) and the dihydrochlorides ($pK_{a_1} = 9.86$; $pK_{a_2} = 6.92$) were obtained with these as were obtained for the diaminocyclohexanes and their dihydrochlorides.*

cis-2-Benzylhexahydrobenzimidazole, (XX). To 1.0 g. (8.8 millimoles) of cis-diamine in a 50 ml. round-bottom flask were added 1.76 g. (8.8 millimoles) of phenylacetimino ethyl ether hydrochloride (prepared by passing dry hydrogen chloride into a solution of equimolar amounts of phenyl acetonitrile and absolute ethanol until the theoretical increase in weight was observed). A vigorous reaction took place almost immediately with liberation of heat and evolution of ammonia. After the reaction had ceased, 25 ml. of an approximately 0.1M solution of potassium hydroxide in absolute ethanol were added. The mixture was refluxed for 4 hours. The ethanol was evaporated off and the residue extracted with ethyl ether. The ether extracts were dried and evaporated.

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*The pK values of ethylene diamine have been reported in the literature for the free base (21) ($pKa_1 = 10.0$; $pKa_2 = 7.0$) and for the dihydrochloride (22) ($pKa_1 = 9.98$; $pKa_2 = 6.98$). The small deviations from the values reported here can be attributed in part to the small samples used (ca. 0.02 g. for the free base and ca. 0.03 g. for the dihydrochloride) and in part to not making an attempt to keep out carbon dioxide during the titration. Though the diaminocyclohexanes absorbed carbon dioxide rapidly and the cis-dihydrochloride was very hygroscopic, the internal consistency of the results indicated that they were significant.

The viscous liquid residue which remained was put into a sublimation apparatus, the benzene evaporated off and the residue (partly solid and partly liquid) sublimed. The sublimate was recrystallized from hot hexane containing a few drops of benzene. After several recrystallizations, long white needles were obtained melting at 75-76°.

Analysis: Calculated for $C_{14}H_{18}N_2$: C, 78.46%; H, 8.47%. Found: C, 78.41%; H, 8.61%.

trans-2-Benzylhexahydrobenzimidazole, (XXI). To 1.0 g. (8.8 millimoles) of trans-diamine in a 50 ml. round-bottom flask were added 1.76 g. (8.8 millimoles) of phenylacetimino ethyl ether hydrochloride. A reaction took place slowly. After vigorous shaking, the odor of ammonia and the liberation of heat were observed. To the resulting solid mass were added 25 ml. of an approximately 0.1M solution of potassium hydroxide in ethanol. The mixture was refluxed for 4 hours. (There was not as much mixing of the solid with the ethanol as in the case of the cis derivative.) The ethanol was evaporated and the residue extracted with ethyl ether. After drying the ether extracts, the ether was evaporated. The residue was not completely soluble in benzene, but the benzene solution along with suspended material was put into a sublimation apparatus and the benzene was evaporated. The first sublimation was carried out at 100°/1-2 mm. for 10 hours. The sublimate (M.P. 93-120°) was resublimed for 4 hours at 100°/1-2 mm. giving a sublimate melting in the range 128-133°. On recrystallization from a hot mixture of hexane and benzene, a material with a sharp melting point was obtained (M.P.

137-137.5°). After three recrystallizations, the sample was submitted for analysis (final M.P. 138-138.5°). Analysis showed that the substance was not the desired imidazoline derivative. The infrared spectrum of this compound showed a strong absorption at 1665 cm^{-1}, suggesting hydrolytic fission of the imidazoline ring to give the corresponding amide.* Repeated sublimations at 60°/1-2 mm. of the residue from the first sublimation produced a lower melting substance, which upon being recrystallized several times from a hot mixture of hexane and benzene was found to have the correct analysis. It crystallized in the form of small white platelets melting at 118-119°.

Analysis: Calculated for $C_{14}H_{18}N_2$: C, 78.46%; H, 8.47%. Found: C, 78.30%; H, 8.68%.

<u>cis</u>-2-Hexahydrobenzimidazolidinethione, (XXII). To the <u>cis</u>-diamine in ethanol was added an excess of carbon disulfide. The mixture was heated on a steam bath until a precipitate formed. The solid was recrystallized from hot water in the form of long white needles melting at 166.5-167°.

Analysis: Calculated for $C_7H_{12}N_2S$: C, 53.81%; H, 7.74%. Found: C, 53.71%; H, 7.77%.

trans-2-Hexahydrobenzimidazolidinethione, (XXIII). To a cooled solution of 0.57 g. (5.0 millimoles) of the trans-diamine in 5 ml. of absolute ethanol was added 0.76 g. (10.0 millimoles) of carbon disulfide.

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*Aspinall (23) has observed this type of cleavage.

On heating the mixture at 50° for a few minutes in a water bath, a precipitate formed. The ethanol was removed and the solid dissolved in a 10% aqueous solution of sodium hydroxide. The solid was reprecipitated by neutralizing the basic solution with hydrochloric acid. The solid was washed with water and recrystallized from a hot ethanol-water (50:50) mixture in the form of white platelets melting at 200-201°.

Analysis: Calculated for $C_7H_{12}N_2S$: C, 53.81%; H, 7.74%. Found: C, 53.89%; H, 7.80%.

cis-2,3-Diphenyl-5,6,7,8,9,10-hexahydroquinoxaline, (XXIV). To 0.2 g. (1.75 millimoles) of cis-diamine was added 0.37 g. (1.75 millimoles) of benzil. The mixture was heated on a steam bath. A homogeneous liquid system was obtained immediately. On further heating a cloudiness appeared. The mixture was cooled in a dry ice-acetone bath, forming a viscous material, which dissolved in hot petroleum ether (B.P. range 60-70°). On cooling the petroleum ether solution in a dry ice-acetone bath, a solid precipitated. The petroleum ether was removed and the solid residue was extracted with ethyl ether. The ether soluble material had a lower melting point (115-118°) than the ether insoluble (131-133°). The ether insoluble material was recrystallized from hot isopropyl ether in the form of pale yellow prisms melting at 132-133°. Analysis combined with the ultraviolet absorption spectrum (see "Spectral analyses" Section) of the compound showed it to be the desired compound.

Analysis: Calculated for $C_{20}H_{20}N_2$: C, 83.29%; H, 6.99%. Found: C, 83.01%; H, 7.05%.

<u>trans-2,3-Diphenyl-5,6,7,8,9,10-hexahydroquinoxaline, (XXV).</u> To 0.2 g. (1.75 millimoles) of <u>trans</u>-diamine was added 0.37 g. (1.75 millimoles) of benzil. On slightly heating the mixture, an evolution of heat was observed. After standing at room temperature for a short time, a yellowish-white solid formed. A single liquid phase was obtained by heating this solid on a steam bath. On cooling this liquid in a dry-ice-acetone bath, a solid was produced which did not melt on heating on the steam bath. The product was recrystallized from hot absolute ethanol in the form of pale yellow platelets melting at 172-173°.

Analysis: Calculated for $C_{20}H_{20}N_2$: C, 83.29%; H, 6.99%. Found: C, 83.22%; H, 7.07%.

<u>2,3-Diphenyl-5,6-dihydropyrazine, (XXVI).</u> The dihydropyrazine compound was prepared by reacting ethylene diamine (3.0 g.; 0.05 mole) with benzil (10.5 g.; 0.05 mole). Pale yellow crystals were obtained on recrystallization from ethanol. They melted at 160-161°.*

Analysis: Calculated for $C_{16}H_{14}N_2$: C, 82.02%; H, 6.02%. Found: C, 82.05%; H, 6.24%.

<u>2,3-Diphenylpyrazine, (XXVII).</u> (XXVII) was obtained by distilling (XXVI) (3.0 g.; 0.128 mole) at 200°/15-20 mm. for two hours. Only a very small amount of distillate was collected. The residue in the pot was taken up in concentrated hydrochloric acid and the solution was

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*Mason (24) gave two different melting points for 2,3-diphenyl-5,6-dihydropyrazine as noted by Beilstein. His first value (M.P. 160-161°) reported in Berichte (25) checks with the value given in this thesis in contrast to 181° mentioned in reference (24).

diluted with water, decomposing the hydrochloride. On cooling, crystals formed. After recrystallization from hot ethanol-water (50:50) mixture, white crystals with a golden tinge were obtained melting at 120-121°.*

Spectral analyses. The infrared spectra** of the *cis*- and *trans*-1,2-diaminocyclohexanes in chloroform were very similar. There may be significance to the triplet of bands in the 900-1000 cm^{-1} region for the *cis*-isomer. The *trans*-isomer has only a singlet in this region (see I.R. spectrum #I, p. 30 and I.R. spectrum #II, p. 31).

The infrared spectra of the *cis*- and *trans*-2-benzylhexahydrobenzimidazoles in chloroform were quite different from each other (see I.R. spectrum #III, p. 32 and I.R. spectrum #IV, p. 33). Also, the spectra of the *cis*- and *trans*-2-hexahydrobenzimidazolidinethiones in chloroform were quite different from each other (see I.R. spectrum #V, p. 34 and I.R. spectrum #VI, p. 35). Likewise, there were observable differences in the spectra of *cis*- and *trans*-2,3-diphenyl-5,6,7,8,9,10-hexahydroquinoxalines in chloroform (see I.R. spectrum #VII, p. 36 and I.R. spectrum #VIII, p. 37). However, no generalization based on the observed spectra could be formulated which would assist in distinguishing between *cis* and *trans* configurations.

It was of interest to know if the hexahydroquinoxaline derivatives lost hydrogen under the conditions used for their preparation. The ultra-

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*Mason (24) gave a value of 118-119°.

**All infrared spectra were taken with a Perkin-Elmer Model 21 spectrophotometer.

violet spectra* of 2,3-diphenyl-5,6-dihydropyrazine and of 2,3-diphenylpyrazine in methanol were compared with the spectra of cis- and trans-2,3-diphenyl-5,6,7,8,9,10-hexahydroquinoxalines. The spectra of the hexahydroquinoxalines were identical with that of the dihydropyrazine, but all showed a marked difference from the pyrazine spectrum (see Figure 1, p. 28). The infrared spectra also upheld this finding. The spectrum of 2,3-diphenyl-5,6-dihydropyrazine (see I.R. spectrum #IX, p. 38) showed marked similarity to the spectra of the quinoxalines, while the spectrum of the 2,3-diphenylpyrazine (see I.R. spectrum #X, p. 39) was quite different. Further, the pyrazine compound had a visual fluorescence of white, while the dihydropyrazine and the cis- and trans-hexahydroquinoxaline derivatives fluoresced with a dull red color. These findings showed that the cis and trans derivatives did not lose hydrogen during their preparation.

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*The ultraviolet spectra were taken with a Cary Model 11M recording spectrophotometer, Applied Physics Corporation, Pasadena, California.

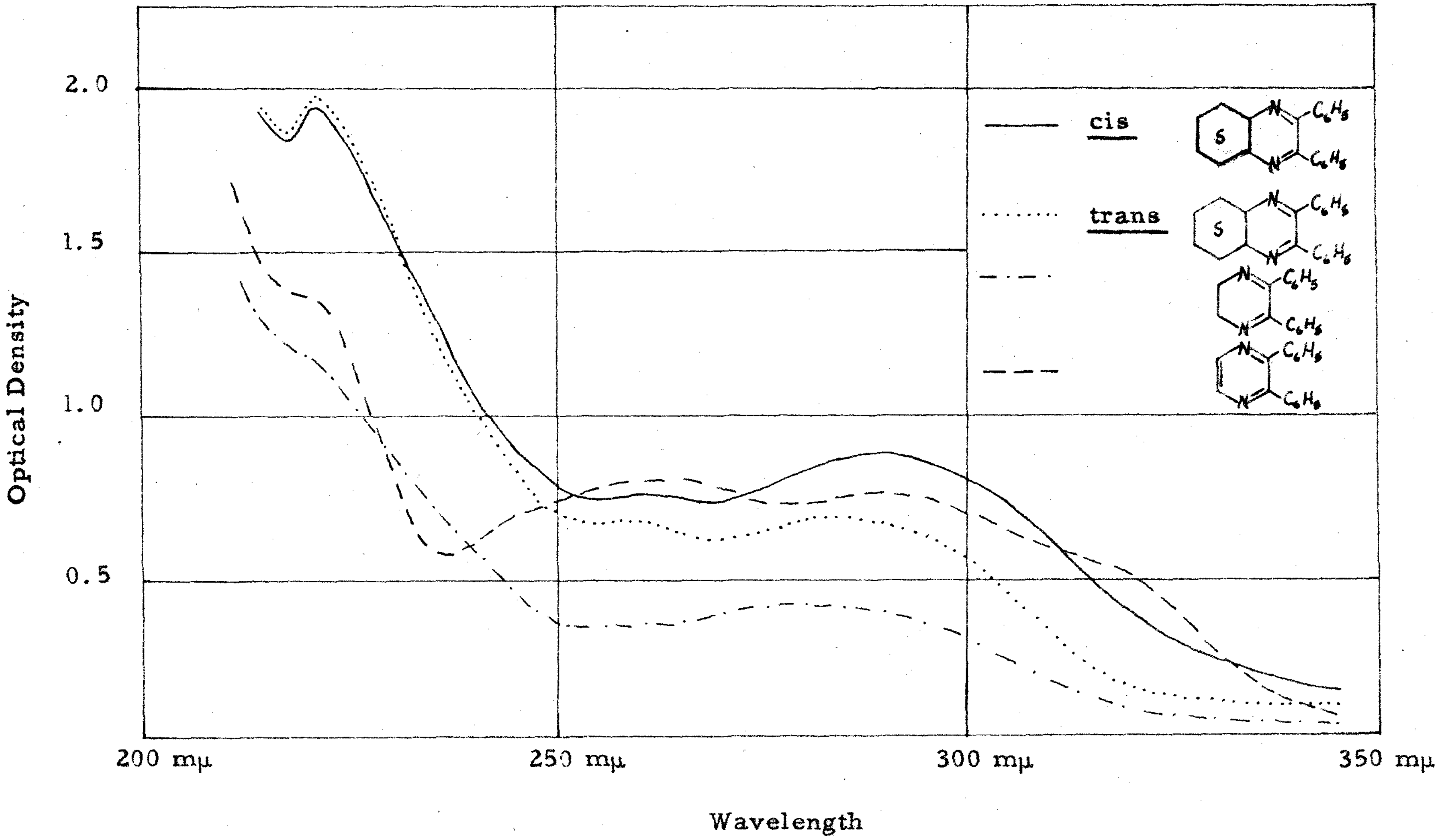
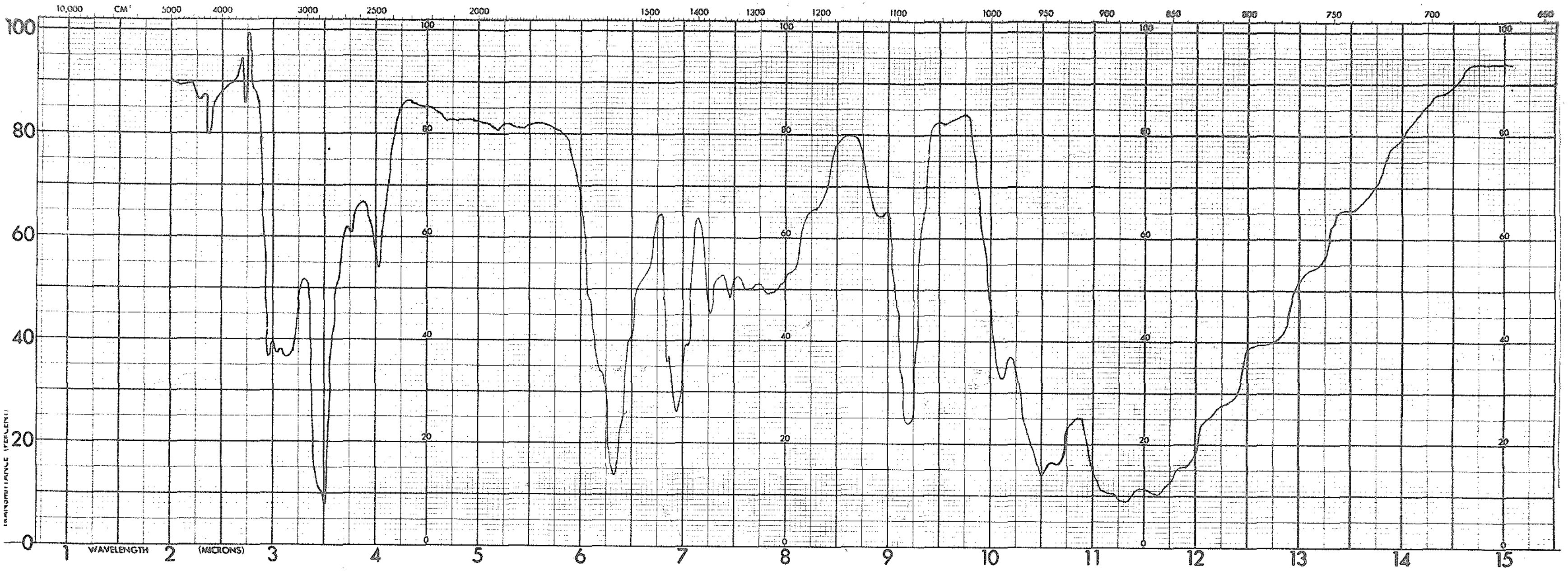

2.0
1.5
1.0
0.5
Optical Density
200 mμ
250 mμ
300 mμ
350 mμ
Wavelength
cis
trans
S
N
C₆H₅

Figure 1

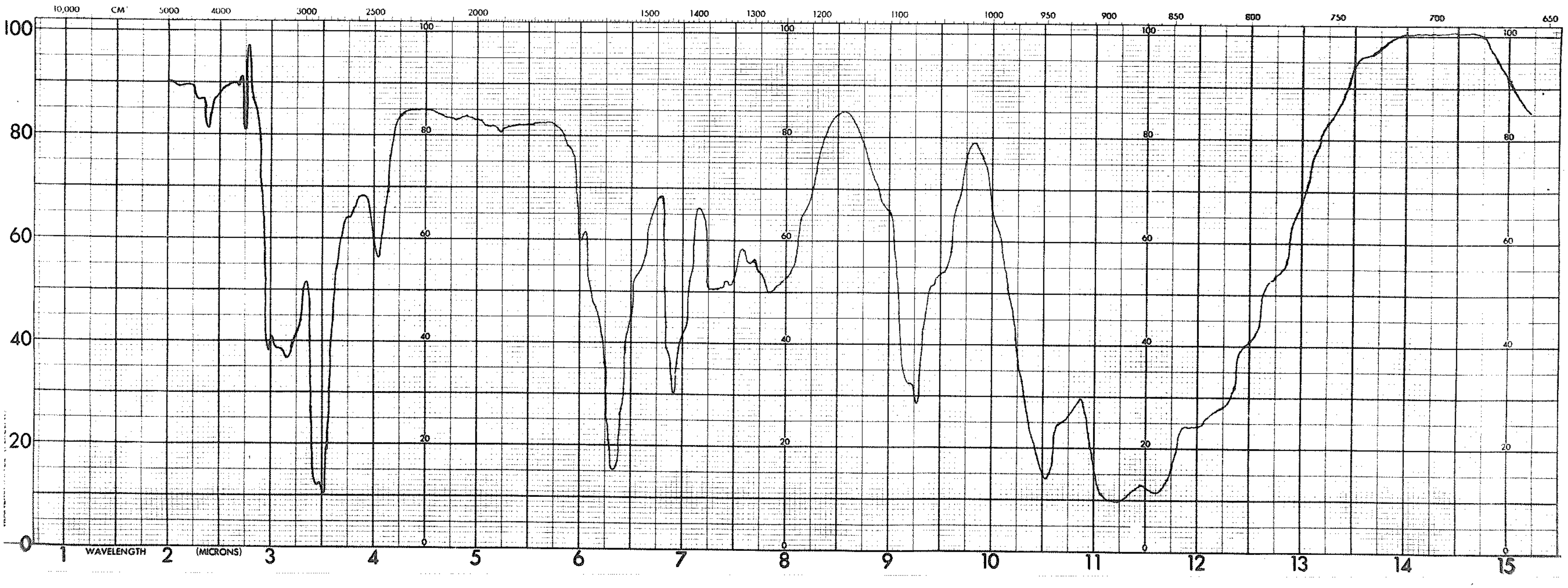
INFRARED SPECTRA



I.R. Spectrum #I

cis-1, 2-Diaminocyclohexane

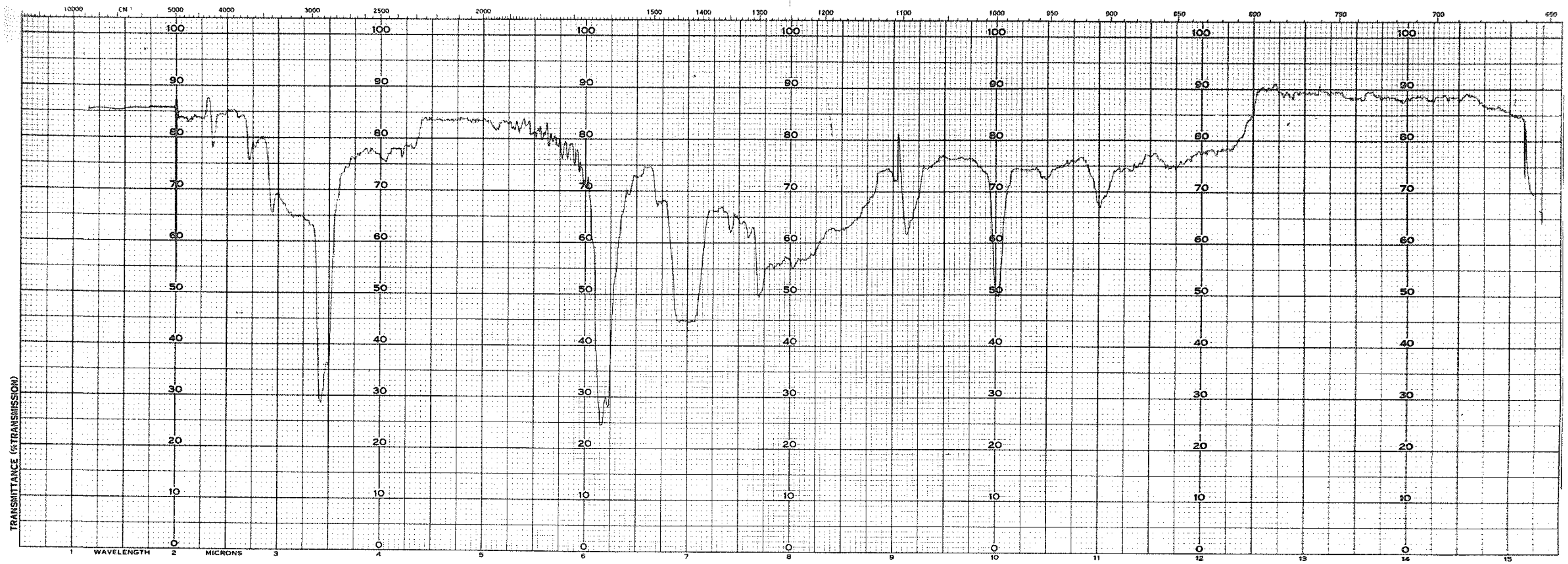
Solvent: Chloroform
Cell: 1 mm. NaCl prism



I.R. Spectrum #II

<u>trans</u>-1, 2-Diaminocyclohexane

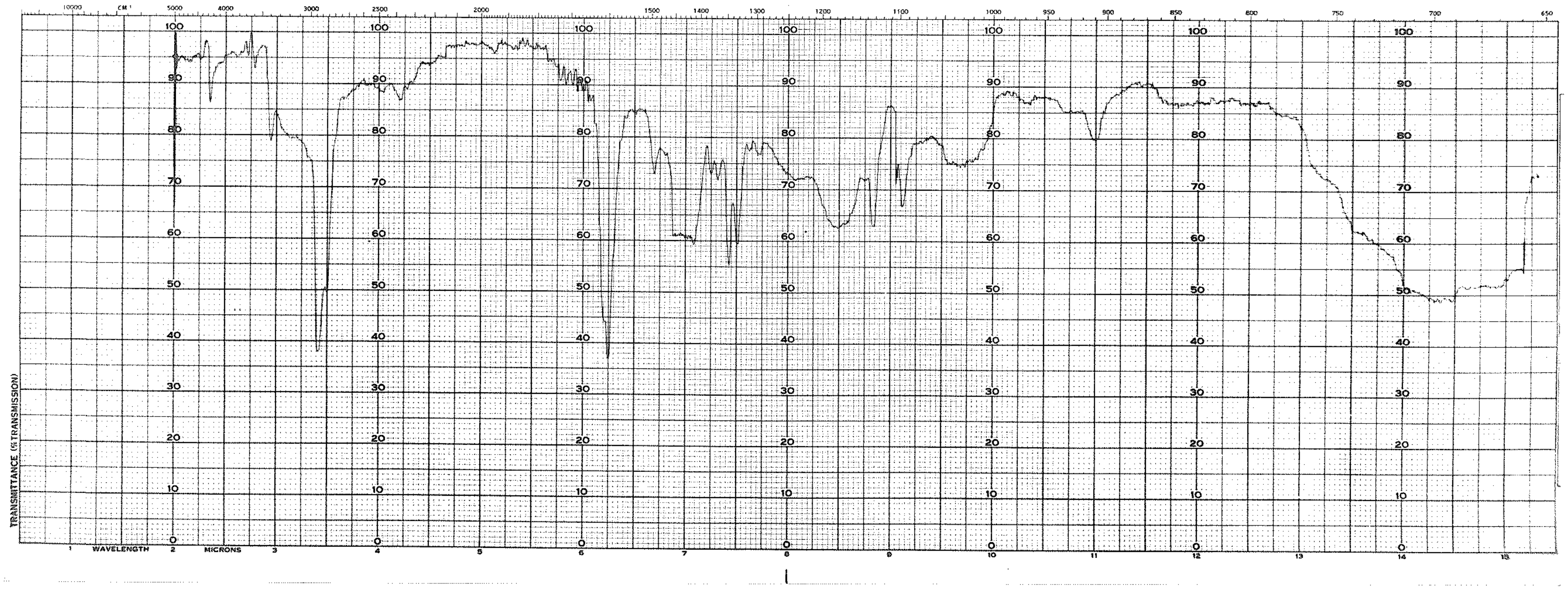
Solvent: Chloroform
Cell: 1 mm. NaCl prism



I.R. Spectrum #III

<u>cis</u>-2-Benzylhexahydrobenzimidazole

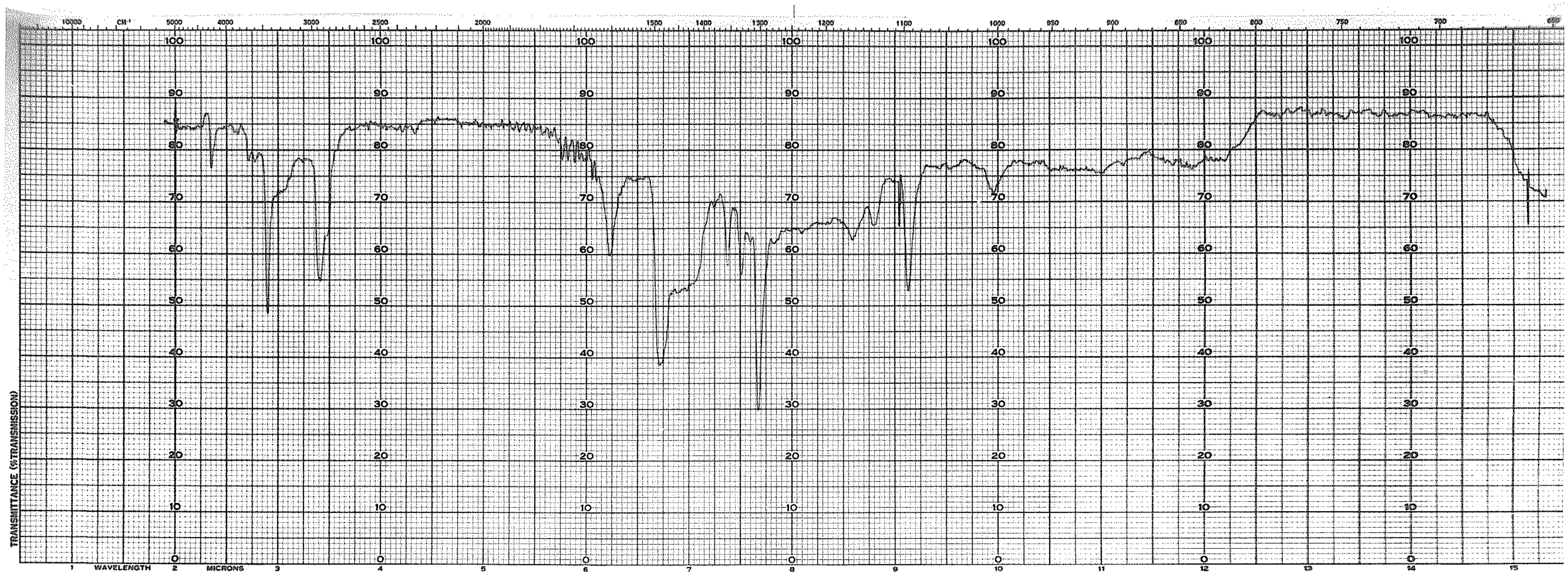
Solvent: Chloroform
Cell: 1 mm. NaCl prism



I.R. Spectrum #IV

trans-2-Benzylhexahydrobenzimidazole

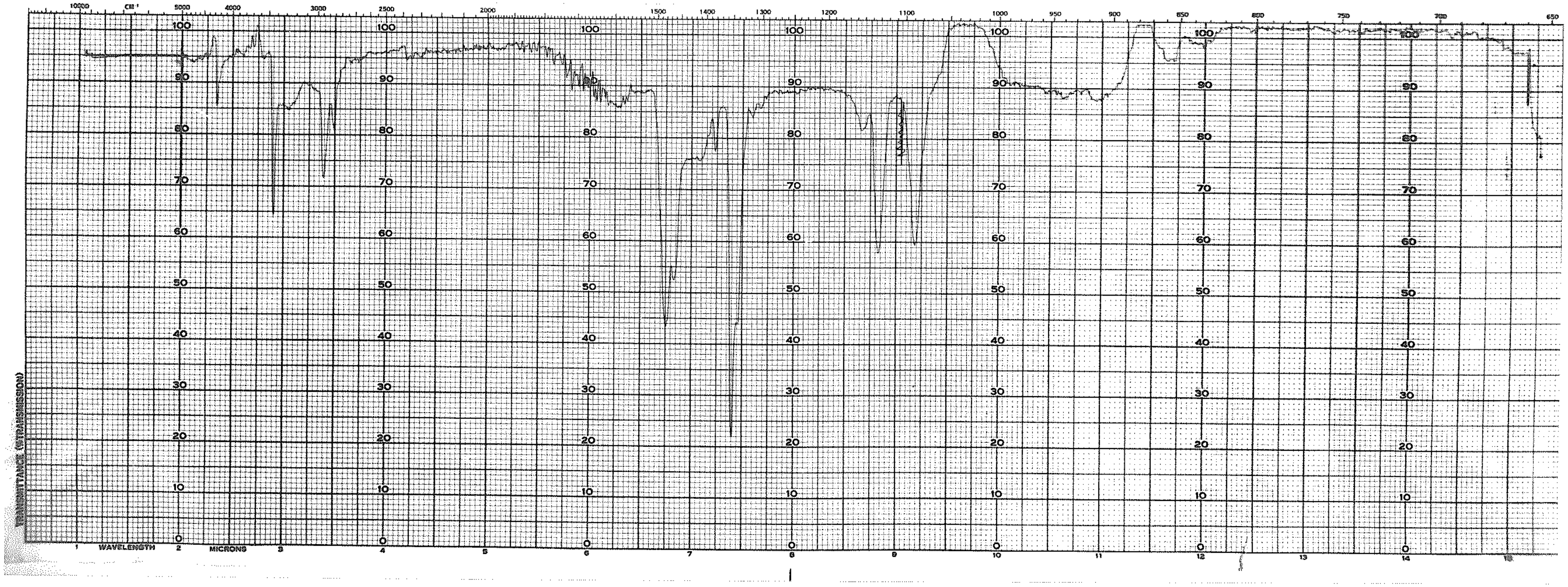
Solvent: Chloroform
Cell: 1 mm. NaCl prism



I.R. Spectrum #V

cis-2-Hexahydrobenzimidazolidinethione

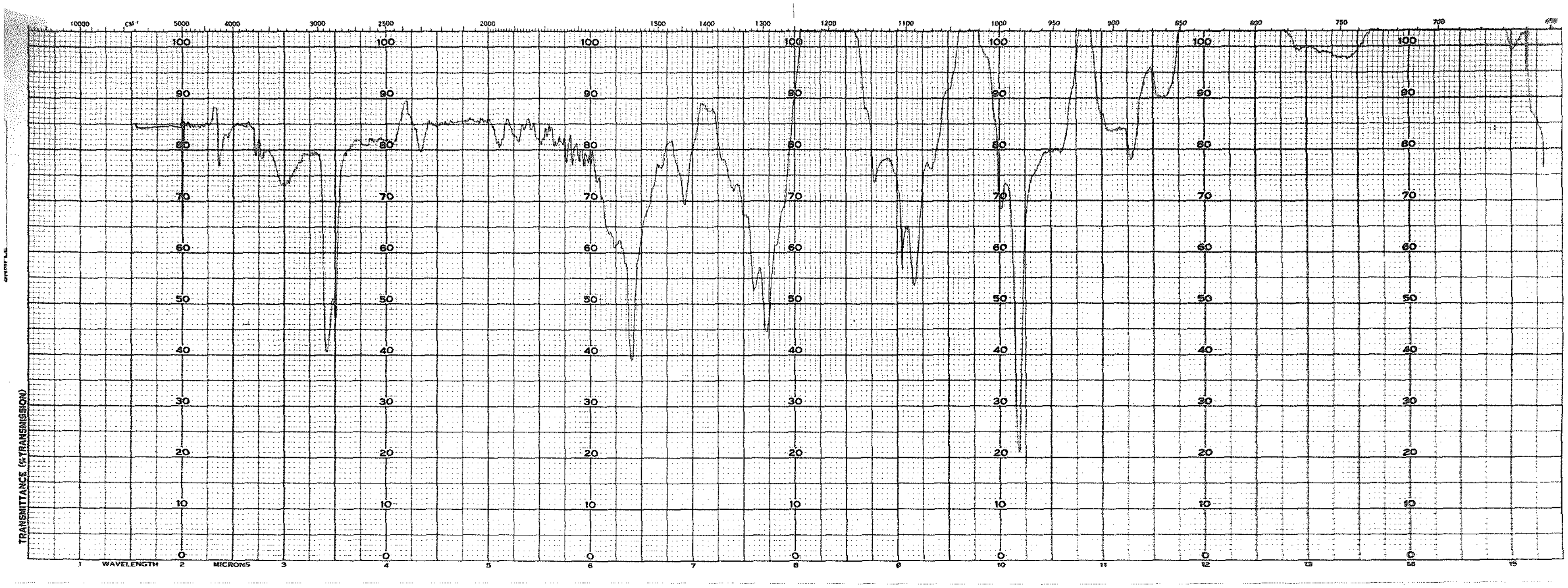
Solvent: Chloroform
Cell: 1 mm. NaCl prism



I.R. Spectrum #VI

trans-2-Hexahydrobenzimidazolidinethione

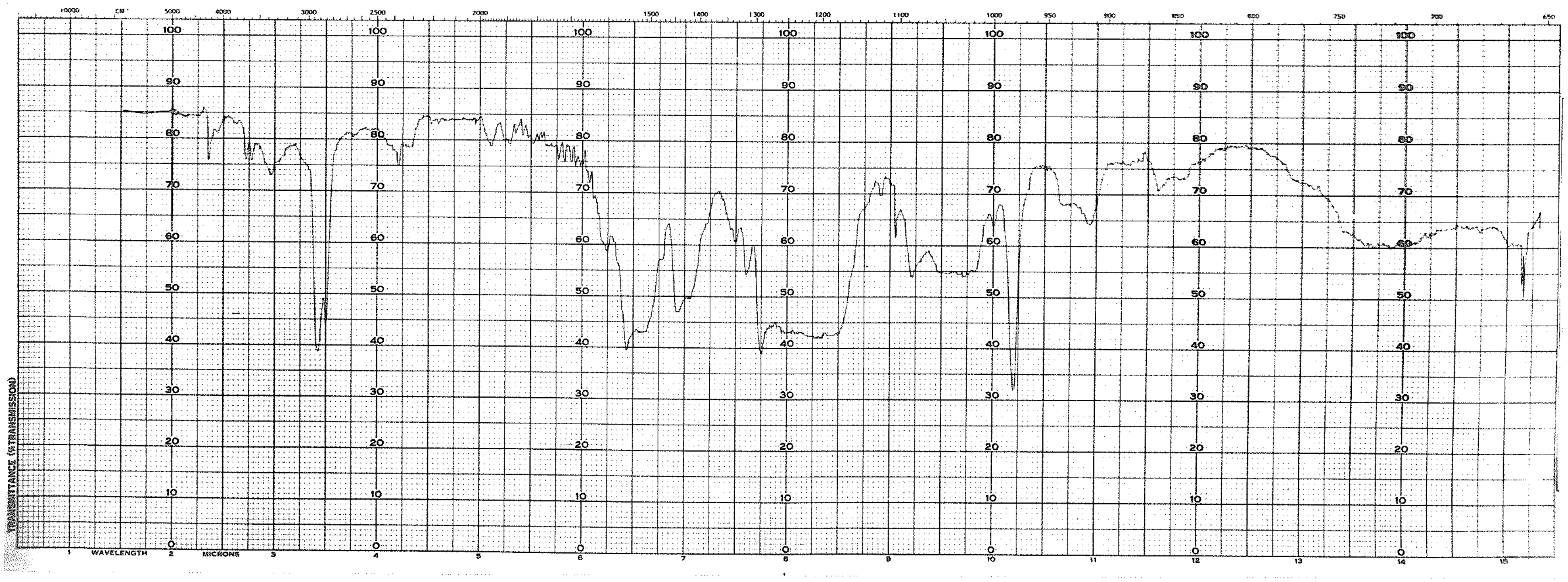
Solvent: Chloroform
Cell: 1 mm. NaCl prism



I.R. Spectrum #VII

cis-2, 3-Diphenyl-5, 6, 7, 8, 9, 10-hexahydroquinoxaline

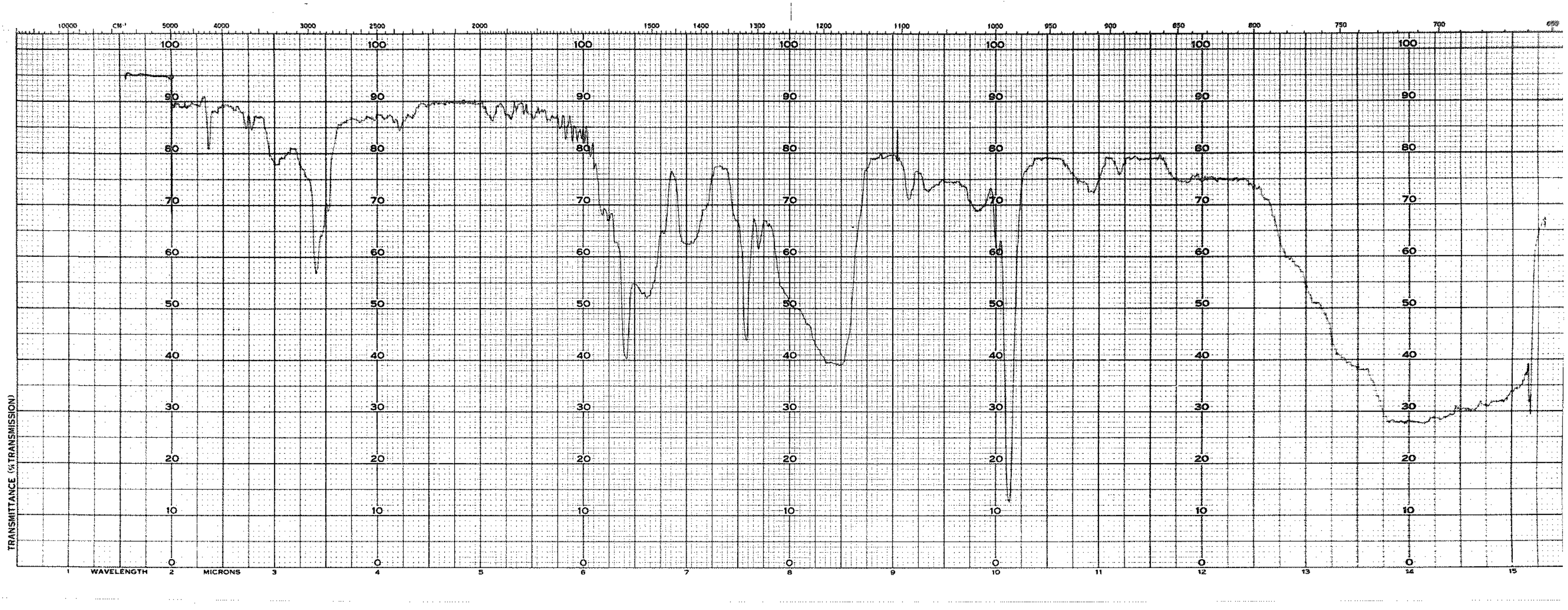
Solvent: Chloroform
Cell: 1 mm. NaCl prism



I.R. Spectrum #VIII

<u>trans</u>-2,3-Diphenyl-5,6,7,8,9,10-hexahydroquinoxaline

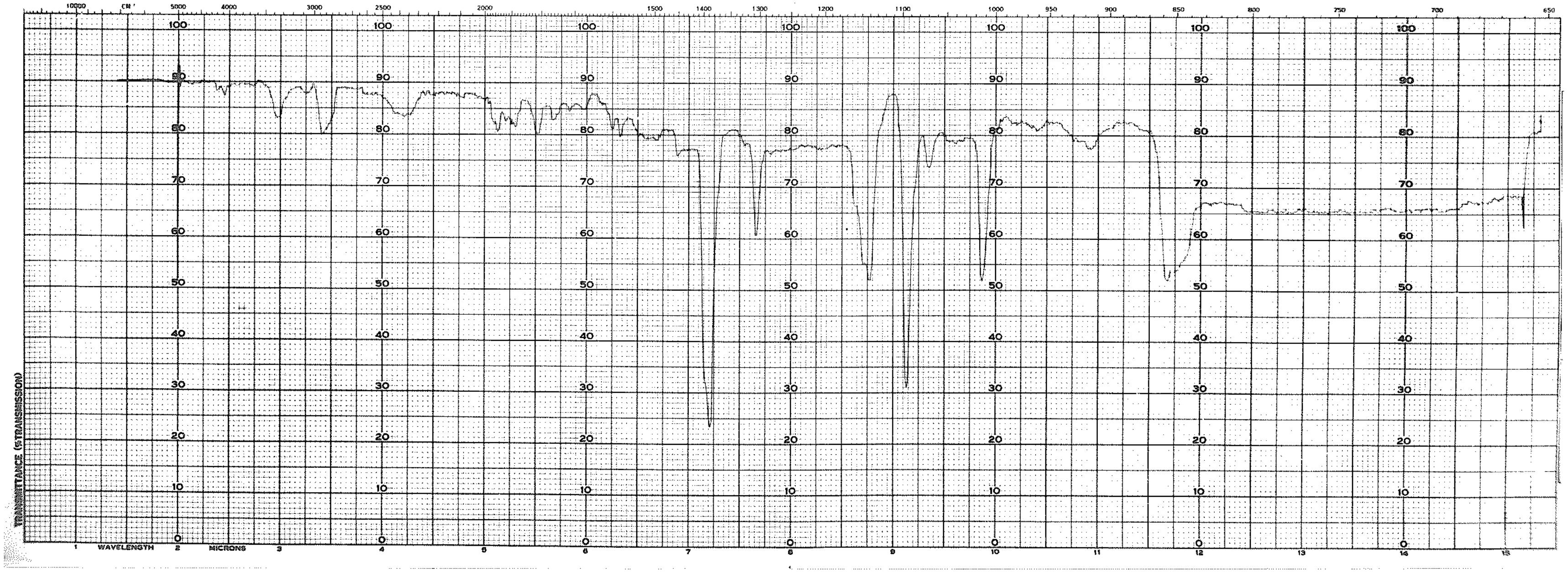
Solvent: Chloroform
Cell: 1 mm. NaCl prism



I.R. Spectrum #IX

2,3-Diphenyl-5,6-dihydropyrazine

Solvent: Chloroform
Cell: 1 mm. NaCl prism



I.R. Spectrum #X

2, 3-Diphenylpyrazine

Solvent: Chloroform
Cell: 1 mm. NaCl prism

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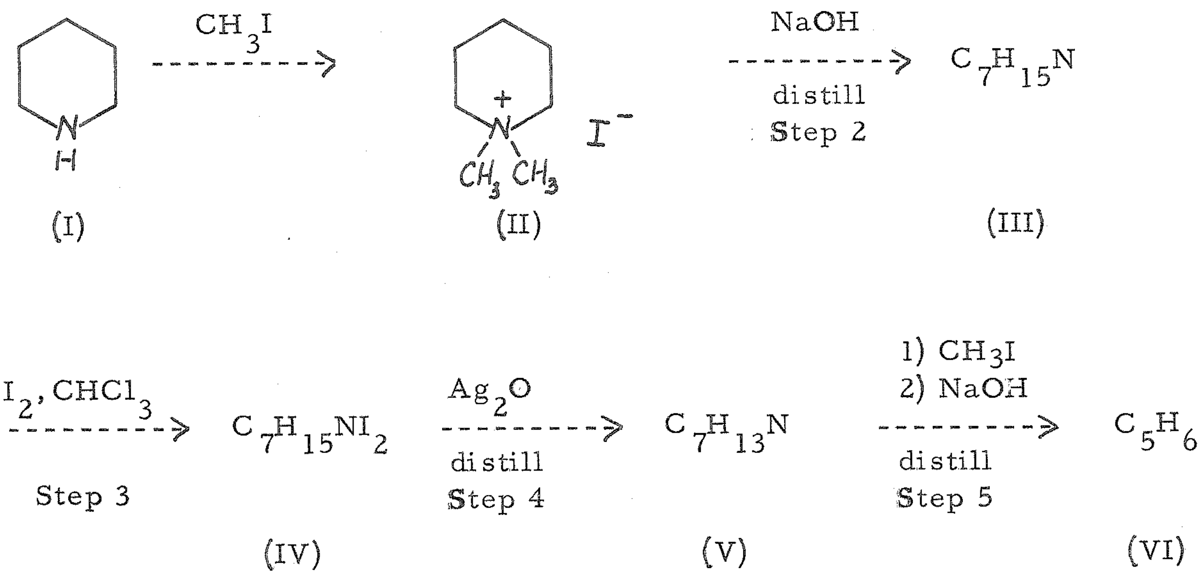
PART II

A STUDY OF THE TERTIARY AMINE PRECURSORS OF PIRYLENE

Introduction

Ladenburg (1), in 1881, reported the preparation of a $C_7H_{13}N$ compound, (V), designated as dimethylpiperideine. The following year (2) he degraded it by the Hofmann exhaustive methylation technique and isolated a C_5H_6 hydrocarbon, (VI), which was named pirylene.

Scheme I



Since he did not know the structures of (III)* (which he called dimethylpiperidine) and (IV), a correct assignment of structure to (V) would have been fortuitous.

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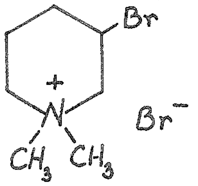
*In the same year, A. W. Hofmann (3) reported the formation of piperylene through a degradation of (III), but he could not establish its structure. Five years later, Howard and Roser (4) postulated it to be 1,4-pentadiene. It was not until 1901, that Thiele (5) established its structure as 1,3-pentadiene.

Merling (6) repeated Ladenburg's work, substituting bromine for iodine in step 3 (Scheme I) and obtained a $C_7H_{13}N$ base, also.

In 1886, Howard and Roser (4) reported that (III) was 1-dimethylamino-4-pentene, (VII), and that (IV) was N,N-dimethyl-β-bromopiperidinium bromide, (VIII).

$(CH_3)_2NCH_2CH_2CH_2CH{=}CH_2$

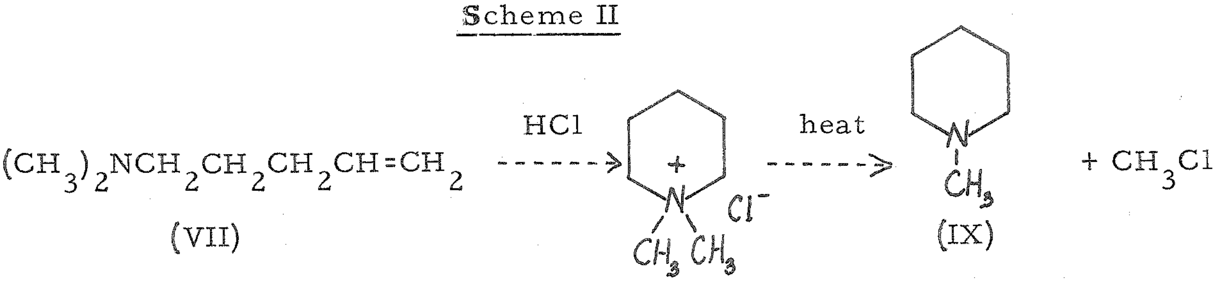
(VII)



(VIII)

The structure, (VII), was deduced from its mode of formation and (VIII) was based on the belief that (VII) yielded N-methylpiperidine, (IX), on treatment with hydrochloric acid, followed by pyrolysis of the salt.

Scheme II

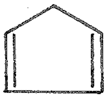


Ladenburg (7) accepted the structure, (VII), proposed for his dimethylpiperidine, (III), but he believed that (IV) was simply the product, (X), resulting from addition of iodine to the double bond.

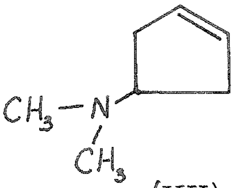
$(CH_3)_2NCH_2CH_2CH_2CHICH_2I$

(X)

Further, he reasoned that, since pirylene did not react with ammoniacal cuprous chloride solution, it was not an acetylene and that it was probably a doubly unsaturated five-membered ring compound, (XI). The structure of the precursor, (V), followed from this; it was postulated to be 4-dimethylaminocyclopentene, (XII).



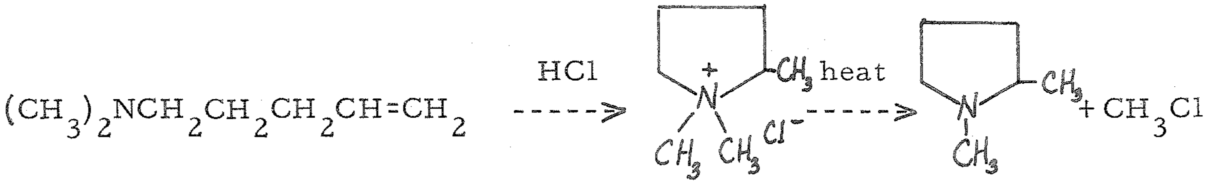
(XI)



(XII)

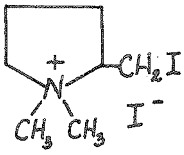
Later, Merling (8) reported that 1-dimethylamino-4-pentene, (VII), gave N-methyl-a-methylpyrrolidine, (XIII), not the isomer, N-methylpiperidine, (IX), on treatment with hydrochloric acid, followed by pyrolysis of the salt.

Scheme III

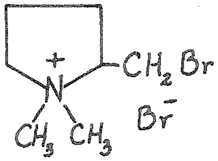


(XIII)

Willstätter (9), in 1900, studied the physical properties of (IV) and observed that they were indeed those of a quaternary ammonium salt and not of a tertiary amine. On treatment with zinc and hydriodic acid, (IV) was reduced to N,N-dimethyl-a-methylpyrrolidinium iodide. The iodide was converted to the chloride and the latter was pyrolyzed to give N-methyl-a-methylpyrrolidine, (XIII). It was clear that Ladenburg's formulation was incorrect and that the halogens reacted with (VII) to give a five- rather than a six-membered ring. N,N-Dimethyl-α-iodomethylpyrrolidinium iodide, (XIV), was thus established for (IV) and the original compound of Merling (6) was assigned the structure of the corresponding bromo-bromide, (XV).



(XIV)



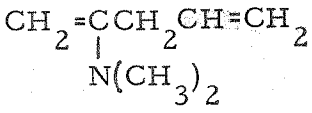
(XV)

Willstätter postulated that (XVI) was the structure of Ladenburg's dimethylpiperideine, (V), though he stated that the positions of the double bonds were questionable.

$$(CH_3)_2NCH{=}CHCH_2CH{=}CH_2$$

(XVI)

At this point the matter rested until, in 1928, v. Braun and Teuffert (10) studied pirylene itself and rejected previous formulations of the $C_7H_{13}N$ base, (V). Reasoning that the elimination occurred within the ring, structures (XVII) and (XVIII) were proposed for (V).



$$CH_2{=}\underset{\underset{\displaystyle N(CH_3)_2}{|}}{C}CH_2CH{=}CH_2$$

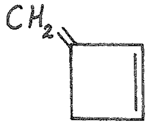
(XVII)

$$(CH_3)_2NCH_2CH_2CH{=}C{=}CH_2$$

(XVIII)

(XVII) was rejected on the basis of the finding that the $C_7H_{13}N$ base gave 1-dimethylaminopentane on hydrogenation.*

As a matter of passing interest, it will be noted here that v. Braun and Teuffert favored two radically different structures, (XIX) and (XX), for pirylene. Though other structures were considered, the observed molecular refraction of pirylene agreed most closely with the calculated values for these two.



(XIX)

(XX)

It was discovered by Sargent, Buchman and Farquhar (11), 60 years after Ladenburg's original work, that the $C_7H_{13}N$ base, (V), was not a single component, but was a mixture of components. At the same time these authors showed that pirylene, (VI), was methylvinylacetylene, (XXI). The structure was also arrived at by an electron diffraction investigation made by Spurr and Schomaker (12).

$$CH_3C \equiv CCH = CH_2$$

(XXI)

Two papers of significance have appeared in the last decade, one

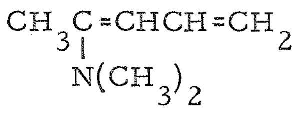
---

*v. Braun and Teuffert detected neither the odor of dimethylamine nor ketone on warming the tertiary amine with dilute sulfuric acid. This indicated to them that they did not have a vinyl amine.

by Russian workers (Slobodin and Khokhlacheva) (13) before the present work was undertaken and the other by Czechoslovakian workers (Lukeš, Pliml and Trojánek) (14) while this work was in progress. On the basis of the Raman spectra of the $C_7H_{13}N$ mixture, the Russian workers came to the conclusion that it consisted of 15% of (XXII) and 85% of (XXIII).

$(CH_3)_2NCH_2CH_2C{\equiv}CCH_3$

(XXII)



$CH_3\underset{\substack{|\\ N(CH_3)_2}}{C}{=}CHCH{=}CH_2$

(XXIII)

The Czechoslovakian workers came to the same conclusion, but with percentages of (XXII)* ranging from 19-27%.

The present study was undertaken to determine the nature of Ladenburg's dimethylpiperideine, (V), mixture. It was found, in the work to be described, to consist of the following:

$(CH_3)_2NCH_2CH_2CH_2C{\equiv}CH$	(XXIV)
$(CH_3)_2NCH_2CH{=}CHCH{=}CH_2$	(XXV)
$(CH_3)_2NCH_2CH_2CH{=}C{=}CH_2$	(XXVI) ≡ (XVIII)
$(CH_3)_2NCH_2CH_2C{\equiv}CCH_3$	(XXVII) ≡ (XXII)
$(CH_3)_2NCH{=}CHCH{=}CHCH_3$	(XXVIII)

Only (XXV), (XXVII) and (XXVIII) were isolated. (XXIV) and (XXVI) were detected by spectroscopic means.

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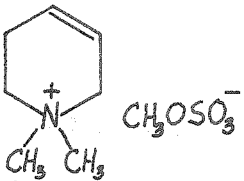
*The structure of (XXII) was proved by synthesis. (XXIII) was inferred from the fact that it was hydrolyzed on treatment with dilute acid to give dimethylamine. The carbonyl component was postulated to be a mixture of ethylideneacetone and vinylacetone.

(XXVII) (identical with (XXII)) was found to be identical with the amine from which Sargent, Buchman and Farquhar obtained pirylene.

Lukeš and Pliml (15) obtained a small amount of pirylene by a Hofmann degradation of the quaternary methiodide of (XXV), which was prepared by degradation of N,N-dimethyl-1,2,5,6-tetrahydropyridinium methosulfate, (XXIX) (16). Later work (14) from Lukeš' laboratory overlooked the fact that (XXV) was one of the products from the degradation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide, (XV).



(XXIX)

Preparation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide.

The preparation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide, (XV), followed the steps shown on Figure 1 (pp. 51-52). Piperidine, (I), was N-methylated with a formic acid-formaldehyde mixture giving N-methylpiperidine, (IX), in yields of 63-67%, after distillation of the crude product over sodium. N,N-Dimethylpiperidinium methosulfate, (XXX), was prepared by treating the N-methylpiperidine with dimethyl sulfate in ethyl ether solution. The very hygroscopic quaternary salt was heated with a concentrated aqueous solution of potassium hydroxide in a copper retort to give 1-dimethylamino-4-pentene, (VII). After fractionation of the latter over sodium, it was taken up in chloroform

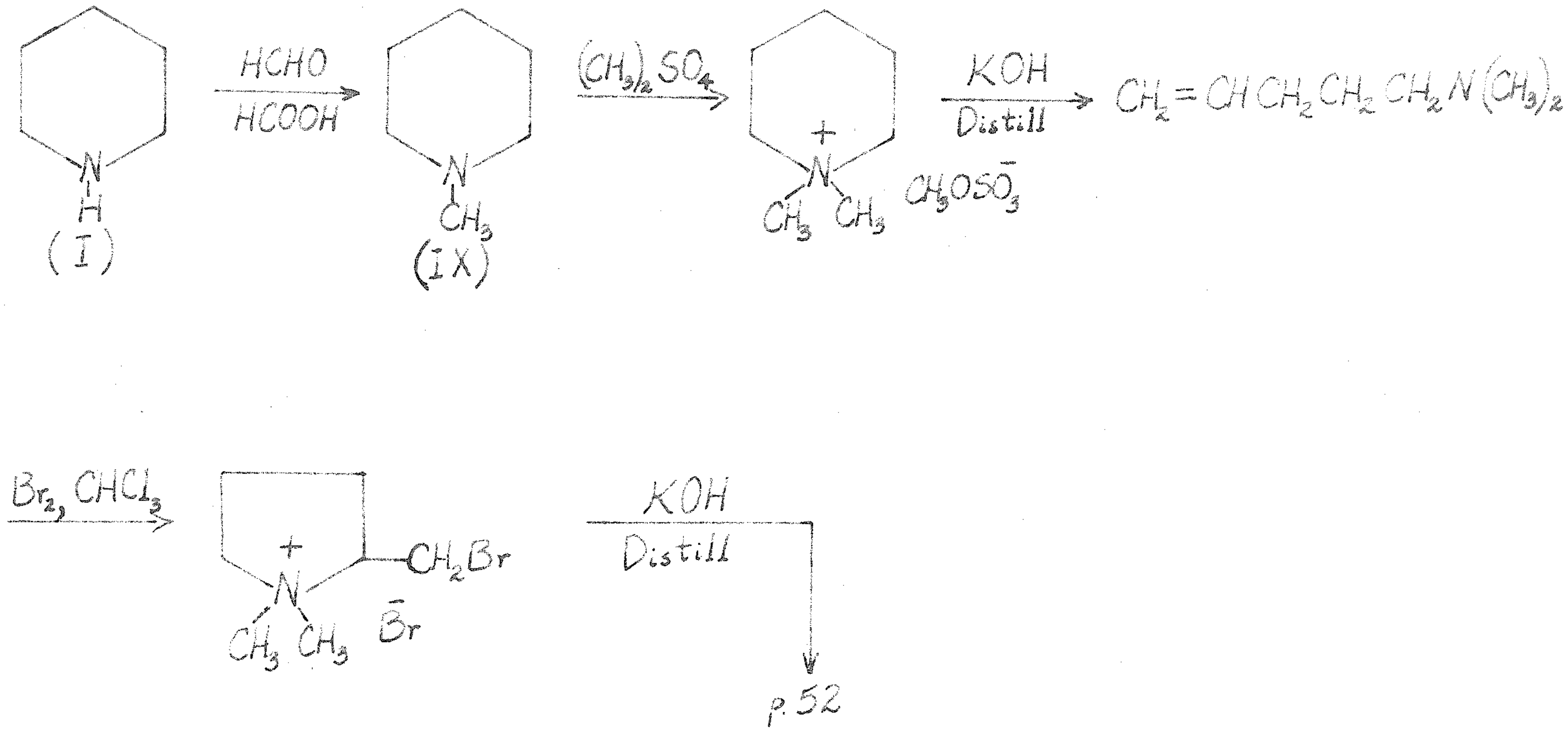


Figure 1. - This figure represents the transformations effected in this work to obtain the $C_7H_{13}N$ bases. The isomers known to lead to pirylene are designated.

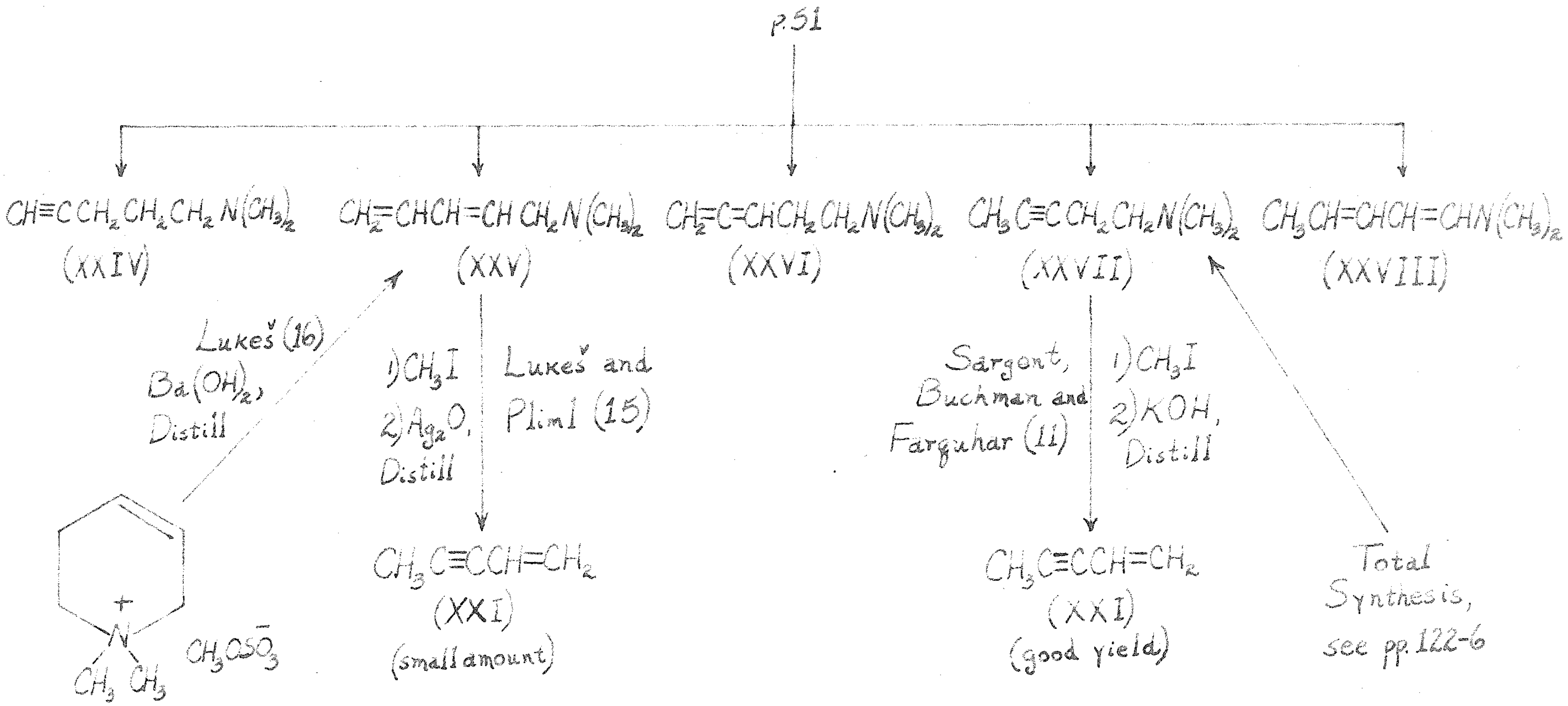


Figure 1 (cont'd.)

and treated with a chloroform solution of bromine. The quaternary bromide, (XV),* which was formed, was easily recrystallized from ethanol-water as white crystals. It was obtained in this way in 73% yield, melting between 220-222°(dec.). It formed a picrate and reacted with bromine to form a perbromide.

The tertiary amine mixture.

The quaternary bromide, (XV), was distilled with concentrated potassium hydroxide solution to give the $C_7H_{13}N$ base mixture in a yield of 73% after a flash distillation of the crude product.

The mixture was fractionated through a 3-foot precision column (packed with glass helices). From the lower and middle boiling fractions, two components (later shown to be 1-dimethylamino-2,4-pentadiene, (XXV), and 1-dimethylamino-3-pentyne, (XXVII), respectively) were obtained in quantities large enough for chemical purification. The infrared spectra** of various fractions in carbon tetrachloride showed the presence of an

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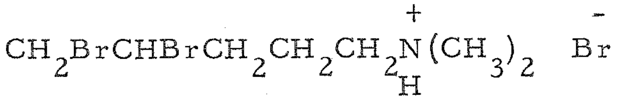
*Farquhar (17) observed that a by-product was formed in the reaction. It was the hydrobromide, (XXXI), of the base formed by addition of bromine to the double bond of (VII). On addition of alkali to the aqueous solution of (XXXI), an oil separated. The latter was transformed into the quaternary bromide, (XV), on standing or on heating.



$$CH_2BrCHBrCH_2CH_2CH_2\overset{+}{\underset{H}{N}}(CH_3)_2 \quad \overset{-}{Br}$$

(XXXI)

**Correlations of infrared absorption bands were taken from Bellamy (18), except in cases where the original literature was consulted.

allene (1-dimethylamino-3,4-pentadiene, (XXVI)) and of a terminal acetylene (1-dimethylamino-4-pentyne, (XXIV)) in the lower and middle boiling fractions, but they were in small amounts as shown by the absorption intensities. Refractionation of higher boiling fractions through the column gave a considerable amount of a constant boiling material (1-dimethylamino-1,3-pentadiene, (XXVIII)). Because of its nature, it could not be purified by chemical means. These studies indicated that there were at least five components of the mixture.

The three isolated amines were chromatographed on a paraffin column by the vapor-liquid partition technique at temperatures in the vicinity of 100°. The recorder plot of the vapor phase chromatogram showed that each sample was a single component. Each component was collected for infrared spectroscopy studies; each spectrum was identical with the spectrum of the material introduced on the column. These studies showed that no decomposition took place on the column. In agreement with the prediction that there were five components of the $C_7H_{13}N$ base mixture, five peaks were observed on the recorder plot of the vapor phase chromatogram of the total mixture.

In two small scale runs, the Hofmann degradation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide, (XV), gave the $C_7H_{13}N$ base mixture in yields of 50-58%. Table I is a compilation of the V.P.C. (vapor phase chromatography) data for these two runs. In the distillation of the crude material from the first run, the total amine mixture was collected in four fractions. Each was put through the V.P.C. column separately and the data were combined. In the second run, the total amine mixture was collected in one fraction. The percentages of components were calculated by triangulating and taking the area under the curve as the width of the base times the width at the half-height. The components are numbered in the order of increasing retention times.

Table I

Component Number	Retention Time(*)	Assignment	% of component calculated from the area	
			Run #1	Run #2
1	57	$(CH_3)_2NCH_2CH_2CH_2C{\equiv}CH$	1%	1%
2	74	$(CH_3)_2NCH_2CH{=}CHCH{=}CH_2$	17%	29%
3	81	$(CH_3)_2NCH_2CH_2CH{=}C{=}CH_2$	5%	11%
4	100	$(CH_3)_2NCH_2CH_2C{\equiv}CCH_3$	62%	41%
5	194	$(CH_3)_2NCH{=}CHCH{=}CHCH_3$	15%	18%

(*) Retention times are listed here only as relative numbers to give an idea of the type of separation achieved.

Having isolated and determined the structures of three of the amines (described in the following three sections) there was no difficulty in identifying three of the components. Components 2, 4 and 5 were identical (retention times and infrared spectra) with 1-dimethylamino-2,4-pentadiene, (XXV), 1-dimethylamino-3-pentyne, (XXVII), and 1-dimethylamino-1,3-pentadiene, (XXVIII), respectively.

Component 3 was not well separated from component 2 on the column. It appeared as a shoulder on the latter. It was assigned the allene structure (1-dimethylamino-3,4-pentadiene, (XXVI), on the basis ofthe infrared spectrum of a sample collected from the V.P.C. column (see I.R. spectrum #I, p. 175). The strong absorption at 1960 cm^{-1} is unequivocal evidence for an allenic structure. Though there has been some discussion in the literature concerning distinction between terminal and non-terminal allenic groups by infrared absorption spectra, notably by Jacobs and co-workers (19), Englehardt (20) has assigned the 842 cm^{-1} band to a terminal allenic group. This band was very strong in the spectrum of component 3.

Component 1 (1-dimethylamino-4-pentyne, (XXIV)) was present in very small amount and was not collected from the V.P.C. column. The characteristic infrared absorption of a terminal acetylene ($\equiv$C-H stretch) at 3300 cm^{-1} is shown as a weak band on I.R. spectrum #II (p. 176) of the total amine mixture. The band appeared stronger in the spectra of the first fractions taken from the precision fractionating column and was absent in higher boiling fractions. Thus, this isomer appears to behave as do the other components in having their retention times increase as their boiling points increase.

The last piece of information to be mentioned at this point is that hydrogenation of the total amine mixture over platinum at room temperature gave 1-dimethylaminopentane, (XXXII),* whose infrared spectrum

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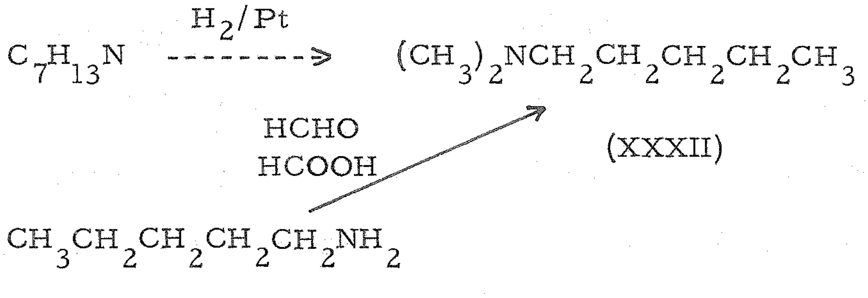
*This had been noted previously by v. Braun and Teuffert (10).

and methiodide and picrate derivatives were identical with those of an authentic sample. The latter was prepared by N,N-dimethylation of 1-aminopentane, (XXXIII), with formic acid-formaldehyde mixture (Scheme IV).

Scheme IV



$$C_7H_{13}N \xrightarrow{H_2/Pt} (CH_3)_2NCH_2CH_2CH_2CH_2CH_3$$

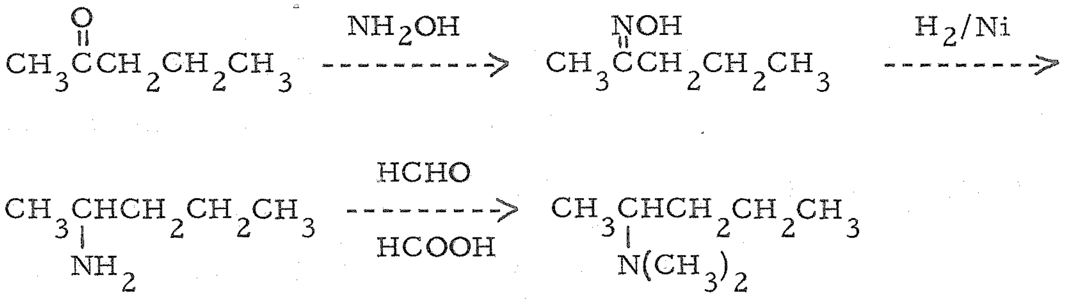
(XXXII)

$$CH_3CH_2CH_2CH_2CH_2NH_2 \xrightarrow[HCOOH]{HCHO} (CH_3)_2NCH_2CH_2CH_2CH_2CH_3$$

(XXXIII)

The corresponding 2-dimethylaminopentane,(XXXIV), was synthesized by the following route (Scheme V).

Scheme V



$$CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2CH_3 \xrightarrow{NH_2OH} CH_3\overset{\overset{NOH}{\|}}{C}CH_2CH_2CH_3 \xrightarrow{H_2/Ni}$$

$$CH_3\underset{\underset{NH_2}{|}}{C}HCH_2CH_2CH_3 \xrightarrow[HCOOH]{HCHO} CH_3\underset{\underset{N(CH_3)_2}{|}}{C}HCH_2CH_2CH_3$$

(XXXIV)

Mixed melting points of the picrate and methiodide of (XXXIV) with those from the hydrogenated amine mixture showed depressions.

It was found that (XXXIV) had exactly the same retention time as (XXXII) on a paraffin V.P.C. column (even a 50:50 mixture of the two could not be separated). Though the infrared spectrum of the 2-isomer (see I.R. spectrum #III, p. 177) was quite different from that of the 1-isomer (see I.R. spectrum #IV, p. 178), it became apparent that at the normal concentrations (in carbon tetrachloride) used, small amounts of the 2-isomer might go undetected. However, a study of more concentrated solutions in the 950-850 cm^{-1} region showed that as little as 5% of the isomer could be detected admixed with the 1-isomer. Using this technique, the hydrogenation product from the $C_7H_{13}N$ total base mixture showed no sign of the presence of the 2-isomer (see Fig. 2, p. 59).

1-Dimethylamino-3-pentyne, (XXVII).

1-Dimethylamino-3-pentyne, (XXVII), was the isomer present in the largest amount. As previously mentioned, it was the base from which Sargent, Buchman and Farquhar (11) obtained pirylene. It was obtained from the middle boiling amine fractions and purified over the diliturate (11). It showed no absorption in the ultraviolet and its infrared spectrum showed no distinguishing absorption bands (see I.R. spectrum #V, p. 179). Since it was the precursor of pirylene, one might have guessed that it was an acetylene, though there was no demanding reason for this. The first chemical evidence that it might be acetylenic came through the finding that on refluxing with water, a quaternary ammonium salt was obtained (identified, at first, as a high melting picrate).

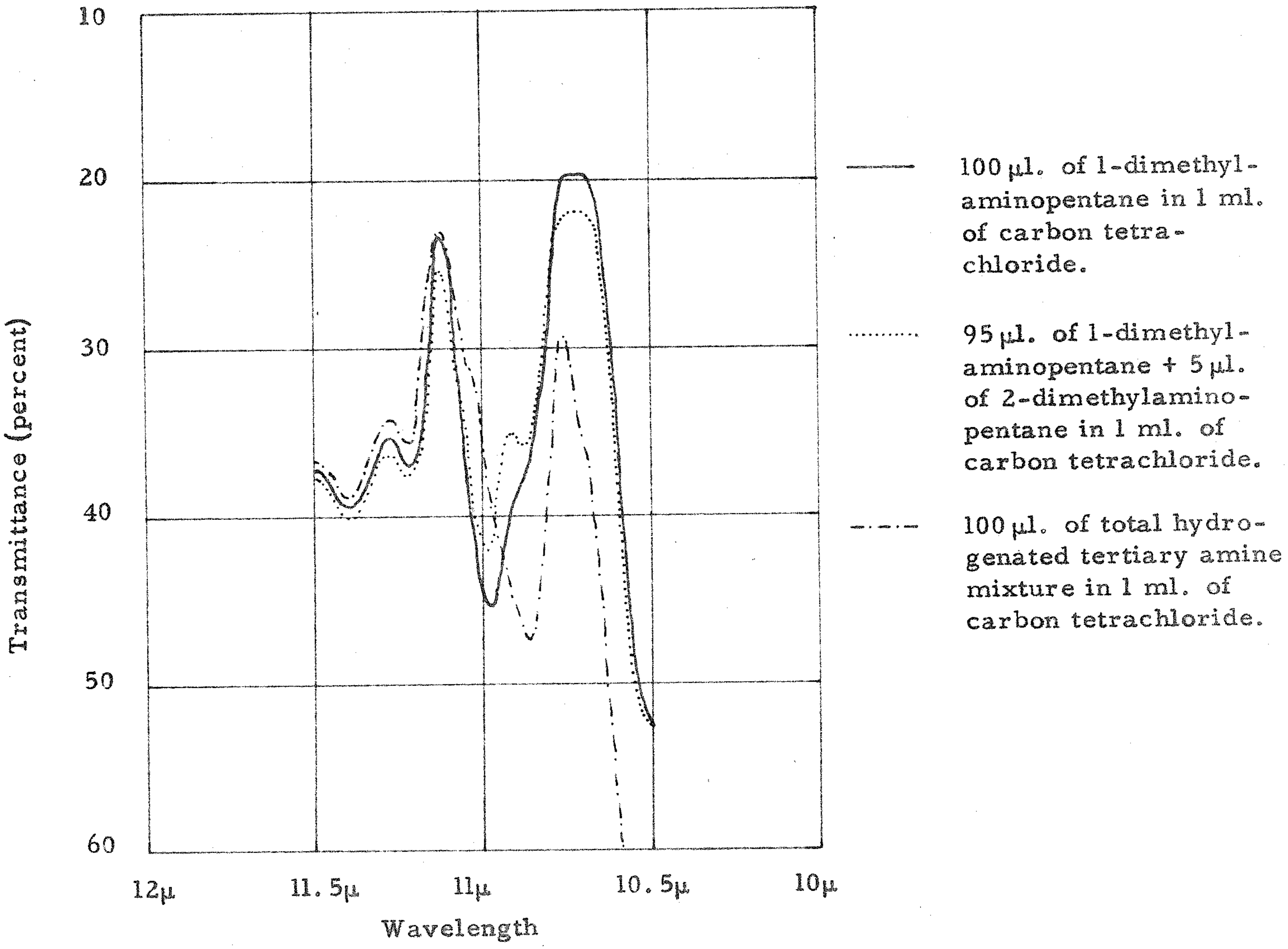
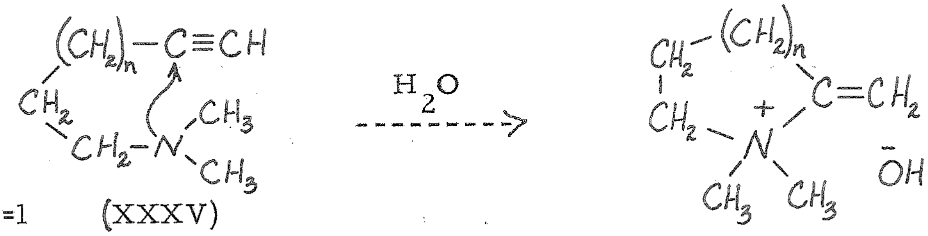


Figure 2. - The infrared spectral studies clearly indicated the absence of significant amounts of 2-dimethylaminopentane in the total hydrogenated tertiary amine mixture.

It has been observed by Campbell and co-workers (21) that certain tertiary acetylenic amines undergo cyclization on treatment with water to form a pyrrolidinium or piperidinium hydroxide. In particular, the compounds observed by these authors to exhibit this behavior were the two terminal acetylenic amines, 1-dimethylamino-4-pentyne, (XXXV), and 1-dimethylamino-5-hexyne, (XXXVI).

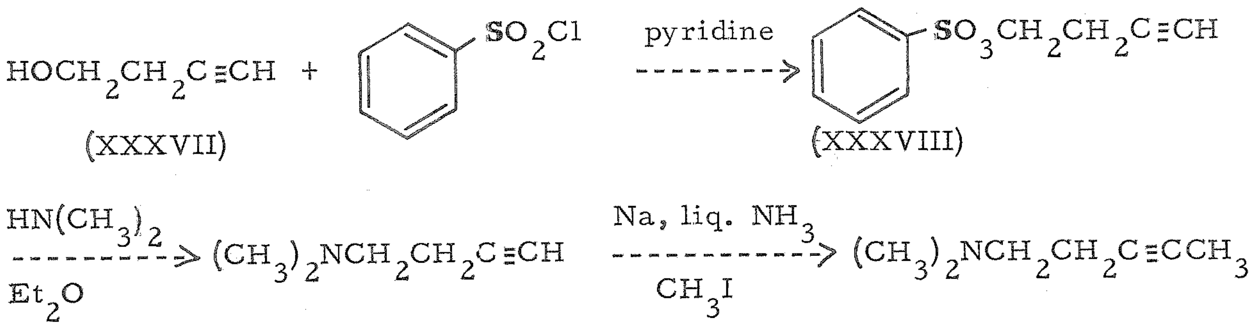
Scheme VI



n=1 (XXXV)
n=2 (XXXVI)

Because the infrared spectrum showed no absorption for a terminal acetylene ($\equiv$ C-H stretch at 3300 cm^{-1}), the assumption was made that the isomer was the 2-acetylene. The latter was synthesized following the procedure of Marszak and Epsztein (22) (Scheme VII).

Scheme VII



(XXXVII) (XXXVIII)

(XXXIX) (XXVII)

3-Butyn-1-ol, (XXXVII), in pyridine was treated with benzenesulfonyl chloride to give the benzenesulfonate, (XXXVIII), in 94% yield (crude --- not purified). The latter was treated with dimethylamine in ethyl ether over a period of five days. After a flash distillation of the product, 1-dimethylamino-3-butyne, (XXXIX), was obtained in only 19% yield. The final step consisted in C-methylating the sodium salt in liquid ammonia with methyl iodide. The yield from the terminal acetylene was approximately 50%. The infrared spectrum and the refractive index ($n_D^{25°} = 1.4410$) of the product were identical with those of (XXVII). Mixed melting points of the picrates (M.P. 101-102°) and the methiodides (M.P. 257-258° (froths)) showed no depressions.

Lukeš and Červinka (23) reported that N,N-dimethyl-α-bromomethylpyrrolidinium bromide on treatment with silver oxide at room temperature gave N,N-dimethyl-α-methylenepyrrolidinium hydroxide, (XL), and that when the bromide was treated with sodium hydroxide solution at 130° for 5 minutes, the product was N,N-dimethyl-α-methyl-Δ^2-pyrrolinium hydroxide, (XLI). The former, (XL), was reported to give a picrate melting at 280° (dec.) and the latter, (XLI), was reported to give a picrate melting at 229° (dec.). Repetition of these experiments gave a picrate melting at 260° (dec.) from the silver oxide treatment and a picrate melting at 282° (dec.)* from the sodium hydroxide treatment at 130°. Conversion of (XL) and (XLI) to the corresponding bromides

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*The picrate melting at 282° was obtained many times in this research. Possibly the 229° value reported by Lukeš and Červinka represents a typographical error.

gave (XLII) melting at 203-204° (Lukeš reported a melting point of 203.5°) and (XLIII) melting at 234-235° (Lukeš reported a melting point of 236-237°). 1-Dimethylamino-3-pentyne, (XXVII), was allowed to stand in a water-methanol (2:1) mixture for 5 days. On treatment with aqueous sodium picrate, a yellow precipitate formed which decomposed violently at 283°. Conversion of the picrate to the bromide gave a substance melting at 230-232°. Analytical data as well as mixed melting points* supported the identification of the cyclized tertiary amine as (XLI). Figure 3 (p. 63) summarizes the above results.

Campbell and co-workers (21) inferred, from the experimentally observed result that back titration of their cyclized amines gave a curve resembling the liberation of a weak base from its salt with sodium hydroxide, that the cyclization was reversible. However, on refluxing 1-dimethylamino-3-pentyne, (XXVII), with water for one hour, no amine could be recovered. Likewise, on refluxing N,N-dimethyl-α-methylenepyrrolidinium hydroxide, (XL), with water for one hour, no tertiary amine was produced. 1-Dimethylamino-3-pentyne, (XXVII), was allowed to stand in water at room temperature. After a couple of months, there was still some amine left as a second phase, but after six months' standing all of the amine had gone into solution. These experiments shed some doubt on the reversibility of the cyclization and the meaning of Campbell and

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*The picrate of the cyclized tertiary amine did not depress the melting point of the picrate of (XLI), but a melting point of 270° was obtained when it was admixed with the picrate of (XL).

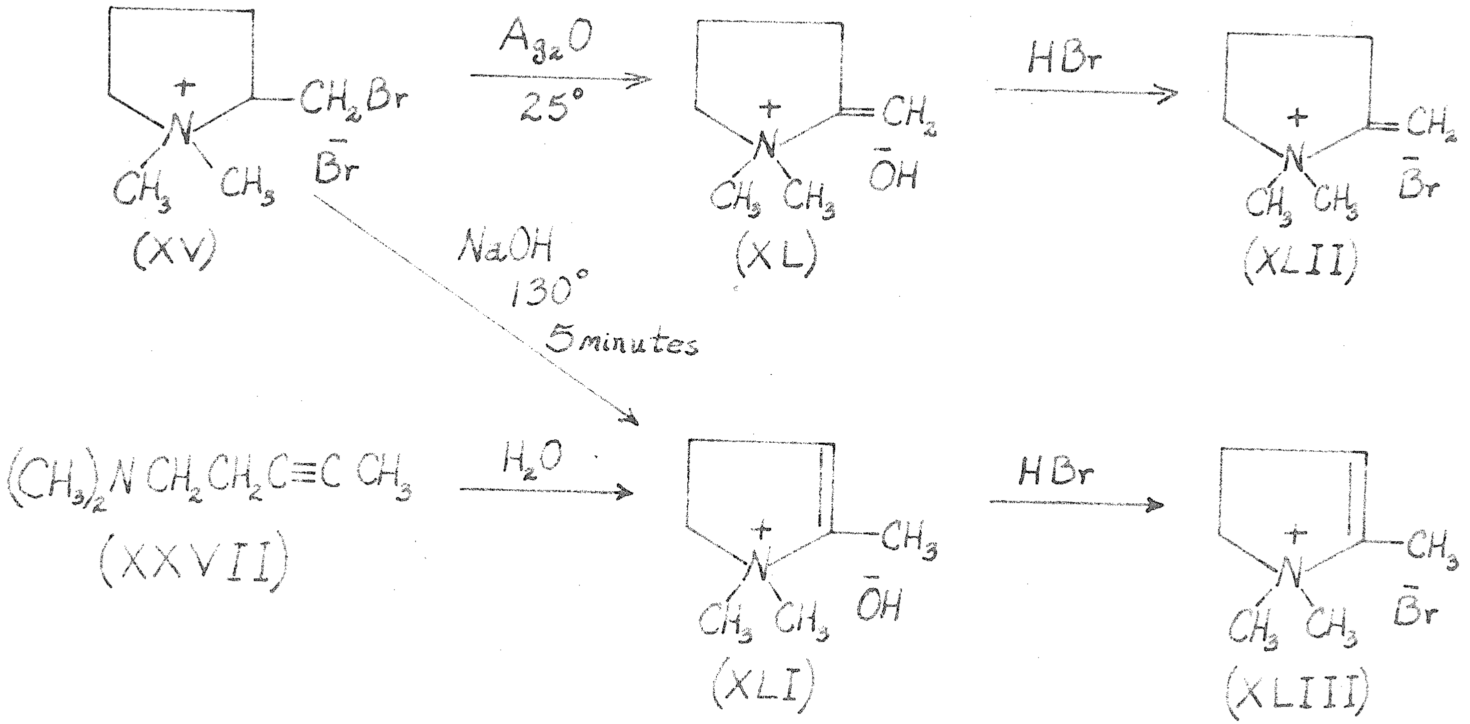
CH_2Br
$\bar{Br}$
CH_3
(XV)
Ag_2O
25°
$=CH_2$
$\bar{OH}$
(XL)
HBr
$\bar{Br}$
(XLII)
NaOH
130°
5 minutes
$(CH_3)_2NCH_2CH_2C\equiv CCH_3$
(XXVII)
H_2O
(XLI)
(XLIII)

Figure 3.

co-workers' result is not clear.

The exact position of the double bond in (XLI) has never been ascertained. Some studies were initiated in an attempt to obtain pertinent evidence. The problem was complicated by the fact that the bromides, (XLII) and (XLIII), were very hygroscopic and difficult to work with.* However, purification of the bromides by recrystallization gave compounds with sharp melting points which were believed to be fairly pure isomers. Their infrared spectra in chloroform (see I.R. spectrum #VI and I.R. spectrum #VII, pp. 180 and 181) were used to characterize these compounds. Absorption at 908 cm^{-1} in the spectrum of (XLII) indicated the presence of $>C=CH_2$. This absorption was absent in the spectrum of (XLIII), but there were no distinguishing bands for a trisubstituted double bond (as in the postulated structure, (XLIII)), or for a disubstituted double bond (if the double bond was allylic to the quaternary nitrogen). Treatment of the bromo-bromide, (XV), with sodium hydroxide at room temperature or with silver oxide at 130° gave mainly the exocyclic double bond compound, (XL). The latter could be isomerized to the endocyclic double bond compound, (XLI), by treatment with sodium hydroxide at 130°.

Attempts to add hydrogen bromide to the double bond of N,N-dimethyl-α-methylenepyrrolidinium bromide, (XLII), both with hydrobromic

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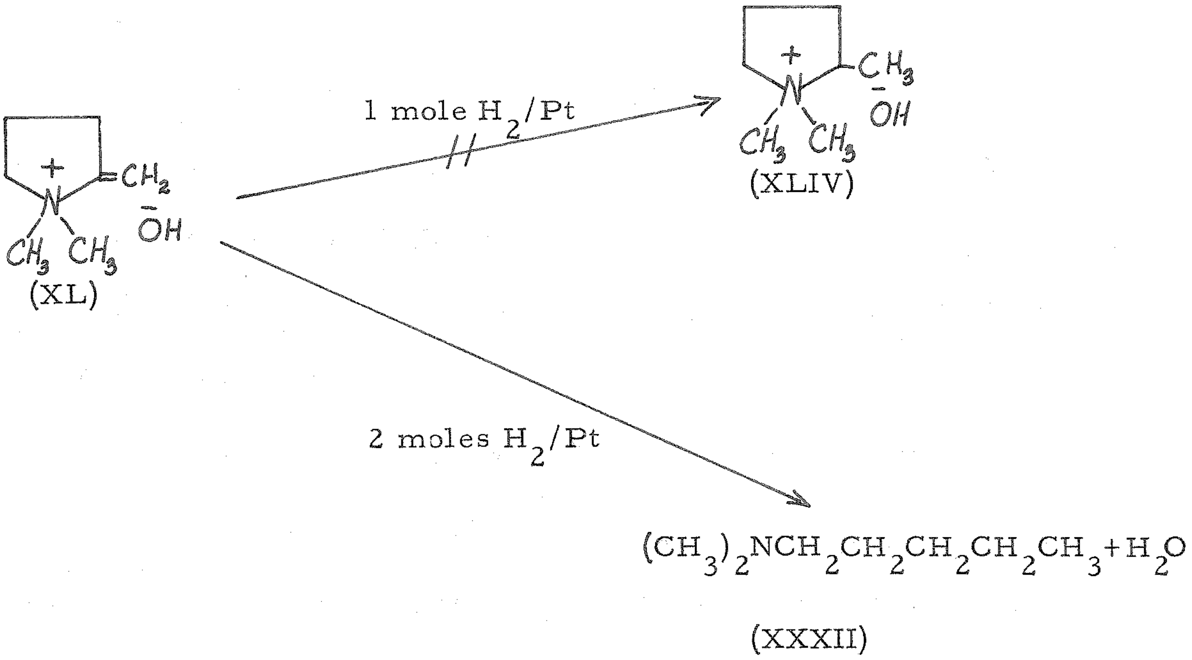
*Attempts to obtain bromine addition products of the bromides (reported by Lukeš and Červinka (23) to be feasible for (XL), from which pure isomers could be regenerated, resulted in failure.

acid alone and in the presence of benzoyl peroxide, resulted in failure.

The best evidence that the exocyclic double bond moved into the ring vinylic to the quaternary nitrogen and not allylic is the result that the tertiary amine on cyclization (mild conditions) gives (XLI). The shift of a double bond from an allylic (β, γ) position with respect to a quaternary nitrogen to a vinylic (α, β) position has been discussed by Woodward and Brehm (24). It is inferred that the isomer with the vinylic double bond is more stable.

An interesting result was obtained in the hydrogenation of N,N-dimethyl-α-methylenepyrrolidinium hydroxide, (XL), over platinum at room temperature and two atmospheres of hydrogen pressure. Instead of one mole of hydrogen being taken up to give the expected product, N,N-dimethyl-α-methylpyrrolidinium hydroxide, (XLIV), two moles of hydrogen were taken up and the product was 1-dimethylaminopentane, (XXXII), whose picrate did not depress the melting point of an authentic sample (Scheme VIII).

Scheme VIII



(XL)

(XLIV)

$(CH_3)_2NCH_2CH_2CH_2CH_2CH_3 + H_2O$

(XXXII)

It is well-known that the C-N bond can be cleaved on catalytic hydrogenation of allylic quaternary ammonium salts.* This type of cleavage in the corresponding vinylic systems has apparently been studied less. At least one case of this type of cleavage has been reported by Lukeš and Červinka (23) (Scheme IX).

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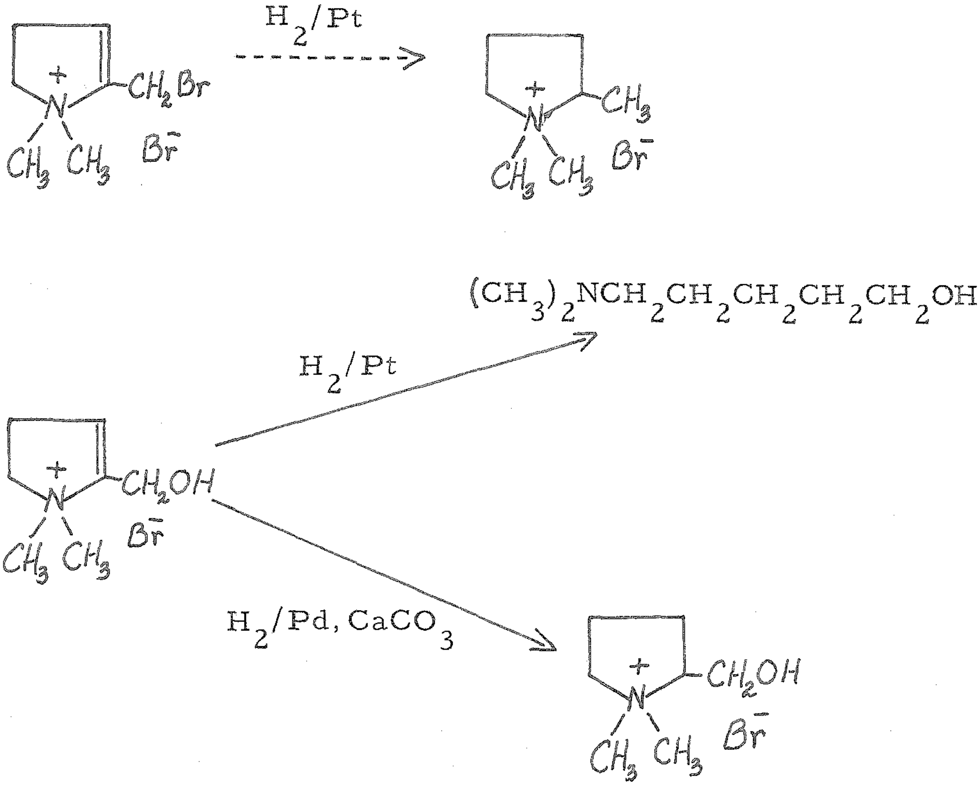
*For a review of this type of fission, see D. R. Howton (25).

Scheme IX



Though catalysts have been observed to play a major role in whether or not fission occurs in allylic systems (25), Lukeš and Červinka's results do not allow this type of rationale for vinylic systems.

Jacobs and co-workers (19) have studied the equilibration of 1-pentyne, 2-pentyne and 1, 2-pentadiene. "Equilibration"* studies of 1-dimethylamino-3-pentyne, modeled after this work, gave very enlightening results. On heating the amine in a sealed tube with ethanolic

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*The term equilibration is enclosed in quotation marks, because no true equilibrium was attained. The word is used only to imply that some of the amine components are capable of equilibrating directly (similar to 1-pentyne, 2-pentyne and 1, 2-pentadiene) under strongly basic conditions.

potassium hydroxide solution at 190° for two hours, there was obtained (Scheme X) a mixture, consisting of precisely the same components (though in different proportions) as resulted from the Hofmann degradation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide, (XV).

<u>Scheme X</u>

$$(CH_3)_2NCH_2CH_2C\equiv CCH_3 \xrightarrow[\substack{190^\circ \\ 2\ \text{hours}}]{\text{ethanolic KOH}}$$

$$(CH_3)_2NCH_2CH_2CH_2C\equiv CH$$

(XXIV)

$$(CH_3)_2NCH_2CH{=}CHCH{=}CH_2$$

(XXV)

$$(CH_3)_2NCH_2CH_2CH{=}C{=}CH_2$$

(XXVI)

$$(CH_3)_2NCH_2CH_2C\equiv CCH_3$$

(XXVII)

$$(CH_3)_2NCH{=}CHCH{=}CHCH_3$$

(XXVIII)

In a similar experiment, with a heating time of twenty hours, the only component isolated (in very low yield) was 1-dimethylamino-1,3-pentadiene, (XXVIII). Though only starting material was obtained on refluxing (XXVII) with ethanolic potassium hydroxide in an open system, these results play a vital role in the elucidation of the mechanism of the Hofmann degradation, discussed in the last section.

1-Dimethylamino-3-pentyne, (XXVII), was found to react with concentrated hydrochloric acid, the elements of HCl being added to the triple bond. Only one molecule of HCl was added per molecule of amine, but no study of the structure of the olefin formed was undertaken. The empirical nature of the compound was arrived at by analyses of its dilituurate and methiodide derivatives (see I.R. spectrum #VIII, p. 182, of the free base).

1-Dimethylamino-2,4-pentadiene, (XXV).

It was found that refluxing the lower boiling amine fractions with water was sufficient to give 1-dimethylamino-2,4-pentadiene, (XXV), in good purity. During the water treatment, any of the highest boiling component, 1-dimethylamino-1,3-pentadiene, (XXVIII), would have been hydrolyzed and the products of hydrolysis, dimethylamine and 2-pentenal and/or 3-pentenal (discussed in the next section), would have been lost in the work-up. Likewise, 1-dimethylamino-3-pentyne, (XXVII), and 1-dimethylamino-4-pentyne, (XXIV), would have been lost in the work-up, by virtue of undergoing cyclizations to their corresponding quaternary ammonium bases. Exactly what happened to the allene, 1-dimethylamino-3,4-pentadiene, (XXVI), is not known, but due to the unstable nature of allenic compounds,* it probably polymerized (tar formation** being noted during the refluxing).

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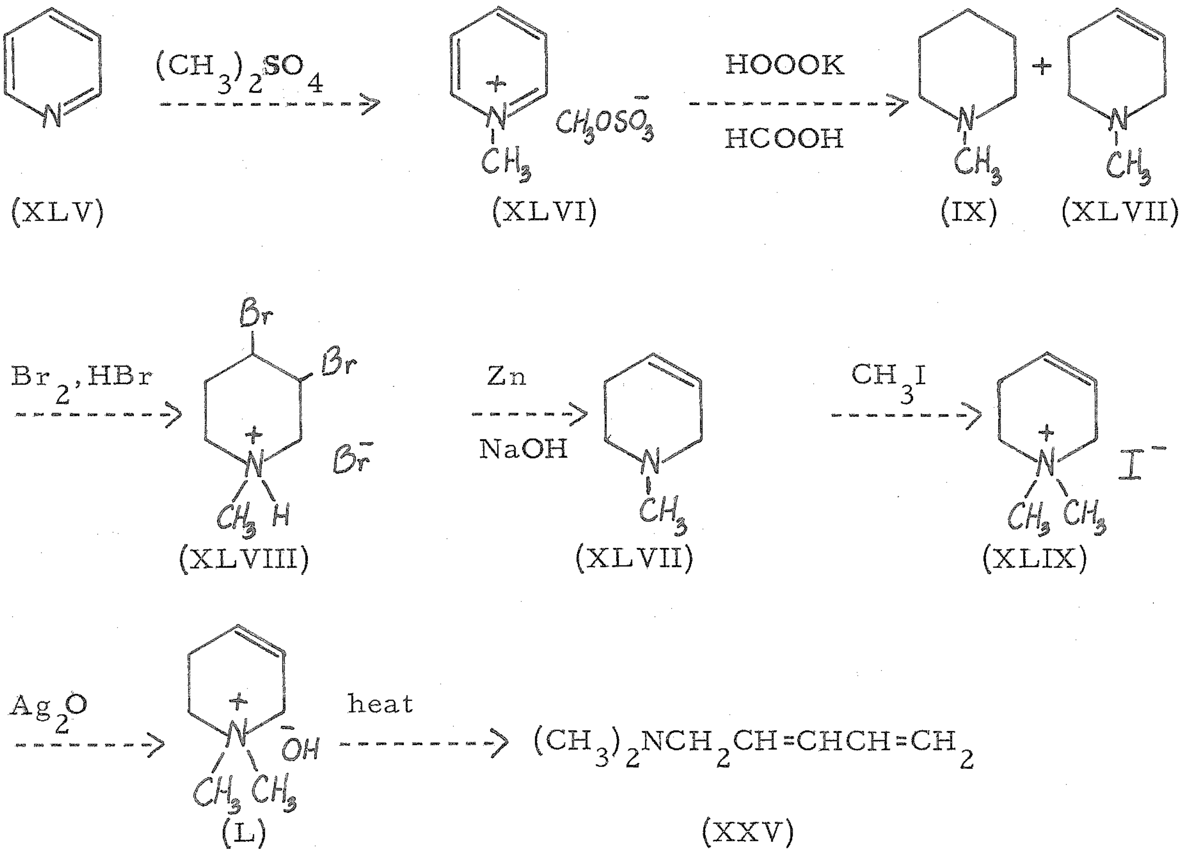
*S. V. Lebedeff (26) has studied the polymerization of allenes on heating.

**Undoubtedly, some tar formation came from (XXV) (see "Experimental"), but the allene would be expected to undergo tar formation faster.

The structure of (XXV) was inferred from its ultraviolet spectrum ($\lambda_{max.}$ = 224 mμ; $\epsilon_{max.}$ = 22, 200 in n-hexane). The infrared spectrum of (XXV) in carbon tetrachloride showed a very strong absorption at 908 cm^{-1} and a weak absorption at 1820 cm^{-1}, typical of the $-CH{=}CH_2$ group in conjugation with an ethylenic linkage. The 1600 cm^{-1} band, characteristic of C=C stretch in conjugated systems, was weak (see I.R. spectrum #IX, p. 183).

Proof of the structure was made through a synthesis based on the work of Lukeš (16) and depicted on Scheme XI.

Scheme XI



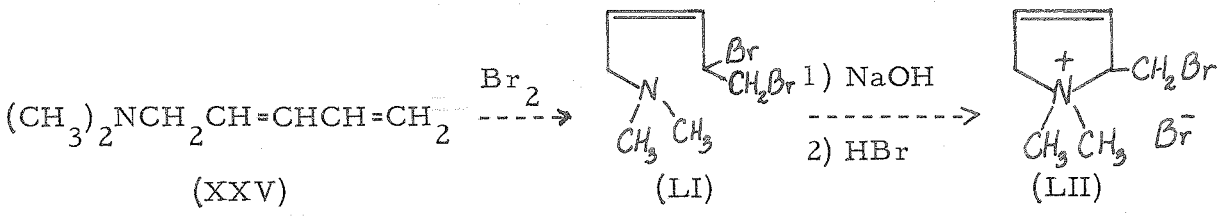
The synthesis was straightforward and gave no undesirable by-products. The N-methylpyridinium methosulfate, (XLVI), obtained as an oil in essentially quantitative yield by reacting pyridine, (XLV), in anhydrous ethyl ether solution with dimethyl sulfate, was reduced with formic acid to a mixture of N-methylpiperidine, (IX), and N-methyl-1,2,5,6-tetrahydropyridine, (XLVII), containing approximately 30% of the latter. A separation could not be effected by fractionation, but bromination in hydrobromic acid solution of the mixture boiling between 105-112° gave a white solid, (XLVIII), (M.P. 191-192°) easily recrystallized from ethanol-water. Regeneration of the unsaturated component was carried out by treatment of an aqueous solution of the dibromo hydrobromide, (XLVIII), with zinc dust and steam distillation after making basic. The N-methyl-1,2,5,6-tetrahydropyridine, (XLVII), (B.P. 110.5°) gave a methiodide, (XLIX), (M.P. 266-267°; from ethanol) which on treatment with silver oxide and final pyrolysis of the quaternary ammonium hydroxide, (L), gave 1-dimethylamino-2,4-pentadiene, (XXV), in 64% yield based on the methiodide. The ultraviolet spectrum, infrared spectrum and refractive index ($n_D^{25°}$ = 1.4610) of this compound were identical with those of the compound obtained from the Hofmann degradation of (XV). Mixed melting points of the methiodides (M.P. 169-170°), the methpicrates (M.P. 104-105°) and the dilituratės (M.P. 173-174°) showed no depressions. The picrate was an oily substance difficultly crystallizable and was not prepared as a characteristic derivative.

In agreement with Lukeš and Pliml's observations (27) on the inertness* of this diene with maleic anhydride, repeated attempts to form a Diels-Alder adduct of 1-dimethylamino-2,4-pentadiene, (XXV), with N-phenylmaleimide (even in a sealed tube at 100° with toluene as a solvent) resulted in failure; mainly starting material was recovered.

It was pointed out (27) that this behavior is good indication of a cis configuration. Craig (29) has shown that cis-piperylene (1,3-pentadiene) does not react with a Diels-Alder dienophile, while its trans-isomer reacts very readily.**

Lukeš and Pliml (27) also pointed out that preservation of the stereochemistry of its cyclic precursor indicated a cis configuration for (XXV). They further observed that bromine added to the 4 and 5 carbons of (XXV) to give (LI) and that the latter cyclized on treatment with base to give (LII). It was stated by these authors that the trans configuration would not allow this cyclization.

Scheme XII



(XXV) (LI) (LII)

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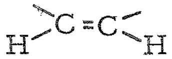
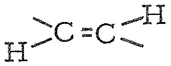
*In a previous publication by these same authors (28), a small amount of the adduct with maleic anhydride was reported to have been isolated.

**In a later publication (30), Craig was able, however, to obtain an adduct between cis-piperylene and maleic anhydride (forced conditions and catalyzed by acetic anhydride).

The infrared spectrum (see I.R. spectrum #X, p. 184) of (XXV) in carbon disulfide showed strong absorption at 773 cm^{-1} and very weak absorption at 824 cm^{-1}. On the basis of the infrared spectra of *cis*- and *trans*-piperylene (in the vapor state) (31), the former would be assigned to the *cis*-  $_{H}{>}C=C{<}_{H}$ linkage and the latter to the *trans*-  $_{H}{>}C=C{<}^{H}$ linkage. One would estimate less than 5 percent of the *trans*-isomer.*

cis-Piperylene was obtained in the work reported here by the method of Frank, Emmick and Johnson (32). Commerical piperylene was treated with maleic anhydride to remove the *trans*-isomer. The infrared spectrum of the *cis*-isomer removed from the Diels-Alder adduct by distillation and redistilled through a 3-foot precision column showed strong absorption at 773 cm^{-1} in carbon disulfide.

The N.M.R. (nuclear magnetic resonance) spectrum of 1-dimethylamino-2,4-pentadiene, (XXV), obtained from the $C_7H_{13}N$ base mixture was identical with that obtained by Lukeš' method (16). This was additional assurance that they both had the same configuration.

Furthermore, the *cis*-piperylene obtained as described above had a N.M.R. spectrum identical with the spectrum of the tertiary amine in the vinyl region ($CH_2{=}CHCH{=}CH{-}$) (see N.M.R. spectrum #I and N.M.R. spectrum #II, pp. 172 and 173).

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*There may have been a small amount of the *trans*-isomer in Lukeš' compound which gave rise to the Diels-Alder adduct; no adduct was obtained in this work.

(XXV) was heated with a small amount of iodine and a trace of trinitrobenzene at 55° for 3 days. The recovered amine was identical with starting material (refractive index, infrared spectrum, ultraviolet spectrum). The evidence for a _cis_ configuration was considered strong enough to warrant no further investigation of equilibration between the _cis_- and _trans_-isomers.

"Equilibration" of (XXV) with ethanolic potassium hydroxide in a sealed tube at 180° for two hours gave a mixture which consisted of* 1-hydroxy-2,4-pentadiene, (LIII), 2-pentenal, (LIV) (from hydrolysis of 1-dimethylamino-1,3-pentadiene), 1-dimethylamino-1,3-pentadiene, (XXVIII), and starting material, 1-dimethylamino-2,4-pentadiene, (XXV). These components were separated by vapor phase chromatography and each component was analyzed separately by infrared spectroscopy. The spectrum of the recovered 1-dimethylamino-2,4-pentadiene in carbon tetrachloride was identical with that of starting material, except for increased absorption in the 950-1000 cm^{-1} region (possibly a result of isomerization to the _trans_-isomer). The spectrum of the 1-dimethylamino-1,3-pentadiene (configuration discussed in the next section) in carbon tetrachloride was identical with the spectrum of material isolated from the Hofmann degradation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide, (XV). 1-Hydroxy-2,4-pentadiene and 2-pentenal were inferred from their infrared spectra; the latter was not well separated

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*Two components were not identified (see "Experimental").

from the former on the V.P.C. column, but its presence was seen by absorption at 1690 cm^{-1} (see I.R. spectrum #XI, p. 185 and I.R. spectrum #XII, p. 186). 1-Hydroxy-2,4-pentadiene has been reported by Lukeš and Pliml (15) from pyrolysis of trimethyl-2,4-pentadienylammonium hydroxide.

Scheme XIII

$$\begin{array}{ccc}
 & & HOCH_2CH{=}CHCH{=}CH_2 \\
 & & \text{(LIII) } \underline{\text{trans}}\text{ (?)} \\
 & & (CH_3)_2NCH_2CH{=}CHCH{=}CH_2 \\
(CH_3)_2NCH_2CH{=}CHCH{=}CH_2 & \xrightarrow[\substack{180^\circ \\ \text{2 hours}}]{\text{ethanolic KOH}} & \text{(XXV) } \underline{\text{trans}}\text{ (?)} \\
\text{(XXV) } \underline{\text{cis}} & & CH_3CH_2CH{=}CHCHO \\
 & & \text{(LIV) } \underline{\text{trans}}\text{ (?)} \\
 & & (CH_3)_2NCH{=}CHCH{=}CHCH_3 \\
 & & \text{(XXVIII) } \underline{\text{trans}}\text{,}\underline{\text{trans}}\text{ (?)}
\end{array}$$

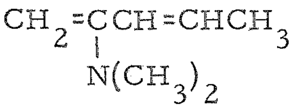
1-Dimethylamino-1,3-pentadiene, (XXVIII).

Since 1-dimethylamino-1,3-pentadiene, (XXVIII), boiled approximately 15° higher than 1-dimethylamino-3-pentyne, (XXVII), (the next highest boiling isomer) it was studied as it was taken from the fractionation column, without further purification. (The hydrolytic reactivity of vinyl amines made a chemical purification of (XXVIII) improbable.) The ultraviolet spectrum of this isomer ($\lambda_{max.} = 269$ mμ; $\epsilon_{max.} = 22,700$ in n-hexane) indicated that it was a vinyl conjugated amine. Jones and co-workers (33) have demonstrated that a diethylamino-group in conjugation with 1,3-butadiene ($\lambda_{max.}$ = 220 mμ) and related systems exhibits a bathochromic shift of 65 mμ. In "cross-conjugated" systems, the effect is smaller, + $\Delta\lambda$ = 45 mμ. A methyl group in similar systems exhibits a bathochromic shift of 5 mμ, e.g., $\lambda_{max.}$ for 1,3-pentadiene = 225 mμ.

The three possibilities for a vinyl conjugated amine were (XXVIII), (LV) and (LVI).

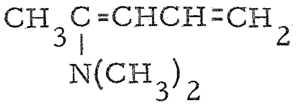
$(CH_3)_2NCH{=}CHCH{=}CHCH_3$

(XXVIII)



$CH_2{=}\underset{\displaystyle N(CH_3)_2}{\underset{|}{C}}CH{=}CHCH_3$

(LV)



$CH_3\underset{\displaystyle N(CH_3)_2}{\underset{|}{C}}{=}CHCH{=}CH_2$

(LVI)

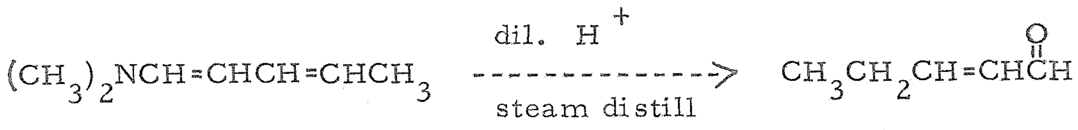
Simply adding substituent effects, (XXVIII) would be predicted to have $\lambda_{max.}$ = 290 mμ; (LV) would be predicted to have $\lambda_{max.}$ = 270 mμ; and, (LVI) would be predicted to have $\lambda_{max.}$ = 290 mμ. The value calculated for (LV) agrees most closely with the observed value. This structure was ruled out, however, by the finding that the vinyl conjugated amine gave 1-dimethylaminopentane on hydrogenation. (LVI) was also ruled out by this finding and (XXVIII) must thus be the structure of the amine.

(XXVIII) exhibited the typical properties of a vinyl amine. On treatment with ethereal picric acid solution, it formed a low melting yellow solid which became a dark colored tarry substance on standing. It reacted with methyl iodide in methyl alcohol solution to give a high melting white solid. Analysis of the compound indicated that the substance was probably tetramethylammonium iodide. The very high refractive index of (XXVIII) ($n_D^{25°} = 1.5223$) was in agreement with its nature.

The infrared spectrum of this compound in carbon tetrachloride solution showed a strong doublet at 1655 cm^{-1} and 1630 cm^{-1}, typical of the $-HC{=}CH-$ group. The absence of absorption in the 910 cm^{-1} region indicated no terminal ethylenic linkage ($-CH{=}CH_2$) (see I.R. spectrum #XIII, p. 187).

1-Dimethylamino-1,3-pentadiene, (XXVIII), on treatment with dilute acid and steam distillation followed by treatment of the distillate with a 2,4-dinitrophenylhydrazine reagent gave the 2,4-dinitrophenylhydrazone of 2-pentenal, (LIV). The hydrazone crystallized as orange needles from alcohol (M.P. 159-160°). That the unsaturated system present was conjugated was shown by the ultraviolet absorption ($\lambda_{max.} = 374$ mμ). (34)

Scheme XIV

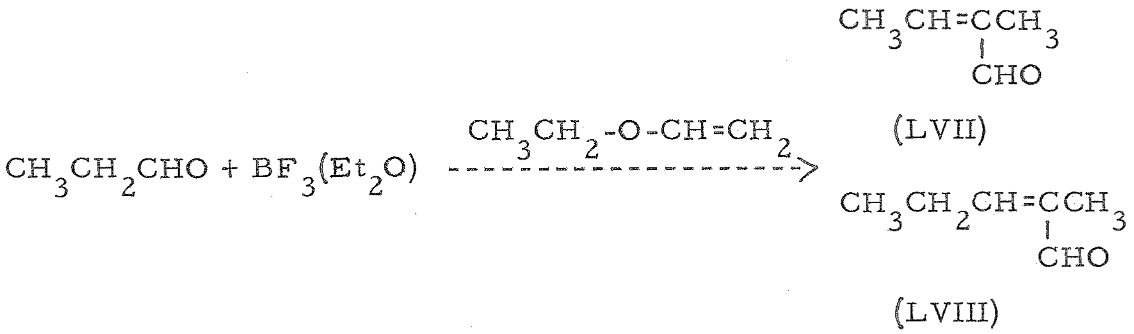


$$(CH_3)_2NCH{=}CHCH{=}CHCH_3 \xrightarrow[\text{steam distill}]{\text{dil. } H^+} CH_3CH_2CH{=}CH\overset{\overset{O}{\|}}{C}H$$

(XXVIII) (LIV)

Although the above facts adequately establish the gross structure of (XXVIII), some unsuccessful attempts to prepare (LIV), starting from propionaldehyde, are reported here. Hoaglin and Hirsh (35) have reported the reaction of saturated aldehydes with vinyl ethers in the presence of boron trifluoride to give α, β-unsaturated aldehydes. Though they reported the preparation of 2-pentenal by this method, attempts to reproduce these results here were unsuccessful. In one run in which ethyl vinyl ether was added to a mixture of propionaldehyde and boron trifluoride in ethyl ether, a mixture consisting of equal parts of tiglic aldehyde, (LVII), and α-methyl-2-pentenal, (LVIII), were obtained (from V.P.C. data). The two aldehydes were identified by chromatographing a 2,4-dinitrophenylhydrazone mixture of the two and isolating the components and comparing with authentic material; no 2-pentenal, (LIV), was found.

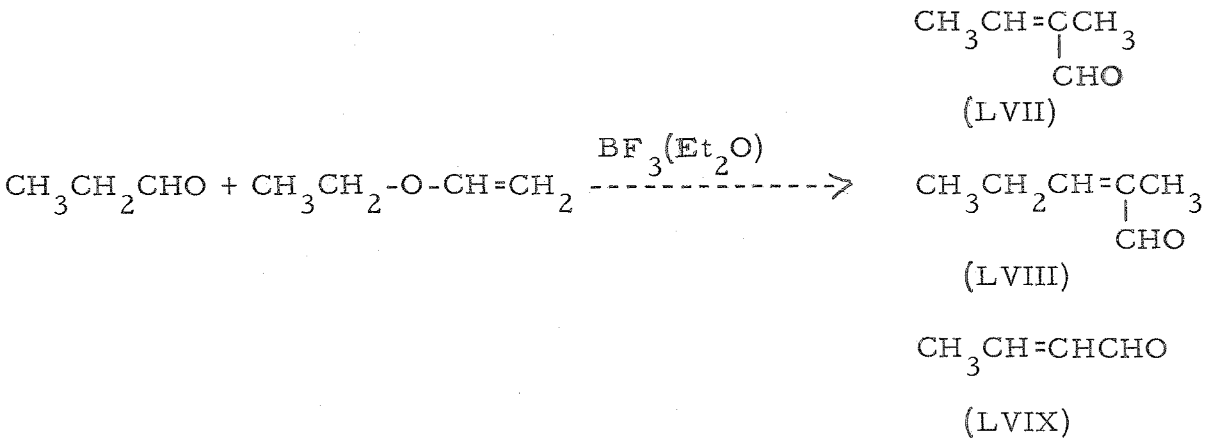
Scheme XV



$$CH_3CH_2CHO + BF_3(Et_2O) \xrightarrow{CH_3CH_2\text{-}O\text{-}CH{=}CH_2} \begin{array}{c} CH_3CH{=}\underset{\underset{CHO}{|}}{C}CH_3 \\ (LVII) \\ CH_3CH_2CH{=}\underset{\underset{CHO}{|}}{C}CH_3 \\ (LVIII) \end{array}$$

In a second run in which the ether solution of boron trifluoride and a mixture of propionaldehyde and ethyl vinyl ether were added simultaneously to the reaction pot, the mixture consisted of 35% of tiglic aldehyde, (LVII), 64% of α-methyl-2-pentenal, (LVIII), and 1% of crotonaldehyde, (LVIX). Again, no 2-pentenal was found.

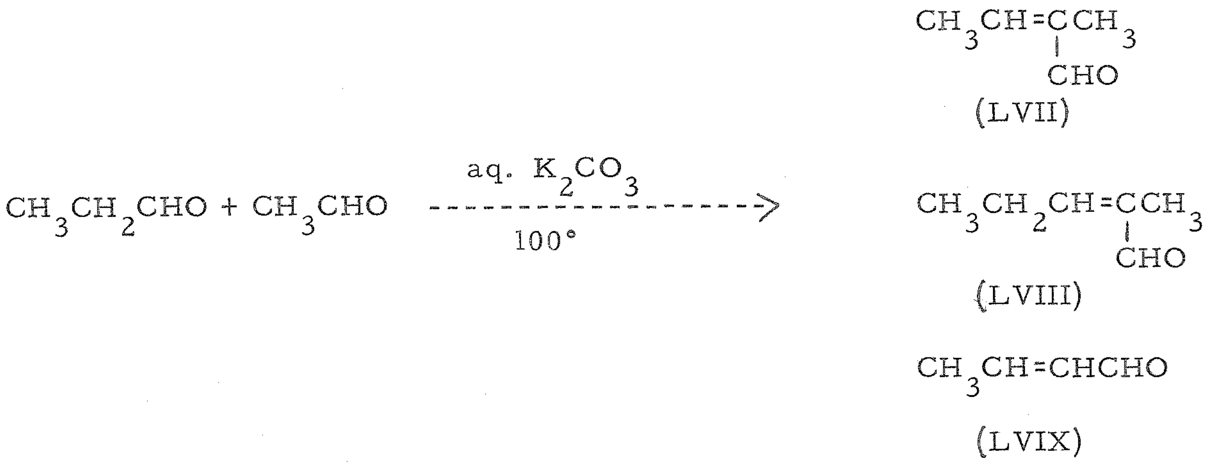
Scheme XVI



$$CH_3CH_2CHO + CH_3CH_2\text{-}O\text{-}CH{=}CH_2 \xrightarrow{BF_3(Et_2O)} \underset{\text{(LVII)}}{CH_3CH{=}\underset{CHO}{C}CH_3} \quad \underset{\text{(LVIII)}}{CH_3CH_2CH{=}\underset{CHO}{C}CH_3} \quad \underset{\text{(LVIX)}}{CH_3CH{=}CHCHO}$$

A cursory examination of the products obtained from reaction of aqueous potassium carbonate solution with a mixture of acetaldehyde and propionaldehyde in a sealed tube showed the presence of tiglic aldehyde, (LVII), (67%) and α-methyl-2-pentenal, (LVIII), (32%), with perhaps a small amount of crotonaldehyde, (LVIX), (ca. 1%), but no 2-pentenal was found.

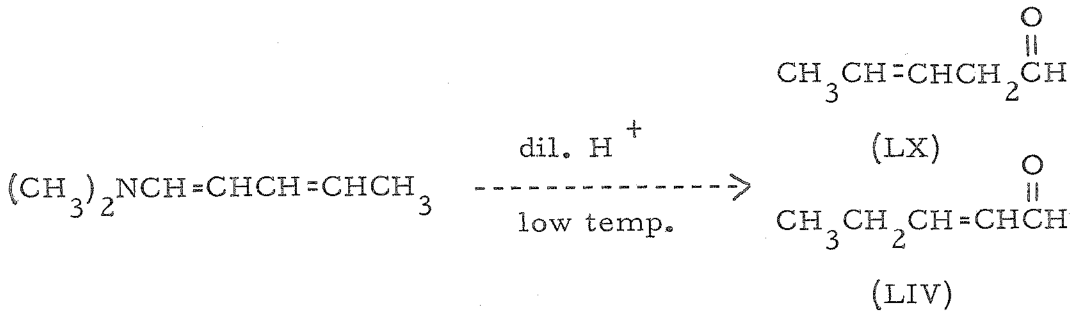
Scheme XVII



$$CH_3CH_2CHO + CH_3CHO \xrightarrow[100°]{\text{aq. } K_2CO_3} \underset{\text{(LVII)}}{CH_3CH{=}\underset{CHO}{C}CH_3} \quad \underset{\text{(LVIII)}}{CH_3CH_2CH{=}\underset{CHO}{C}CH_3} \quad \underset{\text{(LVIX)}}{CH_3CH{=}CHCHO}$$

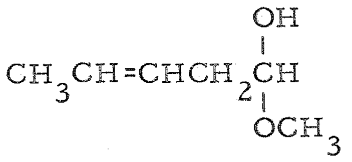
Treatment of 1-dimethylamino-1,3-pentadiene, (XXVIII), at room temperature with dilute acid and extraction of the neutral portion of the product gave, after removal of the ether, a mixture of two aldehydes as observed by vapor phase chromatography. The major component was 3-pentenal, (LX), ($>C=O$ absorption at 1730 cm^{-1}) and the minor component was 2-pentenal, (LIV), ($>C=O$ absorption at 1690 cm^{-1}). The infrared spectrum of 3-pentenal in carbon disulfide showed absorption at 965 cm^{-1}. Since there was no absorption at higher wavelengths, this band must be due to the <u>trans</u>- (${}_{H}\!>C=C<^{H}$) linkage. The obvious inference here is that under mild conditions, the non-conjugated isomer is obtained by hydrolysis of the vinyl conjugated amine and tautomerism to the aldehyde. Under more drastic conditions (steam distillation), however, the double bond goes into conjugation with the carbonyl group.

Scheme XVIII



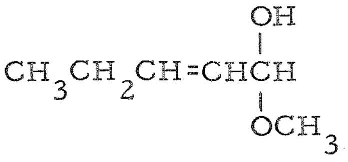
$$(CH_3)_2NCH=CHCH=CHCH_3 \xrightarrow[\text{low temp.}]{\text{dil. } H^+} CH_3CH=CHCH_2\overset{\overset{O}{\|}}{C}H \quad (LX) \qquad CH_3CH_2CH=CH\overset{\overset{O}{\|}}{C}H \quad (LIV)$$

Treatment of (XXVIII) with water at room temperature also led to the aldehyde. This was noted by observing the disappearance of the 271 mμ band in the ultraviolet spectrum, using water as a solvent. Because a band appeared at 225 mμ, some 2-pentenal must have been formed, but the low extinction coefficient indicated the primary formation of 3-pentenal. In methanol, the 271 mμ band of (XXVIII) disappeared and no other band appeared. This was evidence for formation of a non-absorbing hemi-acetal, (LXI).*



$CH_3CH{=}CHCH_2CH(OH)(OCH_3)$

and/or

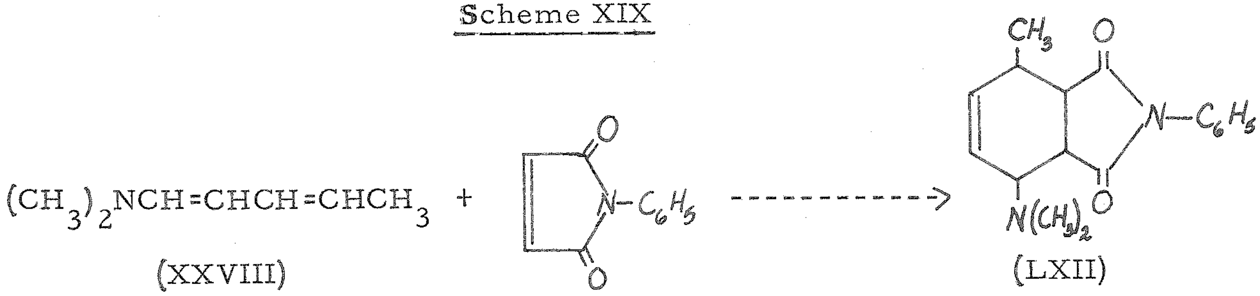


$CH_3CH_2CH{=}CHCH(OH)(OCH_3)$

(LXI)

1-Dimethylamino-1,3-pentadiene, (XXVIII), reacted very readily with N-phenylmaleimide just on mixing the pure components at room temperature. The adduct, presumably (LXII), (M.P. 104-105°), lost dimethylamine on heating with water.

Scheme XIX



(XXVIII) reacted with 1,4-naphthoquinone with almost explosive violence in the pure state, the residue being a black, tarry mass. The procedure of Langebeck and co-workers (37), utilizing reaction of the amine in ethyl ether solution with 1,4-naphthoquinone in the same solvent

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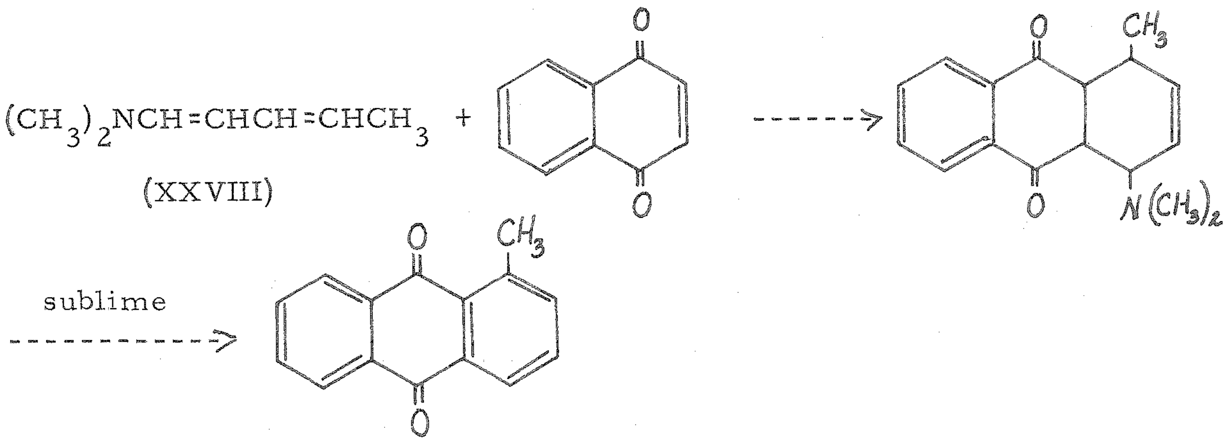
*Braude and Nachod (36) have reported studies of the reversible formation of hydrates and hemi-acetals of aldehydes in aqueous or alcoholic solutions by observing the low-intensity band near 280 mμ.

for four days, was, therefore, used. Sublimation of the residue, after removal of ether, gave 1-methylanthraquinone, (LXIII), which did not depress the melting point of an authentic sample.

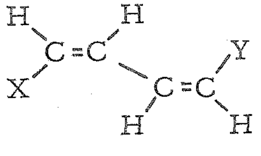
Scheme XX



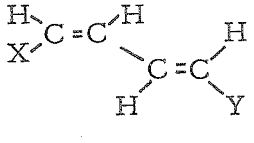
(XXVIII)

(LXIII)

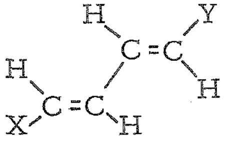
The non-reactivity (or sluggish reactivity) of conjugated dienes with Diels-Alder dienophiles has been used as evidence for a cis, cis (Type A) or cis, trans (Type B) configuration. On the other hand, conjugated dienes which react rapidly with a dienophile have been assigned the trans, trans (Type C) configuration (38).



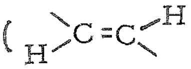
(Type A)

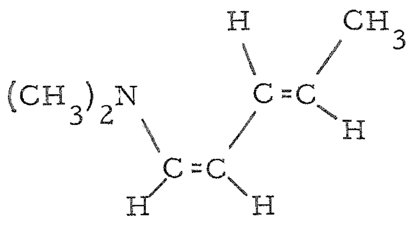


(Type B)



(Type C)

1-Dimethylamino-1,3-pentadiene, (XXVIII), has been shown to undergo a facile reaction with Diels-Alder dienophiles, but its infrared spectrum argues strongly against a trans,trans configuration. Celmer and Solomons (38) have shown that certain 3,5-diene fatty acid esters having a 3(trans), 5(cis) grouping exhibit three characteristic infrared bands at 950, 985 and 1020 cm^{-1} in carbon tetrachloride. The corresponding trans,trans isomers have a strong band at 990 cm^{-1}. A solution of (XXVIII) in carbon tetrachloride had a triplet of bands at 918, 932 and 968 cm^{-1} (see I.R. spectrum #XIII, p. 187). More important is the fact that (XXVIII) in carbon disulfide showed a medium absorption at 704 cm^{-1} and a strong absorption at 815 cm^{-1} (see I.R. spectrum #XIV, p. 188). Since 3-pentenal (obtained from (XXVIII) by hydrolysis) had the trans configuration, the 815 cm^{-1} band must be due to a trans () linkage. The 704 cm^{-1} band is very strong evidence for a cis configuration; trans olefins have not been observed to absorb this low.* (XXVIII), therefore would be assigned the cis,trans configuration.



(XXVIII)

A brief account of postulated mechanisms for the Diels-Alder condensation and pertinent references to the original literature may be

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*See Bellamy (reference (18), pp. 34-56).

found in Hine's text (39). Several important generalizations about the Diels-Alder condensation have been noted.

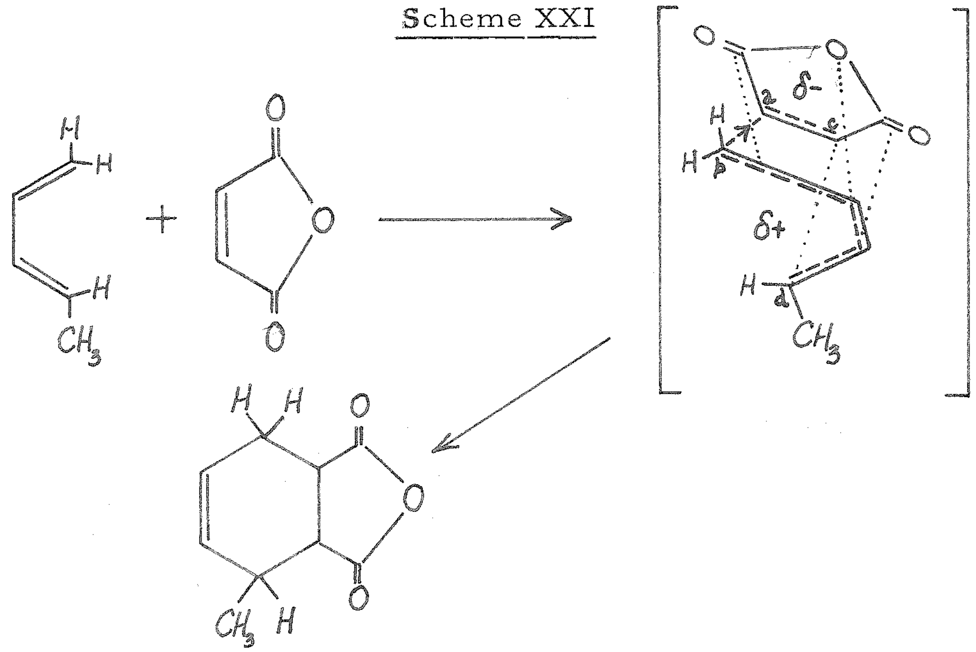
1) The reaction is stereospecific.

2) The reaction is sensitive to steric effects.

3) Electron-donating groups on the diene and electron-withdrawing groups on the dienophile greatly increase their reactivity.

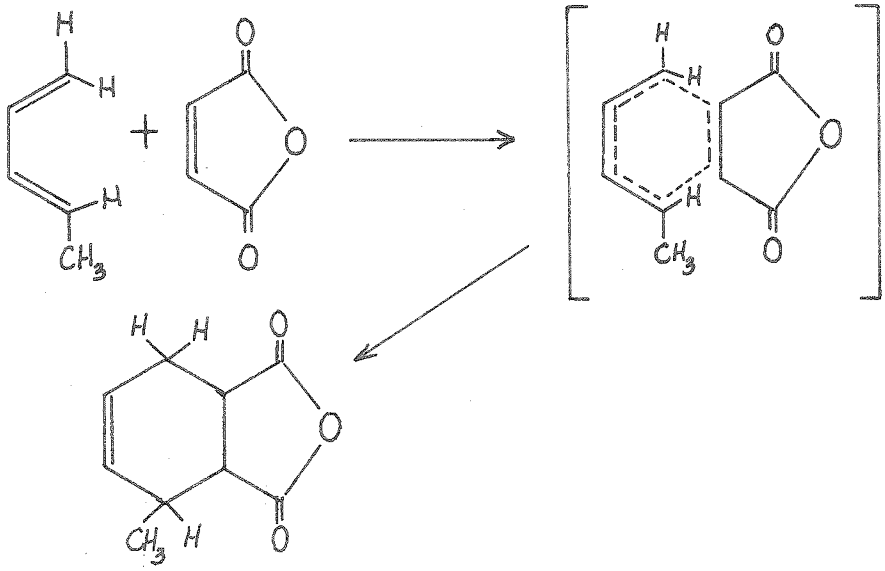
Recently, Woodward and Katz (40) have posulated a mechanism involving two steps. The first step is considered to be approach of a dienophile in a plane parallel to the plane occupied by the diene. A single bond is formed between one terminus of the diene and one of the unsaturated centers of the dienophile. The stereospecificity is maintained by secondary attractive forces. The formation of the second bond, accompanied by necessary geometrical rearrangements, in the next step, completes the process. Thus, the reaction of trans-piperylene with maleic anhydride would be depicted by Woodward and Katz as shown on Scheme XXI (the first bond being formed at ab and the second at cd).

Scheme XXI



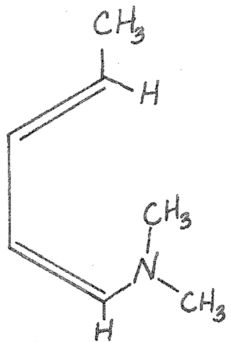
Dewar (41) has disagreed with Woodward and adhered to the view that both bonds are formed simultaneously in a single step. He has called his intermediate a pseudo-aromatic compound and depicted it as shown on Scheme XXII (for maleic anhydride and trans-piperylene).

Scheme XXII

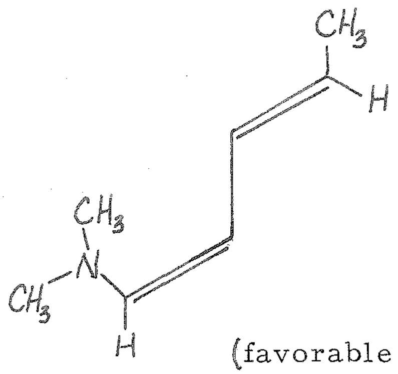


Whether there was any stereospecificity in the reaction of 1-dimethylamino-1(cis), 3(trans)-pentadiene, (XXVIII), with dienophiles is not known; the stereochemistry of the adducts was not studied. Though Dewar's mechanism argues strongly for stereospecificity, Woodward's mechanism does not necessarily require it (though Woodward states that his mechanism can accommodate it).

All postulated mechanisms (including those of Woodward and Dewar) for the reactions of dienes with dienophiles assume a quasi cis (folded-over) conformation for the reacting diene. This conformation for (XXVIII) is very unfavorable, because of the large repulsion between the hydrogen and the dimethylamino-group on carbons 4 and 1, respectively.



(unfavorable conformation)



(favorable conformation)

This does not necessarily mean that some of the postulated mechanisms cannot accommodate the reaction of (XXVIII) with dienophiles. The dimethylamino-group is an excellent electron-donating group. Its effect can apparently override the steric effect with ease. A physical picture of this situation would have little meaning at this early stage and will not be attempted here.*

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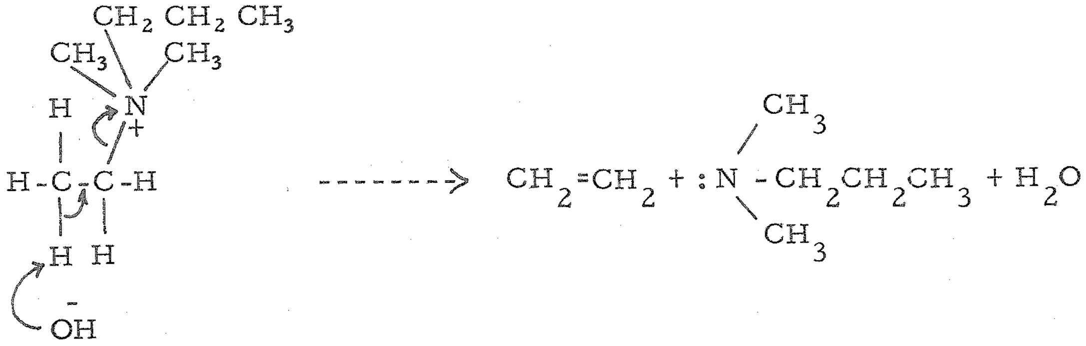
*Not many cases of the Diels-Alder condensation with the activating influence of a -NR$_2$ group are known and furthermore, in cases which are known, such as 1-diethylamino-1, 3-butadiene (37), the configuration of the diene is probably *trans*. One case in which the configuration is known will be cited. Fegley, Bortnick and McKeever (42) have prepared both the *cis, trans*- and the *trans, trans*-isomers of 1, 4-bis-(dimethylamino)-1, 3-butadiene and found that both undergo the Diels-Alder reaction with dienophiles.

A discussion of the Hofmann degradation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide.

It is the purpose of this last section to discuss the Hofmann degradation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide in the light of the results reported in the preceding sections of this thesis.

For many years, the generally accepted mechanism for the Hofmann elimination in quaternary ammonium salts was that due to Ingold and collaborators (43). Kinetic studies of the elimination have shown that it is first order with respect to base and first order with respect to the quaternary ammonium salt. This type of elimination (designated E2) may be illustrated mechanistically for the case of a n-propylethyldimethylammonium salt.

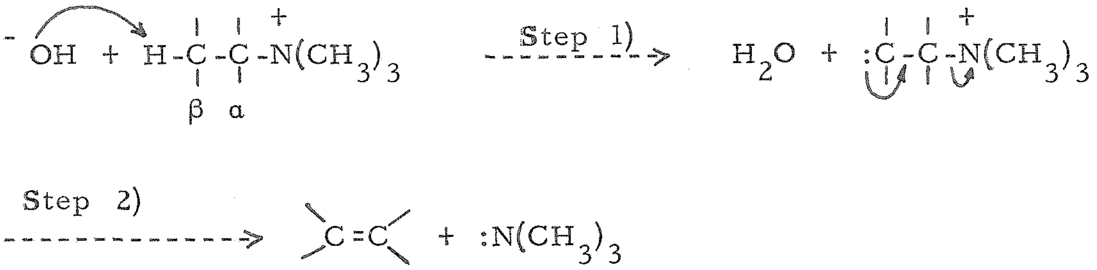
Scheme XXIII



The reaction is assumed to proceed by attack of base ($^{-}$OH) at a proton on a β-carbon followed by trans elimination of a trisubstituted ammonia molecule. That the ethyl group is preferentially attacked is rationalized on the basis of the known electron-releasing power of a methyl group which makes the protons on the β-carbon of the n-propyl group less acidic.

Other mechanisms have been invoked to explain certain observations about olefin-forming eliminations of the Hofmann type. Of particular interest is the carbanion mechanism of Cristol (44) (designated as ElcB by Hughes and Ingold (45)). This mechanism was first postulated by Cristol to explain cis-elimination in the β-isomer of 1, 2, 3, 4, 5, 6-hexachlorocyclohexane (all chlorine trans). The ElcB mechanism would have the form shown on Scheme XXIV.

Scheme XXIV



Most of the discussion in the literature has been unfavorable to a carbanion mechanism. It has been argued that Step 1) is reversible (46). If this is true, one would expect that if the reaction was run in a deuterated solvent and stopped before reaction was complete, the recovered quaternary ammonium salt would contain deuterium at the β-carbon (47). Furthermore, one would expect an optically active compound (asymmetric β-carbon) to be racemized if a free carbanion was formed

---

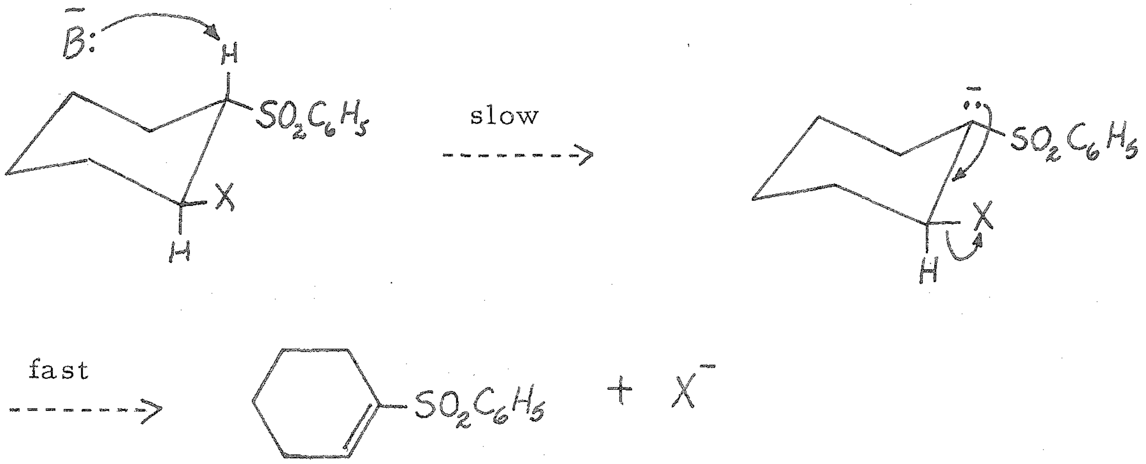
*Cristol (49) observed a small amount of deuterium exchange in the β-isomer of 1, 2, 3, 4, 5, 6-hexachlorocyclohexane, but Hughes and Ingold (45) have used this as an argument against an ElcB mechanism.

(48). Neither of the two above effects has been observed.*

Weinstock, Pearson and Bordwell have shown that the elimination is general base catalyzed (50). This was interpreted to mean that Step 1) could not be a fast step and if the ElcB mechanism has importance, then Step 1) must be the slow step (rate-determining). They stated that there seemed to be no demanding reason for assuming that cis elimination occurs through a carbanion intermediate.

Goering and co-workers (51), on the other hand, have decided that Step 1) (Scheme XXIV) must be irreversible (still rate-determining, however). This was based on a study of the system given on Scheme XXV.

Scheme XXV



It was observed that the rates are identical for two compounds in which X=Cl and in which X=p-toluenesulfonate. Since normally a p-toluenesulfonate undergoes a second order elimination faster than a chloride, the authors state that the loss of X^- must not be in the rate-determining step. If Goering's interpretation is correct, then a carbanion

---

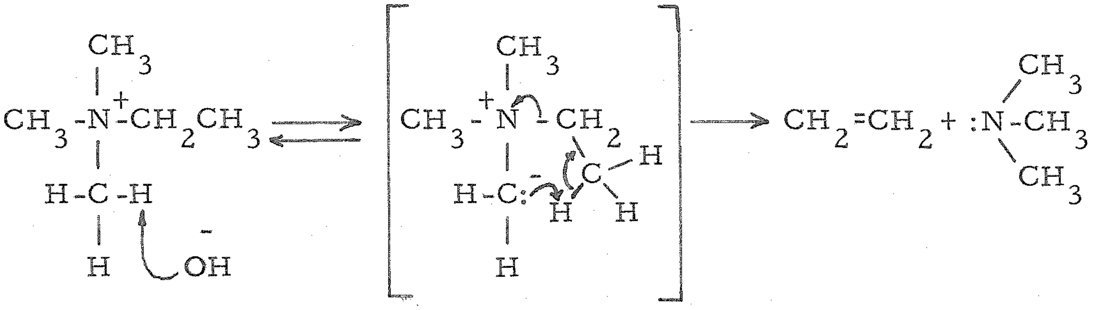
*See footnote on p. 88.

intermediate could be formed without deuterium incorporation in the isotopic exchange experiments.

An α-elimination has been demonstrated by Hauser and coworkers (52) for certain alkyl halides with potassium amide. This involves the simultaneous removal of a proton and the leaving group (halide ion) with a shift of a proton from the β- to the α-carbon at the same time. This type of mechanism has not yet been demonstrated for quaternary ammonium salts and with weaker bases, e.g., hydroxide ion.

Wittig and Polster (53), in 1956, proposed another mechanism. They showed that reactions of quaternary ammonium salts with phenyllithium led to the same products as were obtained in the Hofmann degradation and proposed the existence of an "ylid" intermediate. Weygand, Daniel and Simon (54) found that the thermal decomposition of $((CH_3)_3\overset{+}{N}CH_2CH_2T)\ ^{-}OH$ produced trimethylamine, water and ethylene, containing tritium in the percentages (based on the total amount of tritium in the starting material) of 11.9%, 17.5% and 73.1%, respectively. E2 elimination alone would give only radioactive ethylene and water (the isotope effect for the slower cleavage of C-T bonds compared to C-H bonds was taken into account). Though some exchange between radioactive water and protons on the α-carbons would be expected, the very large amount of tritium found in the trimethylamine cannot be explained in this way. A mechanism (designated Eα'β) was proposed. It was postulated to proceed as illustrated on Scheme XXVI.

Scheme XXVI



The first step of the reaction is formation of an "ylid" by abstraction of one of the methyl protons. Because the "ylid" can be stabilized by electrostatic attraction forces, the protons of the methyl groups are more acidic than the protons on the β-carbon and the former are removed preferentially. The elimination proceeds through a five-membered cyclic transition state (cis elimination) in which a proton is removed from a β-carbon and the olefin is released.

Many factors appear to operate in the Hofmann elimination (steric factors, basicity of the attacking reagent, nature of the leaving group, electronic factors, etc.) and several standard texts (55) have devoted much attention to it. It appears that a single mechanism is not operating in all of the studied cases of the Hofmann elimination and many of the previously quoted authors have mentioned this.

The nature of the products obtained from the Hofmann elimination in N,N-dimethyl-α-bromomethylpyrrolidinium bromide clearly indicated that removal of a proton and neutralization of the positive charge concurrent with ring opening was not random. This conclusion followed from the observation that ring opening occurred on only one side of the nitrogen, i.e., the side adjacent to the exocyclic group.

The postulated scheme for the course of the Hofmann degradation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide is given on Figure 4, pp. 93-94.

Any scheme for the degradation must be able to adequately explain the following observations:

1) cleavage of the C-N bond on only one side, that is, the side adjacent to the exocyclic group;

2) the large amount of 1-dimethylamino-3-pentyne, (XXVII), found and the larger, than expected,* amount of 1-dimethylamino-3,4-pentadiene, (XXVI);

3) the rapid conversion of N,N-dimethyl-α-methylenepyrrolidinium hydroxide, (XL), to N,N-dimethyl-α-methyl-Δ^2-pyrrolinium hydroxide, (XLI);

4) the cis configuration of 1-dimethylamino-2,4-pentadiene, (XXV) and the cis,trans configuration of 1-dimethylamino-1,3-pentadiene, (XXVIII).

In order to present the arguments for the postulated scheme (Figure 4) as concisely as possible, each step will be considered separately.

Step 1)-- This was quite clearly the splitting out of HBr from (XV). The dehydrohalogenated compound, (XL), has been isolated as the bromide

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*In the work of Jacobs and co-workers (19) on the equilibration of 1-pentyne, 2-pentyne and 1,2-pentadiene, the percentages found were 1.4%, 95.0% and 3.6%, respectively.

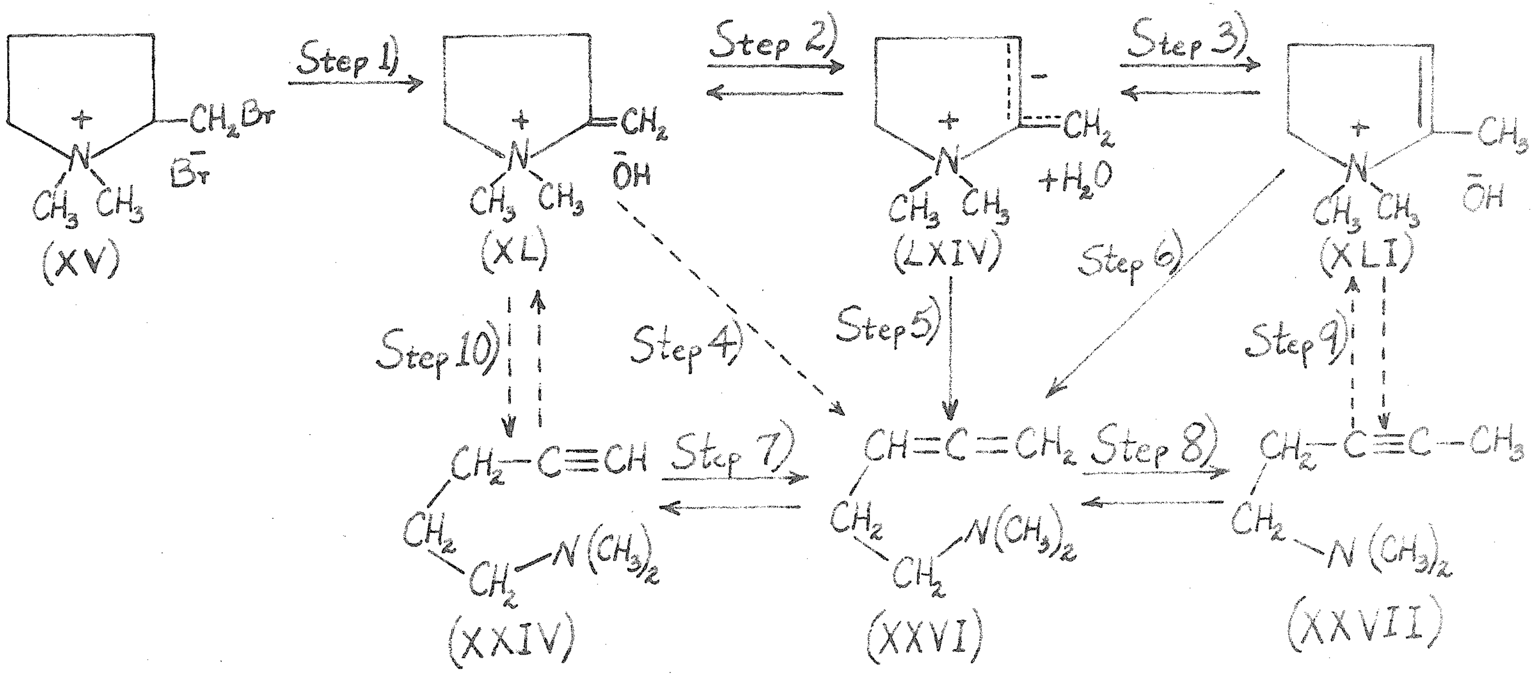


Figure 4. This figure is the postulated scheme for the Hofmann degradation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide.

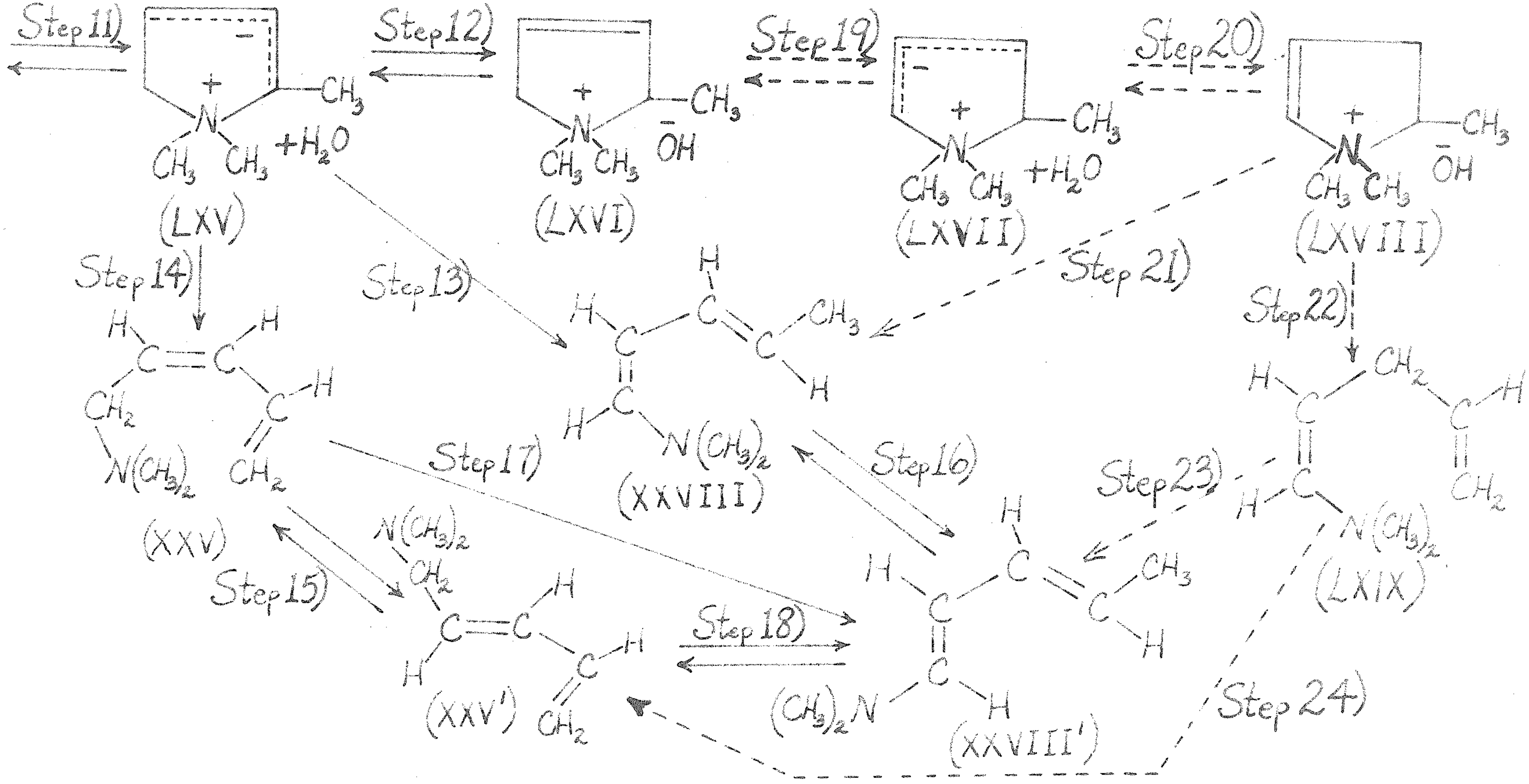
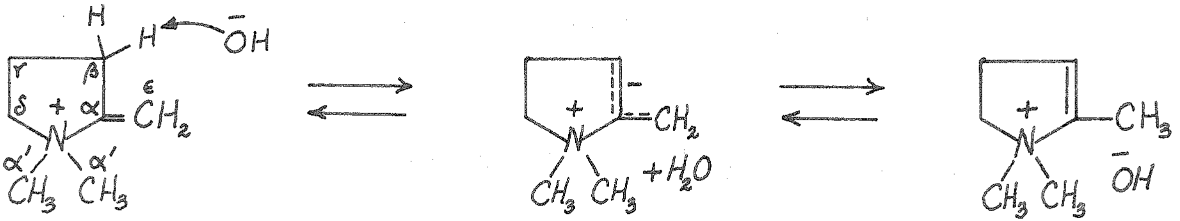


Figure 4 (cont'd.)

after treatment of (XV) with silver oxide followed by neutralization with hydrobromic acid.

Steps 2) and 3)-- Sodium hydroxide treatment at 130° of the exo-methylene compound, (XL), and of (XV) led to the isomer, (XLI), with the double bond in the ring. Work presented in this thesis showed that the equilibrium lies well on the side of (XLI) (under the conditions of the Hofmann degradation). The transformation of (XL) into (XLI) obviously involves removal of a proton. The protons on the β-carbon (Scheme XXVII) of (XL) are very acidic. This is best shown by writing the intermediate as a non-classical carbanion,* (LXIV), which has both resonance stabilization and stabilization from Coulombic attraction forces.

Scheme XXVII



(XL) (LXIV) (XLI)

Steps 4), 5) and 6) -- No data can be offered for how long the carbanion, (LXIV), exists, but if it exists long enough, it can collapse directly to the allene, (XXVI), in Step 5). The latter can also be derived from (XLI) in Step 6) by invoking the Ed'β mechanism (Scheme XXVIII).

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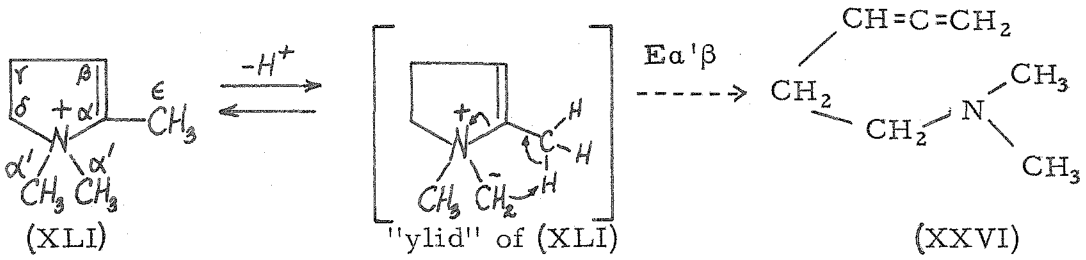
*The existence of a free carbanion in the Hofmann degradation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide has not been demonstrated. However, it is reasonable to assume (at this time) that a carbanion can be formed, because of the exceptional stability it can gain from resonance and Coulombic forces.

Scheme XXVIII

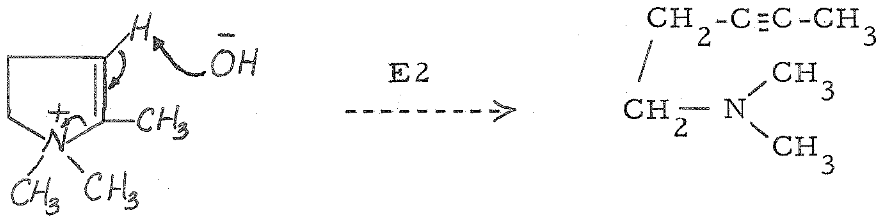


The acidity of hydrogens on an α-carbon in systems undergoing the Hofmann elimination has been demonstrated (46). Of the products observed, none could be obtained by removal of a proton from the δ-carbon of (XLI). The "ylid," however, formed by removal of a proton from an α′-carbon could lead to (XXVI) by the Eα'β mechanism (the protons on the β- and γ-carbons are too far away to be attacked by the carbanion). Of course, (XXVI) can also come from (XLI) by an E2 elimination. Since the protons on the ε-carbon are quite acidic, a concerted attack by base can occur on one of these protons. Step 4) would involve a concerted attack of base on a proton at the β-carbon of (XL) (E2 elimination). Though this is a feasible path to (XXVI), it is probably not as significant as Steps 5) and 6), because (XL) apparently does not exist very long. The step is, therefore, written with a dotted arrow.

Steps 7), 8), 9) and 10) -- Abstraction of a proton from the allene, (XXVI) and rearrangement of bonds can lead to 1-dimethylamino-4-pentyne, (XXIV), in Step 7) and to 1-dimethylamino-3-pentyne, (XXVII), in Step 8). The formation of (XXVII) from (XLI) by an E2 mechanism may well be in competition with the Eα'β elimination giving (XXVI).

Because of the presence of the double bond in (XLI) forcing the proton on the β-carbon to be in a co-planar and trans arrangement with the quaternary nitrogen, the most favorable conditions for E2 elimination are attained. As previously mentioned, the protons on the ϵ-carbon of (XLI) are quite acidic, but it is well-known that protons on unsaturated carbons are more acidic than those on saturated carbons (comparing ethylene with ethane (56) and not with propylene having a saturated carbon adjacent to a double bond). Consequently, given the intermediate, (XLI), a concerted attack by base may occur at the proton on the β-carbon to give (XXVII) in Step 9). The latter is written with a dotted arrow, because its importance is doubtful.

Scheme XXIX



(XLI)

(XXVII)

(XXIV) can be formed from (XL) by the $E\alpha'\beta$ elimination in Step 10). The latter is written with a dotted arrow, because (XXIV) probably is formed by a rearrangement of the allene, (XXVI).

One might expect that the allene, (XXVI), could rearrange to 1-dimethylamino-2, 4-pentadiene, which could then rearrange to 1-dimethylamino-1, 3-pentadiene (Scheme XXX).

Scheme XXX

$$(CH_3)_2NCH_2CH_2CH{=}C{=}CH_2 \rightleftarrows (CH_3)_2NCH_2CH{=}CHCH{=}CH_2$$

$$\rightleftarrows (CH_3)_2NCH{=}CHCH{=}CHCH_3$$

That this almost assuredly is not the case is due to several factors.

(1) The 1-dimethylamino-2,4-pentadiene has been shown to have the cis configuration. This indicates that it comes from a cyclic precursor, because the more stable trans configuration* would be expected in a rearrangement from the allene.

(2) The cis, trans configuration** of the 1-dimethylamino-1,3-pentadiene suggests that it does not come from 1-dimethylamino-2,4-pentadiene by a rearrangement, but rather that it also comes from a cyclic precursor.

(3) Jacobs and co-workers (19) did not find any conjugated diene in their equilibration work.

(4) No allene (or acetylene) was obtained on "equilibration" of 1-dimethylamino-2,4-pentadiene with ethanolic potassium hydroxide. It is assumed that the steps on Scheme XXX are reversible as written.

Because 1-dimethylamino-3-pentyne, (XXVII), on treatment with

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*In conjugated dienes, the trans-isomer is normally found to be the most stable isomer, e.g., piperylene (29).

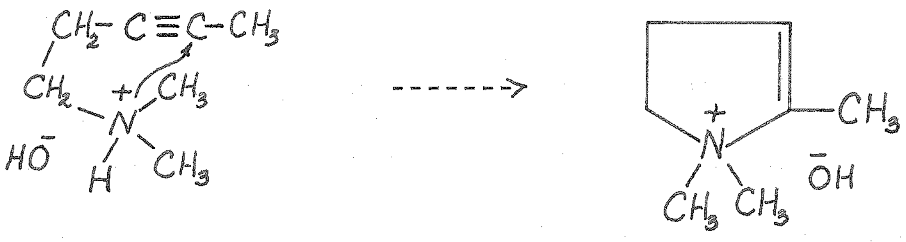
**Admittedly, the cis, trans configuration of the 1-dimethylamino-1,3-pentadiene has not been proved rigorously, but there is good evidence to assume it. In a rearrangement step, the trans, trans configuration would be expected, since it is normally the most stable (38).

ethanolic potassium hydroxide lead to the same products as the Hofmann degradation of (XV), it is inferred that there is a common intermediate.* Likewise, the terminal acetylenic isomer, (XXIV), can probably exhibit the same behavior. Since the importance of the reverse of Step 10) (indicating the preceding) is questionable, the step is written with a dotted arrow. Probably the formation of the allene, (XXVI), from a cyclic

---

*It is not necessary that (XXVII) proceed all the way back to (XLI) (therefore, the reverse of Step 9) is written with a dotted arrow), but it is necessary that there be a cyclic transition state (not necessarily an isolable intermediate) in which the cis configuration can be preserved in the diene, (XXV). The cyclization of 1-dimethylamino-3-pentyne, (XXVII), can be rationalized though, on the basis that the acetylenic linkage is susceptible to nucleophilic attack (57). The fact that the acetylenic amine, (XXVII), gave no cyclized product on simply refluxing with strong base is not necessarily significant, since the sealed tube reaction was carried out under much more drastic conditions. Since the acetylenic linkage is also susceptible to electrophilic attack, it is likely that in water (weakly basic conditions) the cyclization proceeded as shown on Scheme XXXI.

Scheme XXXI



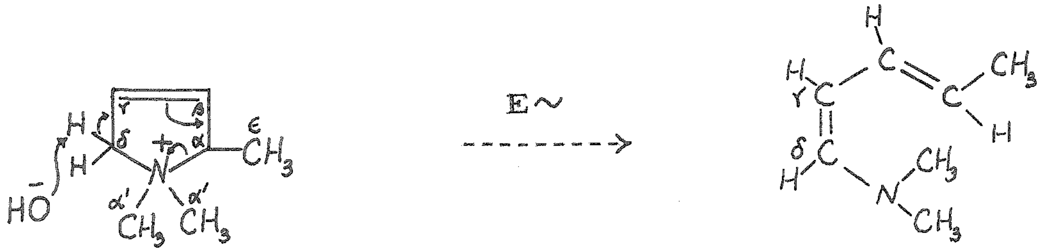
(XLI)

precursor is irreversible.*

Step 11) -- That the C-N bond and the C-H bond are not broken simultaneously (at least, not in all steps) has been shown by the transformation of (XL) into (XLI) without the accompanying olefin formation. It is reasonable that a proton from a γ-carbon of (XLI) can be abstracted leading to another non-classical carbanion, (LXV), in Step 11). It has been predicted (60) that there are systems which have strong C-N bonds (relative to β-C-H bonds), but this has not yet been documented.

Steps 12) and 13) -- Protonation of (LXV) in Step 12) can occur to give (LXVI). The latter is interesting, because it has two protons at the δ-carbon which are very acidic. Attack of base at one of these protons and rearrangement (designated E~) can lead directly to (XXVIII) in Step 13).

Scheme XXXII



(LXVI)

(XVIII)

This transformation can occur in one step, but the γ, δ-double

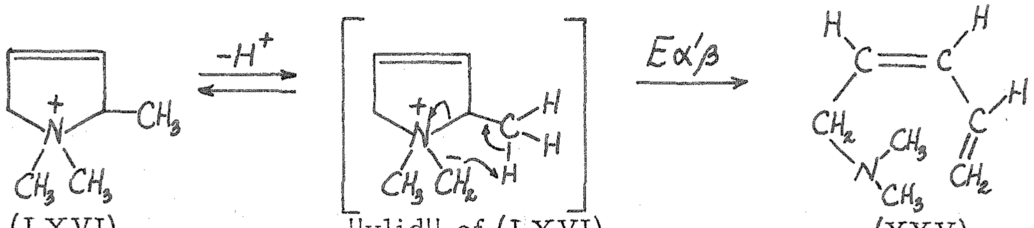
---

*Although relatively little is known about allenes, it has been inferred that they exhibit behavior typical of a simple alkene (58). Recent work by Jacobs and Johnson (59), though, has shown that different allenes react differently with various electrophilic reagents. Whether or not allenes are susceptible to nucleophilic attack has not been established. Probably cyclization of 1-dimethylamino-3,4-pentadiene, (XXVI), would not be expected, but it cannot be ruled out at this time.

bond must be made (or at least, made to the extent that there can be no freedom of rotation) before the C-N bond is cleaved.

Step 14) -- Eα'β elimination in (LXVI) can lead to (XXV) (Scheme XXXIII).

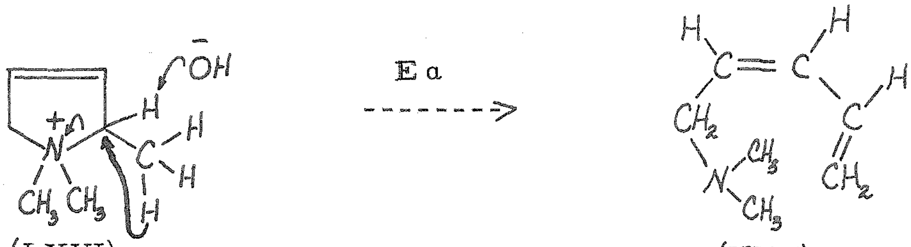
Scheme XXXIII



(LXVI) "ylid" of (LXVI) (XXV)

An alternative mechanism is by α-elimination (designated Eα) similar to that proposed by Hauser (52) (Scheme XXXIV).

Scheme XXXIV



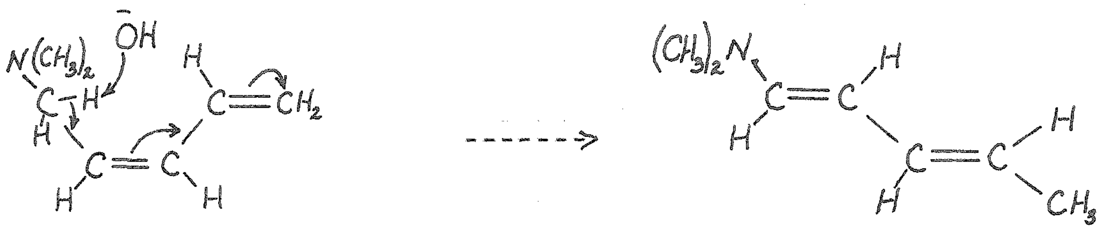
(LXVI) (XXV)

Steps 15) and 16) -- Thermal interconversions of cis- and trans-isomers are known (61). Undoubtedly, this can occur between (XXV) and (XXV') in Step 15) and between (XXVIII) and (XXVIII') in Step 16).

Steps 17) and 18) -- Abstraction of a proton from (XXV) and (XXV') and rearrangement would be expected to lead to (XXVIII') (Scheme XXXV).

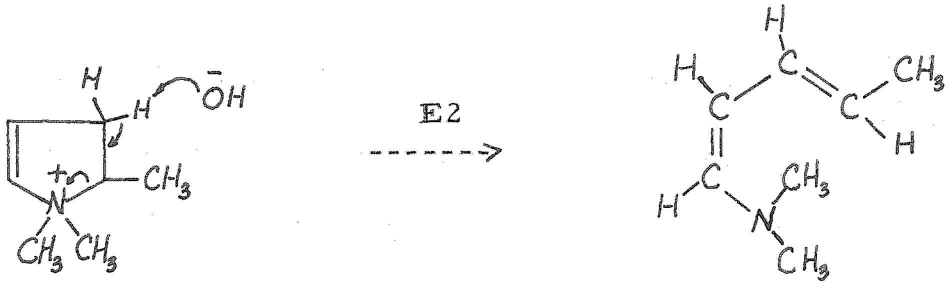
Step 18) would be expected to be reversible and is written with double arrows to indicate this.

Scheme XXXV


(XXV) (XXVIII')

Steps 19), 20), 21), 22), 23) and 24) -- Alternative paths for formation of (XXV'), (XXVIII) and (XXVIII') can be given. The six steps are written with dotted arrows, because they are not expected to be as important as preceding steps. If removal of a proton from the δ-carbon of (LXVI) does not lead all the way to (XXVIII), then a new carbanion, (LXVII), can be formed in Step 19). Protonation of (LXVII) in Step 20) can lead to (LXVIII). (XXVIII) can come from (LXVIII) be an E2 elimination in Step 21).

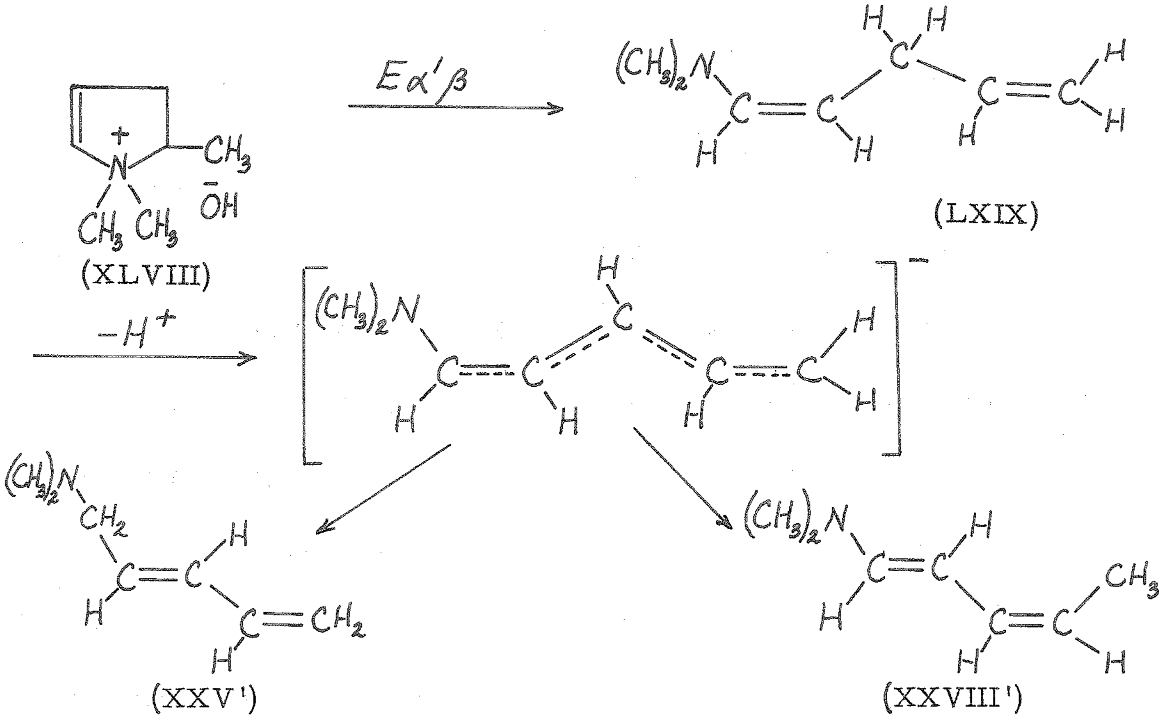
Scheme XXXVI



(LXVIII) (XXVIII)

Eα'β elimination in (XLVIII) would lead to (LXIX) in Step 22). The latter would undoubtedly be unstable* under the reaction conditions and would rearrange. The most reasonable rearrangement of (LXIX) would be through a carbanion intermediate to give (XXVIII') and (XXV') (Steps 23) and 24), respectively).

Scheme XXXVII



All of the observations have been explained except the exclusive cleavage** of the C-N bond on the side adjacent to the exocyclic group. Each intermediate that might be expected to lead to cleavage of the C-N bond on the other side will now be considered. (XLI) could give (LXX) by an E2 elimination.

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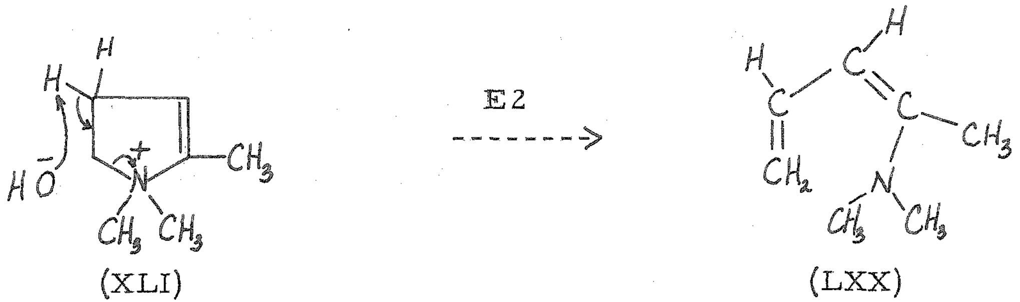
*Trimethyl-4-pentenylammonium hydroxide gives 1,3-pentadiene (not 1,4-pentadiene) when it is pyrolyzed (5).

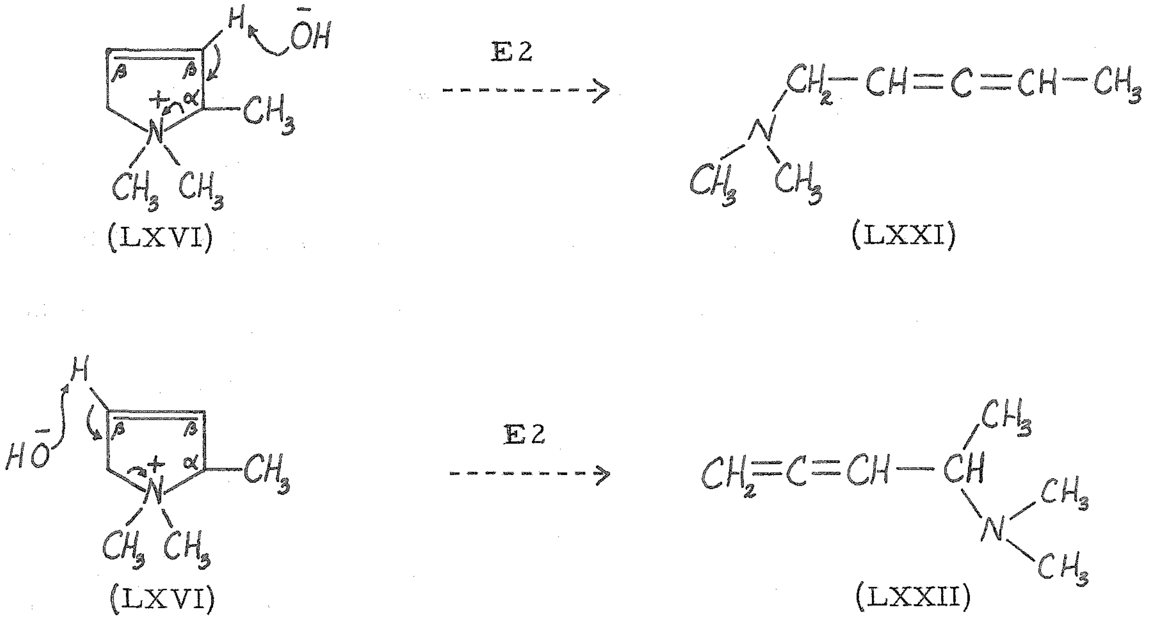
**It is possible that a small amount of 2-dimethylaminopentane went undetected in hydrogenation of the total tertiary amine mixture, but probably not more than 1-2%.

Scheme XXXVIII

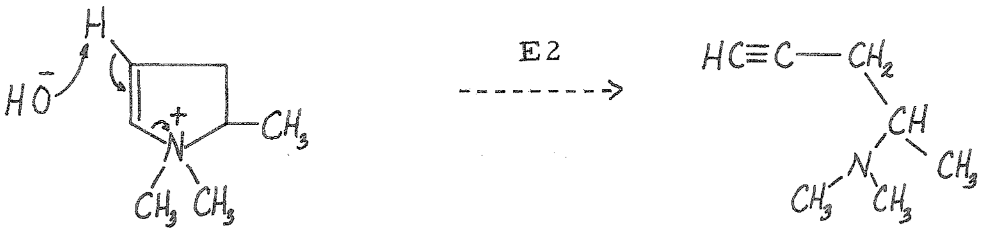

(XLI) (LXX)

A co-planar, trans array of proton and leaving group at the sites of the incipient double bond is believed to be desired in E2 elimination. Since the proton being removed in (XLI) (leading to (LXX)) does not have this favorable disposition of the proton being removed with respect to the C-N bond being broken, the molecule is apparently degraded by another path. If Step 9) of Figure 4 (see Scheme XXIX) is important, one might expect (LXVI) and (LXVIII) to exhibit similar behavior (Scheme XXXIX).

Scheme XXXIX


(LXVI) (LXXI)

(LXVI) (LXXII)



(LXVIII) (LXXIII)

(LXVI) has a nearly co-planar, trans array of β-protons with the C-N bonds. Furthermore, because of the greater negative charge on the α-carbon (induced by the methyl group), the C-N bond on the side adjacent to the exocyclic group should be stronger than the C-N bond on the other side. This would favor formation of (LXXII) over (LXXI). However, the Eα'β, Eα and E∼ eliminations are probably much better processes than an E2 elimination in (LXVI), because of the acidity of the α-protons. Perhaps a small amount of (LXVIII), if it was formed, was degraded to (LXXIII), but the amount was not significant.

Summing up, it should be clear to the reader that much of the foregoing discussion has been speculation. Though the data presented in this thesis are very limited for serious mechanistic considerations, it is becoming evident that the rigid (concerted, trans elimination) E2 mechanism must not be operative in all of the Hofmann degradations. Certainly one would not have predicted the observed products from the degradation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide by considering the E2 mechanism alone.

The reader should be aware that in the present stage of development of elimination mechanisms, mechanistic considerations alone do not suffice to establish the structures of the olefins obtained. In many cases, correct assignments of structures are fortuitous when no definitive proofs are given.

Experimental

All melting points were taken in capillary tubes in a heated metal block and uncorrected. Also, all boiling points are uncorrected. Analyses were made by Elek Microanalytical Laboratories, Los Angeles, except in one case so specified. Refractive indices were taken with a Carl Zeiss, Jena, Germany, refractometer having a constant temperature bath manufactured by the Precision Scientific Company, Chicago. Infrared spectra were taken with a Model 21 spectrophotometer, Perkin-Elmer Corporation, Glenbrook, Connecticut. Ultraviolet spectra were taken with a Cary Model 11M recording spectrophotometer, Applied Physics Corporation, Pasadena, California. The vapor phase chromatography apparatus used was an Aerograph instrument, manufactured by Wilkens Instrument and Research, Inc., Walnut Creek, California, and it had a Varian 100-mv. full-scale recorder (Varian Associates Instrument Division, Palo Alto, California).

Most experiments reported here were performed several times. Each account given is typical of these experiments. Cases in which only a single experiment was performed will be pointed out.

The two amines which were not isolated will be discussed at the end. Otherwise, the "Experimental" section follows the order of the discussion section.

N-Methylpiperidine, (IX). (62) Technical piperidine, (I), (1054 g. (12.4 moles) from the du Pont Co. --- dried and distilled once over solid potassium hydroxide; B.P. range 104-106°) was put into a 5-liter, 3-necked flask, equipped with magnetic stirrer, condenser and dropping funnel. The flask was immersed in a salt-ice bath and 2011 g. of a 36-38% formaldehyde solution (containing approximately 744 g. (24.8 moles) of formaldehyde) were added slowly from the dropping funnel. The addition required about three and one-half hours. The ice bath was removed and the reaction mixture was stirred for two hours. To the homogeneous solution were added 1268 g. of a 90% formic acid solution (containing approximately 1141 g. (24.8 moles) of formic acid). The formic acid was added slowly over a period of three hours, maintaining the temperature between 50-60° by external cooling. Carbon dioxide evolved slowly for three days at room temperature, after which time the mixture was refluxed for one day, gas evolution being negligible after this time. The reaction mixture was cooled in a salt-ice bath and treated with solid potassium hydroxide. The organic base which separated was removed mechanically and dried over solid potassium hydroxide. The crude material (weight = 1076 g.) was distilled over sodium, 822 g. being collected between 102-106° for a yield of 67%.

<u>1-Dimethylamino-4-pentene, (VII)</u>. N-Methylpiperidine, (IX), in ether solution, was treated with the theoretical amount of dimethyl sulfate (Matheson Coleman and Bell, reagent) in small portions. The white, hygroscopic solid obtained in essentially quantitative yield, was dried in a vacuum desiccator. The N,N-dimethylpiperidinium methosulfate, (XXX), (250 g.; 1.11 moles) was put into a copper retort. To this was

added a solution containing 195 g. (3.48 moles) of potassium hydroxide in 200 ml. of water. The retort was heated in a Woods' metal bath until no more material distilled over. (In some cases the aqueous solution was put back into the pot and redistilled, but only a negligible amount of organic base was recovered in this second distillation.) On salting with potassium hydroxide and mechanical separation, followed by drying over solid potassium hydroxide and finally distillation over sodium through a 3-foot column packed with glass helices, 62 g. of material boiling in the range 115-118° were obtained (55% yield based on twelve runs).

N,N-Dimethyl-α-bromomethylpyrrolidinium bromide, (XV). Into a 12-liter, 3-necked, round-bottom flask, equipped with stirrer, thermometer, condenser and dropping funnel were placed 959 g. (8.48 moles) of 1-dimethylamino-4-pentene, (VII), and 4 liters of chloroform (Baker, reagent). To this solution were added, from the dropping funnel, 1358 g. (8.48 moles) of bromine (Baker and Adamson, reagent) dissolved in 4 liters of chloroform. The temperature was maintained below 10° by an ice bath. The addition took five days. Solid quaternary bromide, (XV), was removed by filtration and recrystallized from hot ethanol containing 15% of water. The yield was 1683 g. (73% of the theoretical). (M.P. 220-222° (dec.)).

A picrate was formed by treating an aqueous solution of (XV) with a warm aqueous sodium picrate solution (prepared by adding an aqueous solution of sodium hydroxide to an aqueous solution of picric acid until the pH was 7-8). (M.P. of the picrate 201-202° (yellow needles in fan-like shape from water)).

A perbromide was formed by treating an aqueous solution of (XV) with bromine. (M.P. of the perbromide 73-74° (orange colored solid washed with water, but not recrystallized)).

The tertiary amine mixture. To 250 g. (0.915 mole) of quaternary bromide, (XV), in a copper retort was added slowly a solution of 187.5 g. (3.35 moles) of potassium hydroxide in 400 ml. of water. The copper retort was heated in a Woods' metal bath until no more distillate came over (10-12 hours). After separating 65 g. of the amine mixture and salting the aqueous phase with potassium hydroxide to give 23 g. more of the amine mixture, the aqueous phase was put back into the retort and the distillation was repeated. The amount of organic base which was obtained in this second distillation was negligible. The crude amine mixture* was dried over solid potassium hydroxide. It underwent rapid tar formation. Hydroquinone was of no aid in preventing this.

The tertiary amine mixture was put through a 3-foot precision fractionating column packed with glass helices. The column was wrapped with resistance wire for heating and covered with asbestos cord. Stirring was effected with a magnetic stirrer. (A magnetic stirrer was found to be sufficient to prevent bumping and excessive frothing was broken up early in the column. This technique alleviated the need for using a

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*In one degradation on a 100 g. scale, 29.0 g. (73% yield) of amine mixture was obtained after distilling through a 6-inch Vigreaux column at 40 mm. pressure.

capillary and distilling under nitrogen.) The vacuum set-up was similar to that described by Carney (63), the manostat being of the sintered glass disk type (similar to that illustrated by Carney, fig. 16, p. 164) and the column head was of the Whitmore-Lux total condensation-partial take-off type modified for work under reduced pressure (similar to that illustrated by Carney, fig. 44, p. 117). The pot was heated with a Glas-col heating mantle. A Zimmerli Gage was used to record the pressure and the pump was of 33.4 liter capacity, manufactured by the W. M. Welsh Co., Chicago. The thermometer in the column head dipped into a mercury well and was a 45-102° thermometer, graduated in one-tenths of a degree and manufactured by the Brooklyn Thermometer Co., Middletown, New York.

The tertiary amine mixture (28.7 g.) was put through the column. Table II (p. 113) is a compilation of the data for the fractionation. Eleven fractions were collected for studies by infrared spectroscopy. Table III(pp. 114-16) gives the infrared spectral data. Fractions 4, 5 and 6 had weak absorption at 3300 cm^{-1}, indicating a terminal acetylenic linkage. Fractions 4-10 showed absorption at 1955 cm^{-1}, indicating an allenic linkage; this absorption was strongest in fractions 6 and 7. Absorption at 907 cm^{-1}, indicating a terminal vinyl ($-HC=CH_2$) linkage, was strongest in fractions 4-6.

From 288.5 g. of the total amine mixture fractionated through the 3-foot column, seven fractions weighing 225.1 g. were collected.

Table IV (p. 117) gives the data for this distillation. Fraction 6, weighing 61.3 g., was refractionated through the 3-foot column; six fractions were collected (see Table V for the distillation data). To the residue from the distillation (Table V, p. 118) was added fraction 7 of the previous distillation (Table IV, p. 117). Seven fractions weighing 47.0 g. were collected (see Table VI, p. 119 for the distillation data).

1-Dimethylamino-3-pentyne, (XXVII). Fractions 2 and 3 (Table V, p. 118) were combined with fraction 2 (Table VI, p. 119) for a combined weight of 34.3 g. (0.309 mole). This material was treated with a hot solution of 53.9 g. (0.309 mole) of 5-nitrobarbituric acid (dilituric acid (64), Eastman) dissolved in 350 ml. of water. Initially there were two phases, but on heating on the steam bath, the amine went into solution and a deep green color appeared. A yellow amorphous solid separated first and then long green needles crystallized. There was some orange oily material present. The mixture was filtered and the filtrate, (A'), was cooled in the refrigerator. The residue, (A), was taken up in 250 ml. of hot ethanol containing 40 ml. of water. A light green colored insoluble material, (B), was removed and the filtrate, (B'), was allowed to cool. (B) weighed 4.8 g. and did not melt before 250° (decomposed before 300°). A volatile amine having the odor of dimethylamine and giving a basic test to pH paper was obtained from it on treatment with aqueous potassium hydroxide.

Fraction No.	Weight g.	Temp. °C	Pressure mm.	Reflux ratio	Voltage setting on variac to pot	Voltage setting on variac to column	Appearance	$n_D^{25°}$
1	0.4	33	47.3	5:1	30	30	Cloudy	1.4570
2	0.6	40-45	47.3	7:1	35	35	"	1.4570
3	0.49	43-50	47.3	6:1	35	35	"	1.4570
4	0.44	50.9-52.4	47.3	8:1	35	35	Clear	1.4571
5	2.92	52.4-54.4	47.3	7:1	35-40	35-40	"	1.4571
6	3.91	54.4-56.4	47.3	5:1	35-40	35-40-35	"	1.4568
7	2.32	56.6-58	47.3	6:1	40	35-40	"	1.4561
8	1.91	59.7-61.8	47.3	5:1	40	40	"	1.4561
9	2.07	62.0-64.0	47.3	5:1	40	40	"	1.4568
10	2.19	64.0-66.0	47.3	5:1	40-45	40-45-40	"	1.4571
11	5.25	66.2-67.8	47.3	5:1	45	40	"	1.4635

Total weight of all fractions = 22.50 g.

Weight of the residue = 1.80 g.

Table II

Table III

Infrared Spectral Data for Fractions from Table II

Fraction 4		Fraction 5		Fraction 6	
Wave number (cm^{-1})	Relative intensity	Wave number (cm^{-1})	Relative intensity	Wave number (cm^{-1})	Relative intensity
3300	1	3300	1	3300	1
2925	9	2925	9	2925	9
2830	8	2830	8	2840	8
2780	9	2780	10	2800	9
2750	10	2750	10	2760	10
2100	1	1955	4	1955	5
1955	2	1820	1	1820	1
1820	1	1648	1	1600-1700	(small band)
1650	2	1455	8	1460	7
1455	8	1440	6	1370	4
1440	6	1370	4	1338	2
1370	3	1338	3	1302	1
1340	2	1298	1	1260	2-3
1295	1	1260	2	1170	3
1255	3	1170	4	1143	2
1170	3	1143	2	1095	2
1095	3	1132	1	1039	7
1037	8	1094	2	907	7
994	3	1037	7	842	6
907	8	905	8		

Table III (cont'd.)

Fraction 7		Fraction 8		Fraction 9	
Wave number (cm^{-1})	Relative intensity	Wave number (cm^{-1})	Relative intensity	Wave number (cm^{-1})	Relative intensity
2925	9	2925	9	2925	9
2840	7-8	2830	8	2830	8
2800	9	2780	9	2780	9
2760	10	2750	10	2750	10
1955	5	1955	4	1955	3
1600-1700	(small band)	1645	2	1645	4
1460	8	1612	3	1612	4
1370	3	1460	8	1460	8
1338	1	1372	4	1372	4
1302	1	1337	1	1337	1
1260	2	1305	1	1305	1
1170	2-3	1264	2	1264	2
1143	2	1170	1	1170	1
1095	2	1142	2	1140	2
1039	8	1094	2	1094	2
907	3-4	1050	5	1050	6
842	5	1040	6	1040	7
		907	2		
		848	5		

Table III (cont'd.)

Fraction 10		Fraction 11	
Wave number (cm^{-1})	Relative intensity	Wave number (cm^{-1})	Relative intensity
2925	10	2925	10
2840	9	2850	9
2800	9	2800	9
2760	10	2770	10
1955	1-2	1650	7
1650	5	1630	6
1612	5	1612	6-7
1460	6	1460	6
1414	2	1448	5
1372	4-5	1410	1
1338	1	1373	5
1304	1	1338	2
1263	2	1307	1
1172	2	1267	1-2
1145	3	1173	2
1095	2-3	1144	3
1082	1	1095	4
1050	6	1082	1
1040	6	1053	5
1013	2(broad)	1040	5
963	2	1017	3
915	1-2	962	2-3
855	3(broad)	916	2
		857	2

Fraction No.	Weight g.	Temp. °C	Pressure mm.	Reflux ratio	Voltage setting on variac to pot	Voltage setting on variac to column	Appearance	$n_D^{25°}$
1	21.4	30	46.7	1:1	20-30	10-20	Cloudy,* two phases	1.4529
2	29.8	30	46.7	1:1	20	30	"	1.4550
3	9.9	30-50 (main at 30)	46.7	1:1	30-35	20-25-30	"	1.4542
4	40.7	56.9-57.1	46.7	1:1	35-40	30-35	Clear	1.4588
5	14.8	57.1-64.2	46.7	1:1	40	35	"	1.4550
6	61.3	64.2-66.5	46.7	1:1	40	35	"	1.4566
7	47.2	66.5-69.5	46.7	Total take-off	50	40	"	1.4929

Total weight of all fractions = 225.1 g.

Weight of the residue = 31.0 g.

*The cloudiness and second (bottom) phase was due to water.

Table IV

Fraction No.	Weight g.	Temp. °C	Pressure mm.	Reflux ratio	Voltage setting on variac to pot	Voltage setting on variac to column	Appearance	$n_D^{25°}$
1	7.0	60.5-63.9	42.5	5:1	55	45	Clear	1.4494
2	14.1	63.9-64.4	43.0	6:1	55	45	"	1.4490
3	14.4	64.4-64.9	43.0	6:1	60	45	"	1.4508
4	11.4	64.9-65.3	43.0	6:1	60	45	Clear(strong lines of mixing)	1.4537
5	5.3	65.3-65.8	43.0	6:1	60	45	Clear	1.4598
6	3.3	65.8-66.5	43.0	6:1	60	45	"	1.4678

Total weight of all fractions = 55.5 g.

Table V

Fraction No.	Weight g.	Temp. °C	Pressure mm.	Reflux ratio	Voltage setting on variac to pot	Voltage setting on variac to column	Appearance	$n_D^{25°}$
1	3.2	64.0-65.3	43.0	6:1	60	50	Clear	1.4478
2	6.6	65.3-66.0	43.0	10:1	60	50	"	1.4500
3	3.2	66.9-68.1	43.3	8:1	60	50	Clear(strong lines of mixing)	1.4540
4	4.7	72.5-73.5	43.3	8:1	65	52	Strong lines of mixing-yellow tint	1.4692
5	11.6	73.5-79.3	43.3	8:1	65	52	"	1.5130
6	14.3	79.3	43.3	8:1	65	55	Yellow tint	1.5223
7	3.4	-	5		Total take-off			1.5200

Total weight of all fractions = 47.0 g.

Table VI

(B') gave 24.5 g. of green needles, (C), melting in the range 162-163°. (A') gave 12.9 g. of green needles, (D), melting between 160-161°. Evaporation of (A') to dryness left a brown residue which on recrystallization from hot absolute ethanol (removing a small amount of insoluble) gave black crystals, (E). (E) was recrystallized from ethanol-water to give 10.9 g. of brown crystals, (F), which melted between 161-162°. (F) did not depress the melting point of (C). Work-up of the mother liquors of (C) and (D) and recrystallization gave 4.2 g. of brownish-green material, (G), melting between 160-161°.

The diliturate (52.5 g.) was suspended in 300 ml. of water and while cooling in an ice bath, a cooled solution of 20 g. (a little less than 100% excess) of potassium hydroxide in 100 ml. of water was added. The potassium diliturate which precipitated was removed by filtration through a Büchner funnel having a medium grade sintered glass disk. The residue on the funnel was washed with 150 ml. of petroleum ether (B.P. range 30-60°, Skellysolve F, technical). The aqueous basic filtrate was extracted with two 200 ml. portions and one 100 ml. portion of petroleum ether. All of the extracts were combined and dried over anhydrous Na_2SO_4. Removal of the petroleum ether on a warm steam bath with suction left 16.5 g. of residue (80.5% recovery from the diliturate). Work-up of the original aqueous mother liquor by treating with solid potassium hydroxide and extracting with petroleum ether gave a very small amount of material (0.9 g.).

The amine was distilled through a 3-foot column, four fractions weighing 13.2 g. and boiling between 62.5-63.5°/41.9 mm. were collected. The main fraction weighed 7.0 g. (B.P. 63.3-63.5°/41.9 mm.) and had $n_D^{25°} = 1.4410$. (Except for the first fraction which had some unremoved solvent, the other fractions had the same refractive index.) It was 1-dimethylamino-3-pentyne, (XXVII).

I. R. spectrum in carbon tetrachloride --- see spectrum #V, p. 179.

There was no absorption in the ultraviolet region.

Picrate: An ether solution of the amine was treated with an ethereal picric acid solution to give a flocculent yellow precipitate. M.P. 101-102° (from ethanol-isopropyl ether*).

Methiodide: A methanol solution of the amine was treated with an excess of methyl iodide. After standing for a short time in an ice bath, white crystals formed. M.P. 257-258° (froths) (from ethanol-isopropyl ether).

Methpicrate: An aqueous solution of the methiodide was treated with warm aqueous sodium picrate. Very quickly a flocculent yellow precipitate appeared. M.P. 112-113° (from ethanol-isopropyl ether).

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*Isopropyl ether (Baker and Adamson, purified) was found to be a very useful recrystallization solvent in many cases. Its peroxide impurities, however, caused considerable yellowing of white methiodides due to oxidation of the iodide to iodine. It was conveniently purified by the method of Dasler and Bauer (65). Passage of the ether through an acid-washed, alumina-packed column gave material having a negative Fieser (66) test for peroxides.

Perchlorate: The amine in absolute ethanol was treated with 60% aqueous perchloric acid until the solution became acidic to Congo Red indicator paper. Addition of ethyl ether precipitated a white solid which on recrystallization from absolute ethanol-ethyl ether mixture melted at 115-116°.

1-Dimethylamino-3-pentyne, (XXVII), was the most stable of the three isolated amines. It was clear and water-white after several months' storage in a desiccator in the dark. An hydrochloride separated from its solution in carbon tetrachloride on standing for one day. (Control tests with aniline and isobutyl amine showed that their respective hydrochlorides were formed in carbon tetrachloride.)

1-Dimethylamino-3-pentyne, (XXVII), was synthesized according to the directions given by Marszak and Epsztein (22).

1-Dimethylamino-3-butyne, (XXXIX). 3-Butyn-1-ol, (XXXVII), (57.6 g. (0.824 mole) obtained from the Farchan Research Laboratories, Cleveland, Ohio) and pyridine* (78.2 g.; 0.99 mole) were mixed in a 1-liter, 3-necked flask, equipped with a mechanical stirrer, thermometer and dropping funnel having a calcium chloride drying tube. The dark colored mixture was cooled in an ice-water bath and stirring was started. Benzene sulfonyl chloride** (163 g.; 0.922 mole) (Matheson Coleman and

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*As was pointed out by Eglinton and Whiting (67), it was found that too large an excess of pyridine caused a decrease in yield of the desired sulfonate.

**Though the crude p-toluene sulfonate derivative could be obtained in the yields reported by Eglinton and Whiting using their procedure, this derivative would not undergo the displacement reaction with dimethylamine under the same conditions used for the benzene sulfonate derivative.

Bell) was added dropwise from the dropping funnel over the course of two and one-half hours, maintaining the temperature below 30°. After stirring for an additional hour at room temperature, the dark brown slurry was treated with 100 ml. of water (slight heat effect) and then poured into 500 ml. of water. The bottom layer was extracted with one 200 ml. portion and two 100 ml. portions of ethyl ether. The ether extracts were washed with one 200 ml. portion and two 100 ml. portions of 3N HCl to remove any excess pyridine, followed by washings with one 200 ml. portion and two 100 ml. portions of a saturated sodium bicarbonate solution and with one 100 ml. portion of water. The ether extracts were dried over anhydrous sodium sulfate. The benzene sulfonate, (XXXVIII), (153.9 g.; 0.728 mole) was taken up in 500 ml. of anhydrous ethyl ether and the solution was cooled in an ice bath. This cooled solution was added from a dropping funnel (having a calcium chloride drying tube) to a stirred solution of 81.0 g. (1.80 moles) of dimethylamine (Eastman) dissolved in 500 ml. of anhydrous ethyl ether. The amine solution was cooled in a salt-ice bath. The dropping funnel was connected to the reaction flask by a rubber stopper, which also had an outlet tube containing calcium chloride. The addition required two hours. The solution was kept cooled overnight and then allowed to stand for 5 days at room temperature while stirring slowly with a magnetic stirrer. To the other solution, from which a large amount of solid had precipitated, was added a solution of 112 g. (2.0 moles) of potassium hydroxide in 500 ml. of water. After all of the solid material had dissolved, the ether solution was separated from the aqueous solution; the latter was extracted with one 300 ml. portion of ethyl ether. Drying of the combined extracts over anhydrous sodium sulfate and removal of the ether left a residue which was partially solid. The solid was not examined, but it was probably potassium benzene sulfonate. After removing the solid which separated, the residue was distilled through a 6-inch Vigreaux column. In the boiling range 60-62°/150 mm., 9.6 g. of material were collected ($n_D^{25°} = 1.4275$). The fore-run weighed 3.7 g. and was a mixture of solvent and 1-dimethylamino-3-butyne, (XXXIX).

The I.R. spectrum of (XXXIX) in carbon tetrachloride showed strong absorption at 3300 cm^{-1}, typical of the terminal acetylenic linkage ($\equiv$C-H).

Methiodide: M.P. 212° (froths) (clusters of thick platelets from ethanol-water).

Picrate: M.P. 115-116° (clusters of thin platelets from absolute ethanol).

A brown color was produced when the amine, (XXXIX), was treated with ammoniacal silver nitrate solution,but no precipitate formed. (3-Butyn-1-ol in the same test produced a white cloudiness with the first drop and an orange-brown oil with the third drop. On standing, white crystals formed.) No observable change was noted when (XXXIX) was treated with ammoniacal cuprous chloride solution. (One drop of 3-butyn-1-ol added to the same reagent produced a yellow precipitate, clearly visible in the blue solution.)

<u>1-Dimethylamino-3-pentyne, (XXVII)</u>. Approximately 200 ml. of liquid ammonia were introduced into a 500 ml., 3-necked flask, equipped with a true-bore stirrer, dry ice condenser having a soda lime-potassium hydroxide drying tube and an inlet tube for ammonia. The flask was contained in a 1-gallon Dewar flask filled with dry ice-acetone mixture. To the liquid ammonia was added 0.1 g. of ferric nitrate nonahydrate, whereupon the solution acquired an orange-brown color. The inlet tube was replaced by a dropping funnel. Metallic sodium (2.9 g.; 0.126 g.-atom) was introduced in portions. The pot was removed from the dry-ice bath during the addition of the sodium and the initially formed blue color disappeared rapidly giving a brownish-black color. After one hour, 9.3 g. (0.096 mole) of 1-dimethylamino-3-butyne, (XXXIX), were added slowly from the dropping funnel, fitted with a drying tube. The addition required 30 minutes. After stirring for one hour, 16.3 g. (0.115 mole) of methyl iodide were added from the dropping funnel. Addition required about 25 minutes, the reaction being very violent as observed by frothing in the pot. (During addition of the amine, (XXXIX), and during addition of the methyl iodide, only periodic cooling in the Dewar flask was necessary, the evaporation of the ammonia being sufficient to keep the pot well cooled .) Following the addition of the methyl iodide, the solution was stirred for one hour and then the ammonia was allowed to slowly evaporate. The black residue was treated with 100 ml. of U.S.P. ether (wet). The mixture was stirred and then filtered; the residue was washed with 300 ml. of ether. A small layer of concentrated aqueous sodium iodide was

removed mechanically and the ether solution was dried over anhydrous sodium sulfate. After removal of the ether, the residue was distilled through a 6-inch Vigreaux column. The fore-run weighed 1.61 g. and contained some solvent. Material boiling between 62-63.5°/43.0 mm. weighed 4.02 g. and had $n_D^{25°} = 1.4410$. It was 1-dimethylamino-3-pentyne, (XXVII).

The I.R. spectrum in carbon tetrachloride indicated a very small amount of terminal acetylene (starting material, (XXXIX)).

Picrate: M.P. 101-102°.

Methiodide: M.P. 257-258° (froths).

The infrared spectrum of this material was identical with the spectrum of the material isolated from the Hofmann degradation of (XV). The picrate and methiodide of the latter did not depress the melting points of the same derivatives of the former.

N,N-Dimethyl-α-methylenepyrrolidinium bromide, (XLII). Silver oxide was prepared by reacting 7.5 g. (47.0 millimoles) of silver nitrate in 25 ml. of water with 5.0 g. (89.0 millimoles) of potassium hydroxide in 25 ml. of water. The black precipitate was washed with water until the washings were neutral to pH paper. The silver oxide was suspended in 150 ml. of water and 5.0 g. (18.3 millimoles) of N,N-dimethyl-α-bromomethylpyrrolidinium bromide, (XV), were added to the stirred suspension. An immediate precipitate of silver bromide formed. The mixture was stirred in the dark overnight. The precipitate and excess silver oxide were removed by filtration and the alkaline filtrate was made neutral with hydrobromic acid. After removing most of the water by distillation with suction, a stream of air was directed over the residue until a solid formed. Because of its extremely hygroscopic nature, all of the water could not be removed. The residue was continuously extracted with chloroform. After removing the chloroform and combining the residues of two 24-hour extractions, material weighing 3.26 g. (90% yield) was obtained after drying "in vacuo." Snow-flake shaped crystals melting at 203-204° were obtained on crystallization from ethanol-isopropyl ether mixture. (Normally the crystals obtained had a light tan color. White crystals could be obtained only by repeated Norite A (decoloring charcoal) treatments and recrystallizations.)

Picrate: (obtained by treating the bromide with aqueous sodium picrate) M.P. 260° (dec.). (The melting points varied according to the rate of heating of the melting point block and the temperature of the block when the sample was introduced. The highest value obtained is reported here. It is quite definite that the melting point could not be raised to Lukes' value (23) of 283°.)

Analysis: Calculated for $C_{13}H_{16}N_4O_7$: C, 45.88%; H, 4.74%; N, 16.47%. Found: C, 46.09%; H, 4.85%; N, 16.32%.

N,N-Dimethyl-α-methyl-Δ^2-pyrrolinium bromide, (XLIII). A 25% solution of sodium hydroxide was prepared by dissolving 20 g. of sodium hydroxide in 80 ml. of water. To this was added 5.0 g. (18.3 millimoles) of N,N-dimethyl-α-bromomethylpyrrolidinium bromide, (XV).

The bromide was not totally soluble. The flask was heated in an oil bath at a temperature between 125-132° for 5 minutes. The temperature of the clear yellow, homogeneous reaction mixture at the end of the heating was 105°. After cooling, it was diluted with 50 ml. of water and made neutral with hydrobromic acid. After removal of water, the residue was continuously extracted with chloroform. The material obtained from the two 24-hour extractions weighed 3.29 g. (93.5% yield), after drying "*in vacuo*." Small clusters of white needles in a square array (M.P. 234-235°) were obtained on crystallization from ethanol-isopropyl ether mixture. (Crystals melting at 236-237° were obtained if they were removed before crystallization was complete.)

Picrate: M.P. 282° (dec.).

Analysis: Calculated for $C_{13}H_{16}N_4O_7$: C, 45.88%; H, 4.74%; N, 16.47%. Found: C, 46.02%; H, 4.79%; N, 16.36%.

Reaction of 1-dimethylamino-3-pentyne, (XXVII), with water. 1-Dimethylamino-3-pentyne (0.5 g.) was allowed to stand in 6 ml. of a water-methanol (2:1) mixture for 5 days. On addition of warm aqueous sodium picrate solution, a yellow precipitate formed after a short time.

Picrate: M.P. 283° (dec.) (from methanol-water).

Analysis: Calculated for $C_{13}H_{16}N_4O_7$: C, 45.88%; H, 4.74%; N, 16.47%. Found: C, 46.05%; H, 4.85%; N, 16.36%.

This picrate did not depress the melting point of the picrate of (XLI).

The bromide was formed from the picrate by suspending the latter in water and adding a 10% excess of hydrobromic acid. The precipitated picric acid was extracted with ethyl acetate and the aqueous solution was distilled to near dryness with suction. The residue was crystallized from ethanol-isopropyl ether to give a substance melting between 230-232° (not further purified).

(XXVII), on refluxing with water for one hour, followed by extraction of the homogeneous (one phase) mixture with petroleum ether (30-60°) gave no amine after drying and removing the petroleum ether. (The small residue which was left gave no precipitate on treatment of its ethyl ether solution with ethereal picric acid solution.) The aqueous solution on treatment with aqueous sodium picrate gave a picrate melting with decomposition around 284° (exploded at 285°).

On refluxing N,N-dimethyl-α-methylenepyrrolidinium bromide, (XLII), with water for one hour and working up the mixture in a similar manner, no tertiary amine was detected. On treatment of the aqueous solution with aqueous sodium picrate solution, a picrate melting with decomposition around 272° was obtained (possibly there was partial isomerization of (XLII) to (XLIII)).

Further preparations of (XLII). On treatment of N,N-dimethyl-α-bromomethylpyrrolidinium bromide, (XV), with 25% aqueous sodium hydroxide solution overnight at room temperature and with silver oxide at 130° for 5 minutes, followed by the usual work-ups, (XLII) was obtained in both cases. The infrared spectra of the bromides were identical with the spectrum of material from the low temperature silver oxide treatment (see I.R. spectrum #VI, p. 180). (XLII) was easily isomerized to (XLIII) by treatment with sodium hydroxide solution at 130°. This conclusion was reached by comparing the latter's spectrum with that of (XLIII) obtained previously (see I.R. spectrum #VII, p. 181).

Attempted addition of HBr to (XLII). On refluxing 0.1 g. of (XLII) with 3 ml. of 48% hydrobromic acid for one hour, removing the acid "in vacuo" and crystallizing the residue from ethanol after a Norite A treatment, only starting material was isolated. The same result was obtained when the addition was attempted in the presence of a small amount of benzoyl peroxide.

Bromine treatment of (XLII). (XLII) was prepared from its saturated precursor, (XV), (1.0 g.; 3.66 millimoles) by silver oxide treatment. After addition of hydrobromic acid until the pH was strongly acidic, bromine (0.59 g.; 3.66 millimoles) was added. After a week, 0.9 g. of crude solid was obtained directly from the reaction mixture. This solid was taken up in hot absolute ethanol (removing a small amount of insoluble). Small pale yellow, hygroscopic crystals and larger cubic shaped crystals (transparent) formed. Mechanical separation of the two was extremely difficult because of the hygroscopic nature of one. A partial mechanical separation gave larger crystals which became wet at 128° and which melted mainly between 138-140° (dec.). The smaller crystals also appeared wet at 128°, but were completely melted by 131° (dec.).

Bromine was added to a solution of (XLII) in water until a dark colored bottom layer appeared and then 5 drops more were added. After 5 days' standing, the reaction mixture was heated on a steam bath for two hours. The aqueous portion was evaporated "in vacuo." Crystallization of the residue from ethanol gave crystals melting in the range 138-140° (dec.) (wet below this temperature).

On addition of an excess of bromine in chloroform to a solution of (XLIII) in chloroform, a red oil separated. After standing overnight, the chloroform was evaporated. The residue was taken up in hot ethanol (removing a small amount of insoluble). A brown solid separated which would not go back into solution (M.P. decomposed rapidly at 185°). From the ethanol only starting material, (XLII), was recovered.

(XLII) (1.0 g.; 5.2 millimoles) was dissolved in 10 ml. of 48% aqueous hydrobromic acid solution. A solution of 0.85 g. (5.2 millimoles) of bromine in 5 ml. of 48% hydrobromic acid was added slowly dropwise while stirring. After 4 days' standing, crystals had formed which would not completely dissolve in hot ethanol. They were dissolved in 5 ml. of hot ethanol-water (50:50) mixture. After several recrystallizations, fluffy white needles were obtained which decomposed at 200°.

Analysis: Calculated as the dibromo compound, $C_7H_{14}NBr_2$: C, 23.89%; H, 4.01%. Found: C, 24.66%; H, 4.25%.

Bromine treatment of (XLIII). (XLIII) (0.1 g.; 5.2 millimoles) was dissolved in water and treated with 0.1 g. of bromine. After 5 days' standing, the reaction mixture was heated on a steam bath for two hours. Crystallization of the residue from ethanol-isopropyl ether mixture gave small white crystals melting with decomposition at 112-113°.

(XLIII) (0.1 g.) in chloroform was treated with bromine. After a day's standing, the chloroform was evaporated leaving a red oil. The red oil was completely soluble in cold ethanol, but an insoluble solid appeared. The latter was put into hot solution. A yellow solid, decomposing at 190°, separated on cooling. From the mother liquor, starting material, (XLIII), was obtained on addition of isopropyl ether.

<u>Hydrogenation of N,N-dimethyl-α-methylenepyrrolidinium hydroxide, (XL)</u>. N,N-Dimethyl-α-bromomethylpyrrolidinium bromide, (XV), (50 g.; 0.183 mole) was suspended in 100 ml. of absolute methanol. While stirring, silver oxide (prepared from 75 g. (0.47 mole) of silver nitrate and 75 g. (1.34 moles) of potassium hydroxide in the usual manner) was added in portions. There was a heat effect. The flask was fitted with an Ascarite tube and the mixture was stirred in the dark for two days at room temperature. The mixture was filtered and the filtrate was put into a citrate bottle. Adams' platinum catalyst*(0.8 g.) was added

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*Adams' platinum catalyst was prepared according to directions given in "Organic Syntheses" (68). The chloroplatinic acid was obtained from Baker ("Analyzed," reagent). In a typical preparation, 3.5 g. of chloroplatinic acid were dissolved in 10 ml. of water and 35 g. of sodium nitrate were added. The mixture was heated in a porcelain evaporating dish with a free flame. After the water had evaporated, the orange solid was heated with a strong flame. A brown melt appeared and oxides of nitrogen were given off. The melt was heated for 25-30 minutes and then poured slowly into a beaker. The brown solid which solidified was crushed and ground in a mortar and the powder was stored in an amber bottle. The platinum dioxide was freed of salts by heating the mixture in hot water and washing the platinum dioxide until it threatened to become colloidal. The hydrogenation apparatus used was a Parr apparatus (manufactured by the Parr Instrument Co., Moline, Illinois).

and the mixture was hydrogenated under 2 atmospheres of hydrogen pressure at room temperature. In two hours, two moles of hydrogen per mole of quaternary hydroxide, (XL), had been taken up. The hydrogenation mixture was treated with 40 ml. of 48% hydrobromic acid and the acidic mixture was filtered to remove catalyst. On evaporation of the filtrate, a black, partially solid residue was left.

A small amount of the black residue was taken up in aqueous sodium hydroxide solution. The top layer of amine which appeared was extracted with ethyl ether. The ether extract was treated with ethereal picric acid solution to give a precipitate. This picrate did not depress the melting point (M.P. 100-101°) of the picrate of authentic 1-dimethylaminopentane (to be described later).

"Equilibration" of 1-dimethylamino-3-pentyne, (XXVII), with ethanolic potassium hydroxide solution. 1-Dimethylamino-3-pentyne (2.0 g.) and 3 ml. of ethanolic potassium hydroxide solution (prepared by dissolving 2.47 g. (85% min.) of potassium hydroxide in 10 ml. of absolute ethanol) were sealed in a glass tube. The tube was heated in an oil bath, whose temperature was 120° on introduction. One hour and 15 minutes later, the temperature was 200°. Heating was stopped and the bath allowed to cool slowly. After one hour the temperature was down to near 100°. The sealed tube was opened after cooling briefly in a dry-ice bath and the contents were poured into 20 ml. of cold distilled water. The tube was washed out with 10 ml. of cold distilled water in portions. The cloudy solution was extracted with ethyl ether. The ether extracts were combined (ca. 100 ml. volume) and dried over anhydrous sodium sulfate. After removing the ether, the residue was distilled at 40 mm. through a short Vigreaux column under nitrogen. The collector was cooled in dry ice and near the end of the distillation, the pressure was lowered to ca. 5 mm. to bring over as much material as possible (weight of the distillate = 0.91 g.). Vapor phase chromatography at 105° on a paraffin column showed the presence of the following components:

49% of starting material, 1-dimethylamino-3-pentyne, (XXVII) -- identified by infrared spectrum.

32% of 1-dimethylamino-1,3-pentadiene, (XXVIII) -- identified by infrared and ultraviolet spectra.

18% of a mixture of 1-dimethylamino-3,4-pentadiene, (XXVI), and 1-dimethylamino-2,4-pentadiene, (XXV). These two components were not well separated on the column. The infrared spectrum indicated that the main portion was the allene with a smaller amount of the conjugated diene. The ultraviolet spectrum corroborated the presence of the latter.

1-Dimethylamino-4-pentyne, (XXIV), was inferred from a small peak in the proper place on the vapor phase chromatogram. It was in too small amount (calculated ca. 0.2%) for absolute detection from the infrared spectrum of the total mixture. (Indeed, 1-dimethylamino-2,4-pentadiene did not show up in the infrared spectrum of the total mixture, but after separation by V.P.C., it was clearly present.)

The "equilibration" carried out exactly as described above for 20 hours gave a trace amount of substance having $\lambda_{\text{max.}} = 270$ mμ in the ultraviolet region. The infrared spectrum of this substance was identical with that of 1-dimethylamino-1,3-pentadiene, (XXVIII).

On refluxing 1.0 g. of 1-dimethylamino-3-pentyne, (XXVII), with 1.5 ml. of ethanolic potassium hydroxide solution (of the same concentration as used in the "equilibration" experiments) for one hour and extracting the basic solution with ether, only starting material (identified by treating the ether solution with ethereal picric acid to give a picrate melting at 100-101°) was recovered. The aqueous mother liquor was neutralized with dilute hydrochloric acid. On treatment with aqueous sodium picrate no quaternary picrate was formed (sodium picrate precipitated).

Treatment of (XXVII) with hydrochloric acid. 1-Dimethylamino-3-pentyne (0.50 g.) was treated with 2 ml. of concentrated hydrochloric acid. The mixture was refluxed in a test tube, equipped with a cold finger condenser, for two hours. The reaction mixture was filtered to remove tars. The filtrate was diluted with water and made strongly basic with potassium hydroxide. After extracting the top layer with petroleum ether (30-60°), drying the extracts over anhydrous sodium sulfate and evaporating the extracts, a yellow residue, which gave a positive Beilstein copper wire test for halogen, was left.

Methiodide: M.P. 179-180° (from ethanol).

Methpicrate: M.P. 99-100° (from ethanol-isopropyl ether).

The total tertiary amine mixture (64.3 g. from the Hofmann degradation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide, (XV)) was treated with 200 ml. of concentrated hydrochloric acid (du Pont Co.; specific gravity = 1.187; 36.9% HCl) and the acidic mixture was distilled. After approximately 100 ml. of distillate (two phases) had been collected, the distillation was stopped. On extracting the black distillate with petroleum ether (30-60°), drying the extracts and removing the petroleum ether, a black, viscous residue which could not be distilled was left. The acidic material in the pot was filtered to remove tars and the filtrate was made strongly basic with potassium hydroxide. The top layer was extracted with petroleum ether (30-60°) and the extracts were dried over anhydrous sodium sulfate. After removing the petroleum ether, 44.5 g. of material were collected on distilling through a 6-inch Vigreaux column (boiling range 67-82°/35.5 mm.). A lower boiling fraction (10.1 g. boiling in the range 67-74°/35.5 mm.) was fractionated through a 3-foot heated column. The main fraction (5.17 g.) boiled in the range 82.0-83.1°/45.2 mm. and had $n_D^{25°} = 1.4470$.

Methiodide: M.P. 177-179°. There was no depression of the melting point when it was mixed with the methiodide of the product resulting from addition of HCl to 1-dimethylamino-3-pentyne (preceding page). After several recrystallizations from absolute ethanol, it melted between 186-187°.

Analysis: Calculated for $C_8H_{17}NClI$: C, 33.18%; H, 5.92%. Found: C, 33.30%; H, 6.11%.

Diliturate: M.P. 135-136° (from absolute ethanol).

Analysis: Calculated for $C_{11}H_{17}N_4ClO_5$: C, 41.19%; H, 5.34%. Found: C, 41.15%; H, 5.41%.

Methpicrate: M.P. 99-100° (from ethanol-isopropyl ether).

1-Dimethylamino-2,4-pentadiene, (XXV). Fractions 1, 2, 3, and 4 (combined weight = 101.8 g.) from the 288.5 g. of amine mixture (Table IV, p. 117) were allowed to stand over solid potassium hydroxide for one day. A second phase (concentrated aqueous potassium hydroxide solution) separated and the top amine layer was extracted with petroleum ether (30-60°). The petroleum ether extracts were dried over solid potassium hydroxide and finally over sodium. The petroleum ether was distilled off on a steam bath under water aspirator suction. The residue (weight = 55.6 g.) was fractionated through the 3-foot precision column, six fractions boiling between 50.0-63.3°/46.4 mm. being collected. The fourth fraction (B.P. range 51.6-52.4°/46.4 mm.; weight = 17.1 g.; $n_D^{25°}$ = 1.4599) was refluxed for one hour with 200 ml. of water. There were two phases present before and after the refluxing. The top organic base layer was extracted with six 100 ml. portions of ethyl ether. The ether extracts were dried over anhydrous sodium sulfate and then the ether was removed leaving a 11.2 g. residue. This residue was distilled through a 6-inch Vigreaux column. The total weight of all material distilled was 9.59 g.; the main fraction boiled in the range 50-50.5°/45.0

mm. and weighed 8.58 g. with $n_D^{25^\circ} = 1.4610$. This material was 1-dimethylamino-2,4-pentadiene, (XXV).

U.V. spectrum -- Solvent: n-hexane (Phillips Petroleum Company -- dried over calcium chloride and distilled over sodium).

$\lambda_{max.} = 224$ mμ; $\epsilon_{max.} = 22,200$.

I.R. spectrum in carbon tetrachloride -- see spectrum #IX, p. 183.

Methiodide: This derivative was formed from the components (excess of methyl iodide) in methanol. It crystallized overnight in the refrigerator (-5°) M.P. 169-170° (without recrystallization).

Methpicrate: M.P. 104.5-105° (from ethanol-isopropyl ether).

Picrate: Ethereal picric acid added to an ether solution of the amine separated an oil which partially solidified on stirring. On attempted crystallization from hot ethanol-isopropyl ether (1:1) mixture, yellow crystals and yellowish-orange solid (from solidification of oil) were produced. The mixture melted between 77-80°.

Diliturate: A hot aqueous solution of dilituric acid was added to the amine, followed by heating until the mixture was homogeneous. Green crystals formed on cooling. M.P. 169-170° (from ethanol).

Analysis: Calculated for $C_{11}H_{16}N_4O_6$: C, 46.47%; H, 5.67%. Found: C, 46.54%; H, 5.72%.

(XXV) could be obtained as a clear, water-white liquid, but it formed tars rapidly even on storage in a desiccator in the dark. After five months' standing in a sealed tube, (XXV) turned yellow and a trace amount of tars had formed. Its solution in carbon tetrachloride separated an hydrochloride overnight.

1-Dimethylamino-2,4-pentadiene, (XXV), was synthesized according to the procedure of Lukeš (16).

N-Methylpyridinium methosulfate, (XLVI). Pyridine, (XLV), (100 g. (1.26 moles), Baker, reagent) was put into a 1-liter, 3-necked flask, equipped with a dropping funnel and with a condenser having a calcium chloride drying tube. Anhydrous ethyl ether (500 ml., Mallinckrodt, reagent) was added and the flask was cooled in a salt-ice bath. While stirring with a magnetic stirrer, 160 g. (1.26 moles) of dimethyl sulfate (Matheson Coleman and Bell) were added dropwise from the dropping funnel. Addition required about one hour. The oil which separated was removed from the ether and put into a vacuum desiccator under water aspirator suction. The yield of (XLVI) was essentially quantitative (weight = 253.6 g.).

N-Methyl-1,2,5,6-tetrahydropyridine, (XLVII). Potassium formate* (605.6 g. (7.20 moles) obtained by adding potassium hydroxide to aqueous formic acid to near the neutral point (slightly acid), evaporating the solution down and fusing the solid at 250°) was put into a 3-liter, 3-necked flask, equipped with a thermometer dipping into the pot and with a Claisen head for distillation. To this were added 100 ml. of water

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*It was found that in one of three attempts using sodium formate, some reduced product could be isolated, though in a lower yield (38%, crude).

and 500 ml. of 98-100% formic acid (Baker and Adamson, C.P.). The mixture was distilled until the pot temperature reached 175°. To the residue were added 253.6 g. of N-methylpyridinium methosulfate, (XLVI), followed by 250 ml. of water and 1050 g. of 98-100% formic acid. The mixture was distilled until the pot temperature reached 280°; 1800 ml. of distillate had been collected. The distillate was made basic with potassium hydroxide and the basic solution was distilled. This distillate on treatment with potassium hydroxide yielded 90.0 g. (wet) of organic base. After two dryings over solid potassium hydroxide, 71.4 g. of amine were put through a 3-foot precision column. After taking off 1.8 g. of fore-run, 62.6 g. (approximately 50% yield) of a mixture of N-methylpiperidine, (IX), and N-methyl-1,2,5,6-tetrahydropyridine, (XLVII), boiling between 102-109° were collected. (Fractional distillation was not sufficient to give pure tetrahydro compound and purification over its dibromide was necessary.)

The mixed bases (43.1 g.) were treated with 600 g. of 48% hydrobromic acid solution (Baker and Adamson, reagent) in a 1-liter, 3-necked flask, equipped with stirrer and dropping funnel. After the reaction mixture had come to room temperature, 24.2 ml. (71 g.; 0.44 mole) of bromine (Baker and Adamson, reagent) were added dropwise during 25 minutes. The bromine color disappeared during the first half of addition, but near the end the color persisted and a red oil separated. The reaction mixture was evaporated to near dryness on a steam bath with suction. The residue was taken up in 200 ml. of hot ethanol containing 15 ml. of water and the solution was treated with Norite A. N-Methyl-3,4-dibromo-1,2,5,6-tetrahydropyridine hydrobromide, (XLVIII), (28.6 g.) was obtained on crystallization. It melted at 189-190° (dec.).*

In other preparations, it was found that 77.2 g. of mixed bases gave 81.9 g. of the dibromo hydrobromide (this figure included careful work-up of the mother liquors). The material melted at 191-192° (dec.). (It was found that the melting point was a little higher if the melting point block was heated up before the sample was introduced -- 185° in this case.) Since 81.9 g. of dibromo hydrobromide corresponds to 23.5 g. of tetrahydro base, $\frac{23.5}{77.2} \times 100 = 30.4\%$ of the base mixture was the tetrahydro compound.

N-Methyl-3,4-dibromo-1,2,5,6-tetrahydropyridine hydrobromide (303.6 g.) was taken up in 620 ml. of water. While stirring with a mechanical stirrer, 90 g. of zinc dust (Mallinckrodt, reagent) were added portion-wise over a period of 40 minutes. After standing for one day, the reaction mixture was treated with solid potassium hydroxide. Following the addition of 200 ml. of water, the strongly basic mixture was

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*Lukeš (16) obtained a melting point of 203-204° for his compound. On treatment of a saturated solution of the 189-190° compound with sodium bicarbonate, an oil heavier than water separated. After extraction with petroleum ether and evaporating under water aspirator (which should have removed any N-methylpiperidine), a high boiling liquid residue, which gave a white solid on treatment with hydrobromic acid was left. The solid melted at 189-190° (dec.).

It was concluded that the compound at hand was not admixed with N-methylpiperidine hydrobromide, but that it was the desired compound.

distilled, two 200 ml. portions of distillate being collected. On salting the first portion with solid potassium hydroxide, 77.7 g. of wet organic base were obtained. The second portion yielded none. After drying over solid potassium hydroxide and removing 2.9 g. of fore-run, 62.5 g. (72% recovery) of N-methyl-1,2,5,6-tetrahydropyridine were obtained boiling constantly at 110.5°.

Picrate: M.P. 199-200° (long needles from absolute ethanol).

N,N-Dimethyl-1,2,5,6-tetrahydropyridinium iodide, (L). The tetrahydro base, (XLVII), 30 g.; 0.31 mole) was dissolved in 300 ml. of absolute methanol in a 1-liter, 3-necked flask, cooled in an ice bath. While stirring mechanically, 66 g. (50% excess) of methyl iodide were added dropwise during the course of 40 minutes. A solid formed and then went into solution overnight. The methanol was removed on the steam bath with suction and the yellow solid residue was crystallized from 200 ml. of absolute ethanol. The methiodide, (L), weighed 71.5 g. (96.5% yield) and melted at 266-267° (dec.) (on heating the metal block to 260° before introducing the sample, it melted at 269-270°).

1-Dimethylamino-2,4-pentadiene, (XXV). Silver oxide was prepared by reacting 63.5 g. (0.374 mole) of silver nitrate (Baker and Adamson, reagent) in 100 ml. of water with 28.0 g. (0.50 mole) of potassium hydroxide in 100 ml. of water. The black precipitate was washed with water until the washings were neutral to pH paper. N,N-Dimethyl-1,2,5,6-tetrahydropyridinium iodide, (L), (71.5 g.; 0.299 mole) was dissolved in 250 ml. of water and the silver oxide was added to the solution. The mixture was swirled for a few minutes and then filtered through a Büchner funnel having a medium grade sintered glass disk. The residue on the filter was washed with distilled water. The basic filtrate was distilled. The first fraction of 200 ml. volume had both an unsaturated carbonyl odor and an amine odor. In the second fraction, a second layer began to appear in the distillate after about 50 ml. had been collected. For the third and final fraction, suction was applied giving a pressure around 50 mm. The amount of distillate collected was only about 5 ml. The pot was completely dry at the end, the amount of residue being insignificant. The three fractions were combined and made acidic with 6N HCl. The neutral product was extracted from the acidic solution with the petroleum ether (30-60°). The acidic aqueous was then made basic with potassium hydroxide and the organic base was extracted with petroleum ether. After drying the extracts over anhydrous sodium sulfate and finally removing the petroleum ether with suction on a warm steam bath, 22.4 g. of material was obtained. On distilling through a 3-foot heated column, four fractions of 1-dimethylamino-2,4-pentadiene, (XXV), boiling in the range 50.5-51.8°/47.0 mm. were collected (weight = 16.19 g.). The main fraction (weight = 10.5 g.; B.P. 51.6-51.8°/47.0 mm.) had $n_D^{25^\circ} = 1.4611$.

U.V. spectrum -- Solvent: n-hexane.

$\lambda_{max.} = 224$ mμ; $\epsilon_{max.} = 21,700$

I.R. spectrum in carbon tetrachloride -- identical with spectrum #IX, p. 183.

Methiodide: M.P. 169-170°.

Methpicrate: M.P. 104-105°.

Diliturate: 173-174°.

Picrate: Low melting -- yellow crystals and solidified oil isolated and melted between 81-83°.

The methiodide and the methpicrate did not depress the melting point of corresponding derivatives of the material obtained from the Hofmann degradation of (XV). A mixture of the diliturate of the latter with the above melted between 168-170° (wet at 165°).

N-Phenylmaleamic acid. N-Phenylmaleamic acid was prepared according to the procedure of Sears and Wilson (69). Aniline (50 g. (0.538 mole), Baker, reagent) was added to 90 ml. of water and 90 ml. of isopropyl alcohol (Mallinckrodt, reagent). The resulting solution was treated with 1.0 g. of sodium hydroxide and then it was heated to ca. 70°. While stirring with a mechanical stirrer, 52.7 g. (0.538 mole) of molten maleic anhydride (Matheson Coleman and Bell) were added slowly in portions, maintaining the temperature around 75°. The slurry was stirred for one hour at ca. 60° after addition was completed (addition required 15-20 minutes). The slurry was allowed to cool overnight. The solid which had precipitated was removed by filtration and washed with 120 ml. of a solution of equal volumes of water and isopropyl alcohol. The N-phenylmaleamic acid weighed 93.8 g. (91% yield) and melted at 195-196°.

N-Phenylmaleimide. N-Phenylmaleimide was prepared according to the procedure given by Searle (70). N-Phenylmaleamic acid (57.4 g.; 0.3 mole), 96.5 g. of acetic anhydride and 10 g. of fused sodium acetate were mixed in a 500 ml., 3-necked flask, equipped with stirrer, thermometer and condenser. While stirring, the reaction mixture was heated to 80° and then heating was stopped. The temperature rose to 90°. After stirring for one hour, the mixture had reached room temperature and a solid was forming in the dark colored solution. The mixture was poured onto ice. The brownish-yellow amorphous solid was collected by filtration and then allowed to stand in an evaporating dish overnight. The solid was taken up in 400 ml. of water. On heating, most of the solid went into solution, but a dark colored oil was left as an insoluble bottom layer. The aqueous layer was decanted from the oil through a Büchner funnel while hot. A solid quickly separated from the aqueous solution and the dark colored oil left behind solidified. The latter was dissolved in 100 ml. of hot ethanol and the hot solution was filtered. Well-formed, long yellow needles crystallized from the solution on cooling. The needles weighed 15.3 g. (30% yield) and melted between 87-90°. After two more recrystallizations from absolute ethanol, the crystals melted at 90-91°.

Reaction of N-phenylmaleimide with 1-dimethylamino-2,4-pentadiene, (XXV). 1-Dimethylamino-2,4-pentadiene (0.4 g.; 3.6 millimoles) was sealed in a tube with 0.62 g. (3.6 millimoles) of N-phenylmaleimide, 3 ml. of benzene and a trace of hydroquinone. The sealed tube was heated in a sand bath at 90° for 24 hours. The sealed tube was opened and the benzene solution was poured onto a column of alumina. The material was eluted from the column with benzene containing ethanol in percentages of ethanol increasing up to 100%. After evaporation of the solvent from each fraction collected, the residues from all the fractions had a combined weight of 0.9 g. (1.02 g. = theoretical yield of the adduct). At least 0.5 g. of the material was starting material, N-phenylmaleimide. The remainder consisted of a small amount of a colorless oil which was not examined and a larger amount of brown oil which partially solidified on standing. Nothing constantly melting could be obtained from this solid. There were indications that it contained a basic nitrogen, but if any adduct was present, it was in small amount, at least 80% of starting material being recovered. It is most probable that this solid resulted from polymerization of the amine.

"Equilibration" of 1-dimethylamino-2,4-pentadiene, (XXV), with ethanolic potassium hydroxide solution. 1-Dimethylamino-2,4-pentadiene (2.0 g.) was sealed in a tube with 3 ml. of ethanolic potassium hydroxide solution (contained 2.47 g. of potassium hydroxide per 10 ml. of absolute ethanol). Tar formation was observed on mixing the two. The tube was heated in an oil bath for 2 hours at 170-185°. On opening the tube there was a strong odor of dimethylamine. The contents were poured into 20 ml. of cold distilled water and the tube was washed out with 10 ml. of cold distilled water in portions. The mixture (two phases) was extracted with ethyl ether and the combined extracts (ca. 100 ml. volume) were dried over anhydrous sodium sulfate. After removing the ether, the material remaining was distilled; 0.27 g. of distillate was collected. The residue was viscous and quite large in amount. Vapor-liquid partitioning through a paraffin column at 100° gave the following:

7% of unknown material having an amine odor. The infrared spectrum showed weak hydroxyl absorption and there was no absorption at 910 cm^{-1}, characteristic of a vinyl group ($-CH=CH_2$). Perhaps the product was the result of addition of dimethylamine to the double bond of 1-hydroxy-2,4-pentadiene.

46% of 1-hydroxy-2,4-pentadiene, (LIII). The infrared spectrum showed strong hydroxyl absorption (3500 cm^{-1}) and strong absorption at 910 cm^{-1}, typical of a vinyl group, as well as a weak absorption at 1820 cm^{-1}, typical of a conjugated diolefin (see I.R. spectrum #XII, p. 186

20% of 2-pentenal. The infrared spectrum had a strong absorption at 1690 cm^{-1}, typical of an α,β-unsaturated aldehyde (see I.R. spectrum #XI, p. 185.

1% of unknown material.

5% of starting material, 1-dimethylamino-2,4-pentadiene. The infrared spectrum was identical with that of starting material, except for stronger absorption in the 950-1000 cm^{-1} region.

20% of 1-dimethylamino-1,3-pentadiene. The infrared and ultraviolet spectra were identical with those of material isolated from the Hofmann degradation of (XV).

Treatment of (XXV) with iodine. 1-Dimethylamino-2,4-pentadiene (2.0 g.) was mixed with 0.014 g. of iodine in a 50 ml. flask, equipped with a condenser having a calcium chloride drying tube. As the amine was added to the iodine, there was fuming and the iodine became a viscous oil. A trace of 1,3,5-trinitrobenzene was added and the mixture was stirred with a magnetic stirrer in a bath at 55° for 3 days. On distillation of the material, 0.87 g. (B.P. 38.5-39.0°/34 mm.) was collected. The refractive index ($n_D^{25°}$ = 1.4615), infrared spectrum and ultraviolet spectrum showed no significant differences from those of the starting material.

cis-Piperylene. This was obtained from technical piperylene by the method of Frank, Emmick and Johnson (32). Into a 500 ml., 3-necked flask, equipped with a reflux condenser, stirrer and dropping funnel were added 122.5 g. (1.25 moles) of maleic anhydride (Matheson Coleman and Bell) and 1.5 g. of picric acid (General Chemical Co.). The mixture was heated in an oil bath at 60° to melt the maleic anhydride. While stirring, 136 g. (2.00 moles) of technical piperylene were added from the dropping funnel at such a rate that the mixture was refluxed gently. After addition was completed, the mixture was refluxed for two hours. The unreacted piperylene was distilled from the solid. It was again refluxed for one hour with 13 g. of maleic anhydride in the presence of a trace of 1,3,5-trinitrobenzene. The piperylene was removed by distillation and then redistilled through a 3-foot precision column. The product had the refractive index, $n_D^{25°}$ = 1.4362. (The refractive index,

$n_D^{25°}$, of the technical piperylene distilled through the 3-foot column was 1.4310.) No study was made of the amount of trans-piperylene in the commercial piperylene. The infrared spectrum of the cis-piperylene showed characteristic absorption at 773 cm^{-1} and 955 cm^{-1}.

The N.M.R. spectrum of 1-dimethylamino-2,4-pentadiene, (XXV), was taken and compared with the N.M.R. spectrum of the cis-piperylene. The two spectra were identical in the vinyl (-CH=CHCH=CH$_2$) region (see N.M.R. spectrum #I, p. 172 and N.M.R. spectrum #II, p. 173).

1-Dimethylamino-1,3-pentadiene, (XXVIII). This amine was studied as it was taken from the fractionating column, without further purification. Fraction 6 (Table VI, p.119) weighed 14.3 g. and boiled constantly at 79.3°/43.3 mm. It was 1-dimethylamino-1,3-pentadiene, (XXVIII). The amine had the highest refractive index of all of the isomers ($n_D^{25°}$ = 1.5223).

U.V. spectrum: Solvent	Methanol	n-Hexane
$\lambda_{max.}$	271 mμ	269 mμ
$\epsilon_{max.}$	18,230	22,700

I.R. spectrum in carbon tetrachloride -- see spectrum #XIII, p. 187.

Analysis: Calculated for $C_7H_{13}N$: C, 75.60%; H, 11.79%. Found: C, 75.64%; H, 11.85%.

Attempts to prepare a picrate of (XXVIII) resulted in failure. By adding less than the theoretical amount of ethereal picric acid solution to an ether solution of the amine and decanting off the mother liquor, a yellow precipitate was obtained which melted below 60°. It rapidly turned to a black tar.

On treatment of the amine in methanol with an excess of methyl iodide, a white solid was obtained. Upon recrystallizing from hot ethanol containing a small amount of water, it formed feather-like needles. The needles did not melt up to 285°. Analysis showed the substance to be not a methiodide of 1-dimethylamino-1,3-pentadiene, but most likely to be impure tetramethylammonium iodide.

1-Dimethylamino-1,3-pentadiene distilled as a clear liquid with a slight yellow tinge. After several weeks' standing in a desiccator in the dark, it turned red, but there were little, if any, tars. In carbon tetrachloride (Matheson Coleman and Bell, spectral grade), its solution turned cloudy very shortly and within 1-2 hours a solid had formed.

Hydrogenation of 1-dimethylamino-1,3-pentadiene, (XXVIII). The amine (2.0 g.) was dissolved in 60 ml. of methanol (Baker and Adamson, absolute, refluxed over magnesium turnings and distilled) and the solution was put into a 500 ml. citrate bottle. To this was added 0.2 g. of Adams' platinic oxide. The mixture was hydrogenated at room temperature and two atmospheres of hydrogen pressure. The theoretical amount of hydrogen was taken up in a few minutes. The methanol solution was treated with aqueous hydrochloric acid. After filtration from the catalyst and evaporation on a steam bath, a solid residue was obtained. This residue was taken up in aqueous potassium hydroxide solution. On extracting the organic layer with ethyl ether, drying with anhydrous sodium sulfate and removing the ether by distilling on a steam bath at atmospheric pressure, 0.83 g. of an amine boiling between 43-44°/54 mm. was collected ($n_D^{25°}$ = 1.4034).

Picrate: M.P. 99-100° (from ethanol-isopropyl ether).

Methiodide: M.P. 223-224° (from ethanol-isopropyl ether).

I.R. spectrum in carbon tetrachloride -- see spectrum #IV, p. 178.

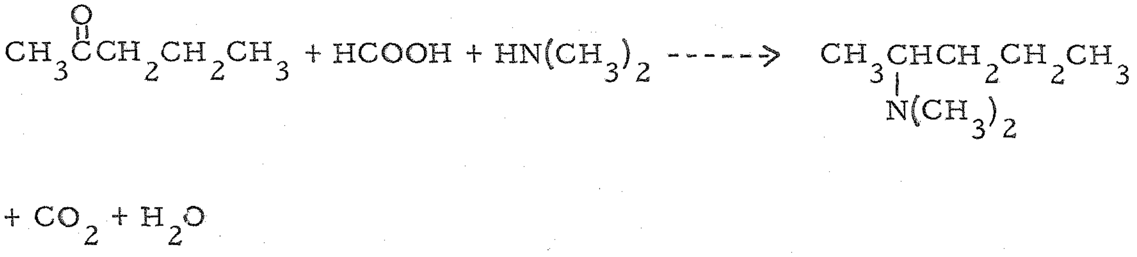
1-Dimethylaminopentane, (XXXII). n-Amyl amine, (XXXIII), (17.2 g. (0.2 mole) from Ames Laboratories) was treated with 154 g. of 36-38% formaldehyde solution(containing 24.0 g. (0.8 mole) of formaldehyde) in a 500 ml. flask, cooled in an ice bath. The flask was connected to a reflux condenser and 41 g. of 90% formic acid solution (containing 36.8 g. (0.8 mole) of formic acid) were added through the condenser. The mixture was refluxed for three hours, gas evolution having ceased. After treatment of the mixture with solid potassium hydroxide, extraction of the organic base with ethyl ether, drying of the ether extracts with anhydrous sodium sulfate and finally removal of the ether, 11.7 g. (50% yield) of material boiling between 50-52°/68.6 mm. were obtained ($n_D^{25°}$ = 1.4045).

Picrate: M.P. 99-100°

Methiodide: M.P. 223-224°

The picrate and the methiodide did not depress the melting points of the corresponding derivatives obtained from the hydrogenated 1-dimethylamino-1,3-pentadiene, (XXVIII). The infrared spectrum of this material in carbon tetrachloride was identical with that of the hydrogenated (XXVIII).

2-Dimethylaminopentane, (XXXIV). Several procedures for the preparation of this compound were tried, but only one was successful. Procedure I:

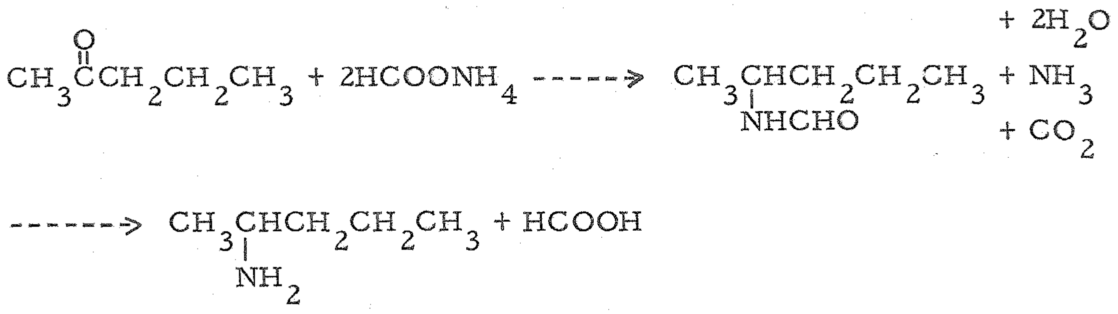


$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3 + HCOOH + HN(CH_3)_2 \dashrightarrow CH_3\underset{N(CH_3)_2}{\underset{|}{C}}HCH_2CH_2CH_3 + CO_2 + H_2O$$

This type of reaction, under the general name of the Leuckart reaction, is discussed in "Organic Reactions" by Moore (71). Primary amines can be obtained in good yields from many aliphatic ketones and ammonia + formic acid (or their equivalent), but secondary and tertiary amines have been reported only with more reactive ketones (phenylacetone, e.g.) and a primary or secondary amine, respectively, and formic acid.

In a single run, 720 g. of 25% aqueous dimethylamine solution (Matheson Coleman and Bell, containing 180 g. (4.0 moles) of dimethylamine) were added slowly to a cooled solution of 205 g. of 90% formic acid solution (containing 184 g. (4.0 moles) of formic acid) in 200 ml. of water. Using a descending West condenser, the mixture was distilled until a separate phase appeared in the pot. The West condenser was replaced by a total condensation-partial take-off head and 86 g. (1.0 mole) of methyl n-propyl ketone (Matheson Coleman and Bell, reagent) and 205 g. of 90% formic acid solution were added. The mixture was refluxed for 4 days, during which time distillate was taken off from time to time and the top layer was added back to the pot. The maximum head temperature was 145° (pot temperature = 160°). The nature of the gas which evolved slowly and which was collected in an inverted flask by water displacement was not examined. The residue in the pot was made basic with potassium hydroxide solution. The basic solution was extracted with ethyl ether. After extracting the ethyl ether solution with dilute hydrochloric acid, the ether extracts were dried over anhydrous sodium sulfate. The acidic solution was made basic with potassium hydroxide and then extracted with ethyl ether. The ether extracts were dried over anhydrous sodium sulfate. From neither of the ethyl ether extracts was any material recovered. An identical work-up of the distillate, which had been taken off during the refluxing, produced no basic material, but produced 58.3 g. of neutral material (67.8% recovery calculated on the basis of methyl n-propyl ketone).

Procedure II:



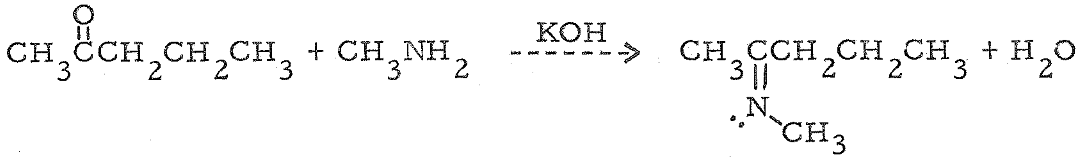
$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3 + 2HCOONH_4} \dashrightarrow \mathrm{CH_3\underset{NHCHO}{\underset{|}{C}}HCH_2CH_2CH_3 + 2H_2O + NH_3 + CO_2}$$

$$\dashrightarrow \mathrm{CH_3\underset{NH_2}{\underset{|}{C}}HCH_2CH_2CH_3 + HCOOH}$$

This transformation has apparently been carried out (see footnote 10, reference (71)), but under the experimental conditions of a single run reported here, the desired product was not obtained.

Methyl n-propyl ketone (100 g.; 1.16 moles) and 200 g. (3.18 moles) of ammonium formate (Baker and Adamson, reagent) were mixed in a 500 ml., 3-necked flask, equipped with thermometer dipping into the pot, dropping funnel and Claisen head for distillation. The solid was insoluble in the cold liquid. After 12 hours of heating only 18 liters of gas had evolved. The distillate had two phases. The top layer (ketone) was added back to the pot dropwise while the pot temperature was in the range 175-190°. Only three liters of gas evolved as material (two phases) distilled over. The top layer of the distillate weighed 75 g. (wet). The dark residue in the pot was treated with 200 ml. of water in a separatory funnel. The mixture was extracted with two 60 ml. portions of benzene. The benzene extracts were added back to the pot with 50 ml. of concentrated hydrochloric acid. The mixture was distilled until all the benzene had been removed. On treatment of the residue in the pot with aqueous potassium hydroxide solution, a dark colored top layer separated. This layer was extracted with ethyl ether, the extracts being dried over anhydrous sodium sulfate. A small portion of the ether extract on treatment with ethereal picric acid solution gave no precipitate. It was concluded that no 2-aminopentane was formed, most of the starting ketone being recovered.

Procedure III:

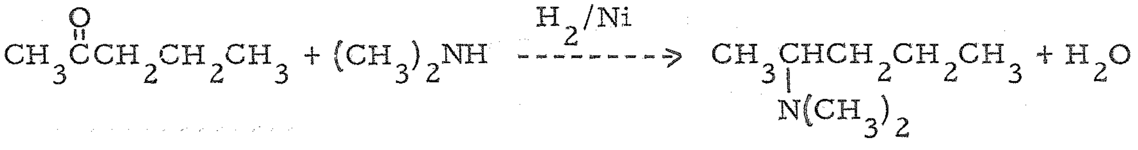


$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3 + CH_3NH_2 \xrightarrow{KOH} CH_3\underset{\underset{\ddot{N}\diagdown CH_3}{\|}}{C}CH_2CH_2CH_3 + H_2O$$

The procedure used was that of Bruce and Blomberg (72).

Methylamine from a cylinder (Matheson) was passed through a soda lime-potassium hydroxide drying tower into a 500 ml., 3-necked flask having a potassium hydroxide drying tube. The flask was cooled in a salt-ice bath (the temperature being maintained between -10° and -2°) and contained 86 g. (1.0 mole) of methyl n-propyl ketone and 112 g. (2.0 moles) of solid potassium hydroxide. The increase in weight due to the methylamine was 83.2 g. (2.68 moles). The flask was stoppered and allowed to stand at room temperature. The following day the flask had lost 70.6 g. in weight. More methylamine was bubbled into the flask (increase in weight = 75.5 g.). The flask was allowed to stand in an ice bath at a temperature near 0°. Two days later the decrease in weight was 34.5 g. After two more days the bath had warmed up to 15° and the loss was 65.5 g. The flask was allowed to stand at room temperature, whereby only 16.6 g. of the methylamine remained on the following day. The liquid was filtered from the potassium hydroxide and the orange filtrate was distilled through a 1-foot Vigreaux column under reduced pressure. A total condensation-partial take-off head was used to separate fractions. The first two fractions weighed 44.2 g. (B.P. range 35-50°/80 mm.; mostly 43-50°) and were mainly starting ketone. The fourth fraction weighed 5.0 g. and was high boiling material. The third fraction weighed 5.3 g. (B.P. range 52-65°/80 mm.) and had a strong acetamide-like odor. This material was treated in benzene with an excess of methyl iodide. A flocculent precipitate formed after a short time. The solid melted over a wide range and was insoluble in hot ethyl acetate, 1,4-dioxane, n-hexane and glacial acetic acid. It dissolved somewhat in cold dimethylformamide (ca. 0.2 g. in 5 ml.). It decomposed very rapidly on standing; a ketonic odor could be detected after a short time.* The imine (1.0 g. (10.1 millimoles), crude) was dissolved in 50 ml. of dimethylformamide (Matheson) in a citrate bottle and 3.0 g. (21.1 millimoles) of methyl iodide were added. Adams' platinic oxide (0.1 g.) was added and the mixture was hydrogenated. No observable up-take in hydrogen was noted. The hydrogenation was stopped and the mixture was filtered. The greenish colored filtrate was treated with potassium hydroxide solution. There was a heat effect and a powerful amine odor. After cooling in an ice bath, the mixture was extracted with 125 ml. of ether. Treatment of a portion of the ether solution with ethereal picric acid solution gave an abundant precipitate (M.P. wet at 150° -- main melted between157-159°; undoubtedly the picrate of dimethylamine). The aqueous mother liquor was extracted with another portion of ether and the extracts were combined and dried with anhydrous sodium sulfate. After removal of the ether, 5.2 g. of yellow residue having no amine odor was left. It did not form a precipitate on treatment with ethereal picric acid solution.

Procedure IV:



$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3 + (CH_3)_2NH \xrightarrow{H_2/Ni} CH_3\underset{N(CH_3)_2}{\underset{|}{C}}HCH_2CH_2CH_3 + H_2O$$

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*H. Decker and P. Becker (73) caution that the quaternary salts of imines decompose easily in air and light and decompose at once with water and alcohol.

Using a platinum catalyst and 3 atmospheres of hydrogen pressure, Skita and Keil (74) were able to convert isovaleraldehyde to the corresponding dimethylamino- compound.

Methyl n-propyl ketone (17.2 g. (0.2 mole) from Eastman, technical), 50 ml. of 25% aqueous dimethylamine solution and 9 ml. of concentrated hydrochloric acid were mixed in a citrate bottle. The resulting mixture (two phases) was basic (pH ca. 8). Seven small spatulafuls of nickel catalyst* were added and 10 ml. of water were used to wash it into the bottle. The mixture was hydrogenated at 2 atmospheres hydrogen pressure and room temperature. After 24 hours' hydrogenation, the theoretical amount of hydrogen had been taken up (one mole per mole) and the hydrogenation was stopped. The mixture was filtered to remove the catalyst. The filtrate was made acidic with dilute sulfuric acid and steam distilled to remove neutral material. After making basic with potassium hydroxide solution, the solution was steam distilled again. On treatment of the distillate with potassium hydroxide, there was no persistent second layer (some dimethylamine was still present and quickly boiled off).

Procedure V:

$$CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2CH_3 \xrightarrow{NH_2OH} CH_3\overset{\overset{NOH}{\|}}{C}CH_2CH_2CH_3 \xrightarrow{H_2/Ni}$$

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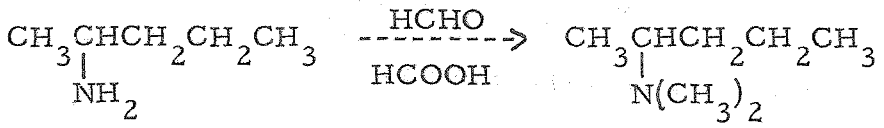
*The nickel catalyst was prepared according to the directions given in "Organic Syntheses" (75). The nickel-aluminum alloy was obtained from the Gilman Paint and Varnish Co., Chattanooga, Tenn.



$$CH_3\underset{\displaystyle NH_2}{CH}CH_2CH_2CH_3 \xrightarrow[HCOOH]{HCHO} CH_3\underset{\displaystyle N(CH_3)_2}{CH}CH_2CH_2CH_3$$

The oxime was prepared according to the procedure of Pearson and Bruton (76).

A cold aqueous solution of sodium hydroxide (48.0 g.; 1.20 moles) in 144 ml. of water was added slowly to a cold solution of 55.6 g. (1.60 moles) of hydroxylamine hydrochloride (Matheson Coleman and Bell) in 240 ml. of water. The resulting solution was basic, but the pH was adjusted to neutral with dilute hydrochloric acid. Methyl n-propyl ketone (68.8 g. (0.8 mole) from Eastman, technical) were added and the solution was refluxed for two hours. Ethanol was added so that a homogeneous solution was obtained at the boiling point. After distilling the mixture (two phases) on a steam bath with suction, the residue was extracted with ethyl ether. The extracts were dried with anhydrous sodium sulfate and then the ether was distilled off. On distillation of the residue through a 1-foot heated Vigreaux column, 46.3 g. (57% yield) of material boiling in the range 87-88°/32 mm. were collected.

2-Oximinopentane (15.1 g.; 0.15 mole) was dissolved in 125 ml. of 95% ethanol and seven small spatulafuls of nickel catalyst* were added. The mixture was hydrogenated under two atmospheres hydrogen pressure and room temperature. After the theoretical amount of hydrogen had

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*Low pressure hydrogenation of oximes over nickel catalyst has been reported by Iffland and Yen (77). It was found in the present work that in a single run, platinum catalyst gave unsatisfactory results.

been taken up, the mixture was filtered to remove catalyst and the filtrate (having a strong amine odor) was made acidic with 20% sulfuric acid solution. The mixture was steam distilled until 400 ml. of distillate had been collected. On treatment of the residue in the pot with sodium hydroxide a second top layer separated. This was removed by steam distillation. The distillate was salted out with potassium hydroxide and the amine was extracted with ethyl ether. After drying the extracts over anhydrous sodium sulfate, the ether was removed. The residue was distilled to give 4.57 g. (35% yield) of 2-aminopentane boiling in the range 69-70° ($n_D^{25°}$ = 1.4010).

The 2-aminopentane gave a picrate melting at 125-126° and reacted with phenylisothiocyanate to give a thiourea melting between 64-66° (not recrystallized).

While cooling 4.5 g. (0.052 mole) of 2-aminopentane, contained in a 100 ml. round-bottom flask, in an ice bath, 16.8 g. of 36-38% formaldehyde solution (containing 6.21 g. (0.207 mole) of formaldehyde) were added slowly. The flask was connected to a reflux condenser and 10.6 g. of 90% formic acid solution (containing 9.5 g. (0.207 mole) of formic acid) were added slowly through the condenser. After two hours of refluxing, gas evolution had ceased. The reaction mixture was diluted with an equal volume of water and the amine was salted out with solid potassium hydroxide. The amine layer was separated mechanically from the aqueous layer in a separatory funnel. The amine was then taken up in ethyl ether and the solution was dried over anhydrous sodium sulfate. After taking off the ether, the amine was distilled; 1.58 g. was collected boiling in the range 38-40°/48.5 mm. ($n_D^{25°}$ = 1.4078). It was 2-dimethylaminopentane.*

Picrate: M.P. 122-123° (from ethanol). This picrate depressed the melting point of both picric acid and the picrate of 1-dimethylaminopentane (from hydrogenation of 1-dimethylamino-1,3-pentadiene).

Analysis: Calculated for $C_{13}H_{20}N_4O_7$: C, 45.34%; H, 5.85%; N, 16.27%. Found: C, 45.44%; H, 6.00%; N, 16.18%.

Methiodide: M.P. 179-180° (from ethanol-isopropyl ether). This methiodide depressed the melting point of the methiodide of 1-dimethylaminopentane (from hydrogenation of 1-dimethylamino-1,3-pentadiene).

Analysis: (by Truesdail Laboratories, Los Angeles) Calculated for $C_8H_{20}NI$: C, 37.36%; H, 7.84%; N, 5.45%. Found: C, 37.21%;
37.40%
H, 7.60% N, 5.59%
7.76% 5.33%

The infrared spectrum of 2-dimethylaminopentane was quite different from that of 1-dimethylaminopentane (see I.R. spectrum #III, p. 177 and I.R. spectrum #IV, p. 178). 2-Dimethylaminopentane could not be separated from 1-dimethylaminopentane on a paraffin V.P.C. column at 100°.

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*A compound assumed to have the structure of 2-dimethylaminopentane has been reported at least once in the literature (78). It gave a picrate melting between 208-210°. Comparison of its method of preparation (reaction of n-propyl magnesium iodide with α-dimethylaminopropionitrile and work-up with sulfuric acid) with the more straightforward method used in this work, leads to the conclusion that their assignment of structure is erroneous.

2-Pentenal, (LIV). 1-Dimethylamino-1,3-pentadiene (1 ml.) was put into a 50 ml. flask with 15 ml. of water. A solution of 1 ml. of concentrated sulfuric acid in 5 ml. of water was added. The acid solution was steam distilled until 20-25 ml. of distillate had been collected. (A previous attempt to isolate the aldehyde resulted in polymerization of the small amount of material on distillation.) To the distillate was added 40 ml. of ethanol, followed by a freshly prepared 2,4-dinitrophenylhydrazine solution* (prepared by treating 0.8 g. of 2,4-dinitrophenylhydrazine with 4 ml. of concentrated sulfuric acid, followed by dropwise addition of 6 ml. of water and then 20 ml. of 95% ethanol)). After standing overnight, the orange-red precipitate was removed by filtration and crystallized from ethanol-chloroform mixture. Because the melting point was lower than that reported in the literature,** the red needles were chromatographed on alumina, eluting with benzene. This very effectively removed unreacted 2,4-dinitrophenylhydrazine, which remained immobile at the top of the column. After recrystallization from ethanol of the residue, from the benzene fractions, fluffy orange needles melting at 159-160° were obtained.

U.V. spectrum: Solvent: dichloromethane (Matheson Coleman and Bell)

$\lambda_{max.} = 374$ mμ; $\epsilon_{max.} = 40,500$.

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*The method described by Shriner, Fuson and Curtin (79) was used.

**Royals and Brannock (80) reported a melting point of 159-159.5° (from ethanol-chloroform).

Attempts to prepare 2-pentenal; tiglic aldehyde, (LVII), α-methyl-2-pentenal, (LVIII), and crotonaldehyde, (LVIX). Into a 500 ml., 3-necked flask, equipped with mechanical stirrer, reflux condenser, thermometer and dropping funnel were placed 30 ml. of anhydrous ethyl ether. Boron trifluoride was bubbled into the ether while cooling the flask in an ice bath. The amount of boron trifluoride was unknown, but it was bubbled into the ether at a vigorous rate for 5 minutes. To the ether solution was added from the dropping funnel 90 g. (1.5 moles) of propionaldehyde (Matheson Coleman and Bell). The latter was added rapidly during the course of 5-10 minutes. The temperature rose to 80° during this time. Following this, a heating mantle was connected to the flask and 36.7 g. (0.51 mole) of ethyl vinyl ether (distilled, Carbide and Carbon) were added dropwise from the funnel during the course of 15 minutes. The temperature rose to 47°. Stirring was continued for an additional two hours, while heating; the maximum temperature was 55°. To the pale yellow solution was added a solution of 10 g. of sodium acetate in 90 ml. of water. The mixture (two phases) was stirred for 10 minutes and the aqueous layer was separated and set aside. The upper organic layer was added to 100 ml. of dilute sulfuric acid (contained 5 ml. of concentrated sulfuric acid in 95 ml. of water). The mixture was steam distilled. After 400 ml. of distillate had been collected, the distillation was stopped and the top layer was extracted with ethyl ether. The extracts were combined and dried with anhydrous sodium sulfate.

Removal of the ether and distillation of the residue gave 11.1 g. of material boiling in the range 52-58°/50 mm. Vapor phase chromatography of the mixture on a paraffin column at 102° showed that it was a mixture consisting of two components of approximately equal amounts. The mixture was fractionated through a 3-foot precision column at 52.4 mm. Vapor phase chromatography studies of the mixture showed that one fraction weighing 1.65 g. (boiling range 51-53°/52.4 mm.) contained 90% of one component and 10% of the other and that another fraction weighing 3.64 g. (boiling range 56-58°/52.4 mm.) contained 20% of the first component and 80% of the second. Preparations of 2,4-dinitrophenylhydrazones of these two fractions in the usual way, gave from the lower boiling component, after chromatographing on alumina, small red crystals melting between 210-212° (from ethyl acetate). The ultraviolet spectrum had a $\lambda_{max.}$ = 377 mμ and an $\epsilon_{max.}$ = 29,000. From the higher boiling component, after chromatographing on alumina, red platelets melting at 161-162° (from ethanol) were obtained. The ultraviolet spectrum had a $\lambda_{max.}$ = 377 mμ and an $\epsilon_{max.}$ = 26,500. The 210-212° material did not depress the melting point of tiglic aldehyde DNPH (tiglic aldehyde obtained from Eastman). The 161-162° material did not depress the melting point of authentic α-methyl-2-pentenal DNPH.

In another preparation, 30 ml. of anhydrous ethyl ether were cooled in an ice bath and boron trifluoride was bubbled through it for 5 minutes at a vigorous rate. This solution was put into a dropping funnel connected to a 500 ml., 3-necked flask, equipped with another dropping funnel, a stirrer, thermometer and reflux condenser. Into the other dropping funnel was placed a mixture of 90 g. (1.5 moles) of propionaldehyde and 36.7 g. (0.51 mole) of ethyl vinyl ether. While stirring, the two solutions were added simultaneously to the flask. A vigorous reaction took place and initially a black liquid was noted in the pot. As the addition proceeded, the temperature rose to ca. 50°. The boron trifluoride solution could be observed turning dark as it dropped into the pot. The addition required 20 minutes. A heating mantle was connected to the flask and the dark colored reaction mixture was heated while stirring. After an hour the temperature had risen to 65° and heating was stopped. Stirring was continued for an additional one and a half hours. After standing overnight, the dark colored solution was dropped into a solution of 100 ml. of dilute sulfuric acid while steam distilling. The 300 ml. of distillate (two phases) was extracted with three portions of ethyl ether and the combined extracts (ca. 600 ml. volume) were dried with anhydrous sodium sulfate. After removing the ether and distilling the residue through a short column, 23.4 g. of material were obtained boiling in the range 60-69°/65.5 mm. Vapor phase chromatography showed the mixture to consist of crotonaldehyde (1%), tiglic aldehyde (35%) and α-methyl-2-pentenal (64%).

In a third preparation, 11 g. (0.25 mole) of acetaldehyde (Eastman) and 14.5 g. (0.25 mole) of propionaldehyde were mixed in a combustion tube. A solution of 12.3 g. of potassium carbonate in 32 ml. of water was added and the tube was sealed. The tube was heated in an oven at 101° for 24 hours. Though the top of the tube blew out sometime after 12 hours of heating, very little material was lost (as observed by the final volume of material). The mixture (two phases) was poured from the tube and the organic layer was extracted with ethyl ether. The extracts were dried with anhydrous sodium sulfate. After removal of the ether, distillation of the residue gave 3.5 g. of material boiling in the range 45-50°/59.5 mm. Vapor phase chromatography showed the mixture to consist of tiglic aldehyde (67%) and α-methyl-2-pentenal (32%). A very small amount (ca. 1%) of a component had the same retention time as crotonaldehyde. Chromatography of the 2,4-dinitrophenylhydrazone mixture on alumina yielded no 2-pentenal DNPH.

Dilute acid treatment of 1-dimethylamino-1,3-pentadiene, (XXVIII). 1-Dimethylamino-1,3-pentadiene (0.2 g.) was treated with 1 ml. of dilute sulfuric acid at room temperature (there was a slight heat effect). At first the amine went into solution and then a top layer of oil appeared. The oil was extracted with ethyl ether. Evaporation of the ether and vapor phase chromatography of the residue on a paraffin column at 85° gave two components. The component in largest amount (greater than 75%) had a strong absorption at 1730 cm^{-1} in the infrared. It was undoubtedly 3-pentenal. Because the second component was not well separated from the first, the infrared spectrum showed a mixture to be present. It had absorption at 1690 cm^{-1} and was undoubtedly 2-pentenal. Gouge (81) reported a difference of 17° in the boiling points of

3-pentenal and 2-pentenal. However, since the method of preparation and the infrared spectra were almost unequivocal evidence for the structures, this identification presented no problem.

Reaction of (XXVIII) with N-phenylmaleimide. 1-Dimethylamino-1,3-pentadiene (0.2 g.; 1.8 millimoles) was mixed with 0.31 g. (1.8 millimoles) of N-phenylmaleimide at room temperature. On stirring the mixture there was partial solidification. The mixture was washed with cold n-hexane and then dissolved in a small amount of benzene. The benzene mixture was heated and a small amount of insoluble was removed. The cooled benzene solution was treated with n-hexane which precipitated a solid. Two recrystallizations from this mixed solvent gave large white needles melting at 104-105°.

Analysis: Calculated for $C_{17}H_{20}N_2O_2$: C, 71.80%; H, 7.09%; N, 9.85%. Found: C, 71.65%; H, 7.08%; N, 9.91%.

The pure adduct (0.22 g.) was heated with water (10 ml.) for two hours at 70° in an oil bath. The crystalline solid dispersed itself as a flocculent white solid. There was a strong odor of dimethylamine. The mixture was treated with benzene, whereupon the solid went into the benzene and the mixture (two phases) was distilled with suction to near dryness. A yellow oily residue remained and was taken up in benzene, the extracts were dried with anhydrous sodium sulfate and then poured onto a column of alumina. Elution with benzene-ethanol and recovery of material gave no starting N-phenylmaleimide; the exact nature of the material was not determined. The conclusion was that the dimethylamine came from the adduct and not from a retrograde Diels-Alder.

1-Methylanthraquinone. 1,4-Naphthoquinone (0.20 g. (4.5 millimoles), Eastman, recrystallized) was taken up in 100 ml. of anhydrous ethyl ether (not totally soluble) and the solution was added dropwise to a cooled solution of 0.5 g. (4.5 millimoles) of 1-dimethylamino-1,3-pentadiene in 10 ml. of anhydrous ethyl ether. A transient dark color could be observed during the addition. The resulting solution was dark colored and was allowed to stand at room temperature in a flask equipped with a calcium chloride drying tube. After 4 days, the ether was decanted off from golden brown crystals (probably 1,4-naphthoquinone), which were washed twice with ether. The ether solution was filtered and evaporated in a stream of dry air. A flocculent yellow solid and a black tarry material were left as a residue. On sublimation at 1 mm. pressure from an oil bath maintained at 100°, a fluffy cotton-like solid melting at 167-168° was obtained after crystallization from acetic acid. It did not depress the melting point of an authentic sample of 1-methylanthraquinone.

Hofmann degradation of N,N-dimethyl-α-bromomethylpyrrolidinium bromide, (XV), for V.P.C. studies. N,N-Dimethyl-α-bromomethylpyrrolidinium bromide (50 g.; 0.183 mole) and a solution of 37.5 g. (0.67 mole) of potassium hydroxide in 80 ml. of water were mixed in a copper retort. The mixture was distilled. After the bath temperature had risen to 230°, very little distillate was being collected. The top layer of the distillate was extracted with ethyl ether and the aqueous was treated with solid potassium hydroxide, followed by one more ether extraction. After addition of the aqueous back to the pot and redistillation, followed by work-up, a small amount of amine was obtained. The latter was combined with the previous fraction. After drying the extracts with anhydrous sodium sulfate, the ether was removed by distilling from an oil bath at atmospheric pressure. The residue was distilled from the same pot through a 6-inch Vigreaux column. A free flame was used to break up frothing in the column. After the volatile material had been removed, 12.0 g. (58% yield) of material boiling between 40-80°/50 mm. were collected in a single fraction. (The pressure was reduced to ca. 5 mm. near the end to bring over hold-up, but loss of material from the collector was prevented by cooling in a dry ice bath.) The residue weighed 0.8 g. and the hold-up was not large. The material distilled over colorless, but acquired a yellow color during the distillation. By keeping the mixture in a dry ice bath overnight, no tars formed. Vapor-liquid partitioning through a paraffin column at 100° separated five components (excluding undetermined amounts of solvent and a small amount of an aldehyde (probably 2-pentenal)) from the mixture. Table I (p. 55) shows the pertinent data. The data on the right side of the column headed "% of component calculated from the area" was from this run.

Three of the components were identified by comparison of their retention times with the three isolated amines, 1-dimethylamino-2,4-pentadiene, (XXV), 1-dimethylamino-3-pentyne, (XXVII), and 1-dimethylamino-1,3-pentadiene, (XXVIII). They were also collected from the column and their infrared spectra (and ultraviolet spectra in the case of (XXV) and (XXVIII)) were compared with authentic samples.

A fourth component, 1-dimethylamino-3,4-pentadiene, (XXVI), was identified by collecting it and studying its infrared spectrum (see I.R. spectrum #I, p. 175). It was not isolated in quantities large enough for characterization.

The fifth component (component 1 of Table I, p. 55) was assigned the structure of 1-dimethylamino-4-pentyne, (XXIV). It was present in barely more than a trace amount and no attempt for isolation and characterization of it could be made. That a terminal acetylenic compound was present in the total amine mixture was observed by studying various fractions taken from the 3-foot precision column by infrared spectra. The 3300 cm^{-1} absorption band was strongest in lower boiling fractions (see I.R. spectrum #XV, p. 189; also, see I.R. spectrum #II, p. 176 of the total amine mixture in which the terminal acetylenic compound shows weak absorption).

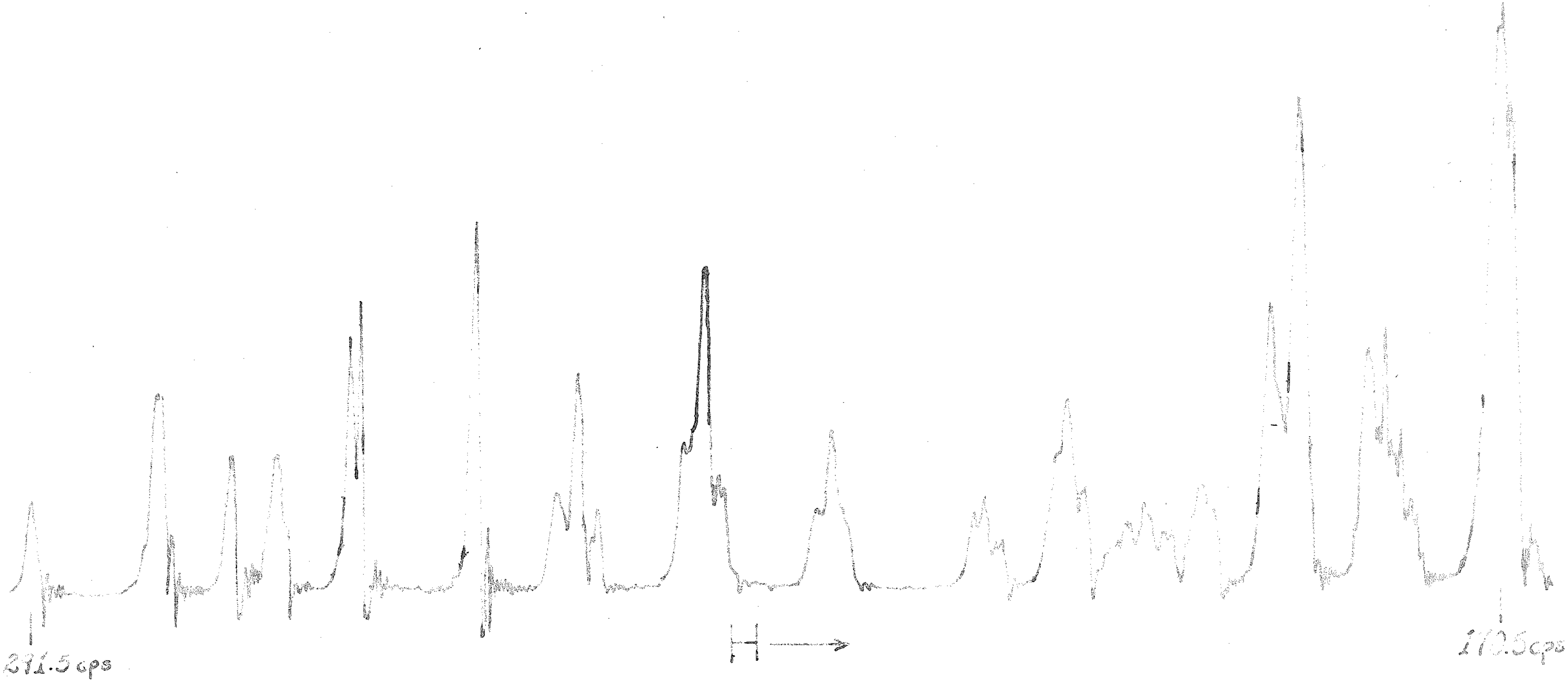
Hydrogenation of the total tertiary amine mixture. The total amine mixture (2.0 g.) was taken up in 60 ml. of methanol and 0.15 g. of Adams' platinic oxide were added. The mixture, contained in a citrate bottle, was hydrogenated. The hydrogenated mixture was treated with 5 ml. of concentrated hydrochloric acid and the acidic solution was filtered to remove the catalyst. The acidic filtrate was evaporated on a steam bath. The residue was treated with potassium hydroxide solution to salt out the amine. The top amine layer was extracted with ethyl ether. After drying the ether extracts over anhydrous sodium sulfate and removing the ether, 0.82 g. of amine was collected on distillation (B.P. 59°/90 mm.).

Picrate: M.P. 99-100°.

Methiodide: M.P. 223-224°.

These derivatives did not depress the melting points of corresponding derivatives of 1-dimethylaminopentane. The infrared spectrum of the amine in carbon tetrachloride was identical with the infrared spectrum of 1-dimethylaminopentane. 2-Dimethylaminopentane could not be separated from 1-dimethylaminopentane on a paraffin V.P.C. column at 100°. Therefore, as a further check on the absence of 2-dimethylaminopentane, the infrared spectrum was studied in the 950-850 cm^{-1} region. The 1-isomer has a doublet at 900 and 935 cm^{-1}, while the 2-isomer has only a singlet at 915 cm^{-1}. The spectrum of a solution of 100 µl. of authentic 1-dimethylaminopentane in 1 ml. of carbon tetrachloride was compared with the spectrum of a mixture of 95 µl. of authentic 1-dimethylaminopentane and 5 µl. of authentic 2-dimethylaminopentane in 1 µl. of carbon tetrachloride; the 2-isomer could be detected. The spectrum of a solution of 100 µl. of the hydrogenated total amine mixture in 1 ml. of carbon tetrachloride showed no presence of the 2-isomer. These results are shown clearly on Figure 2 (p. 59).

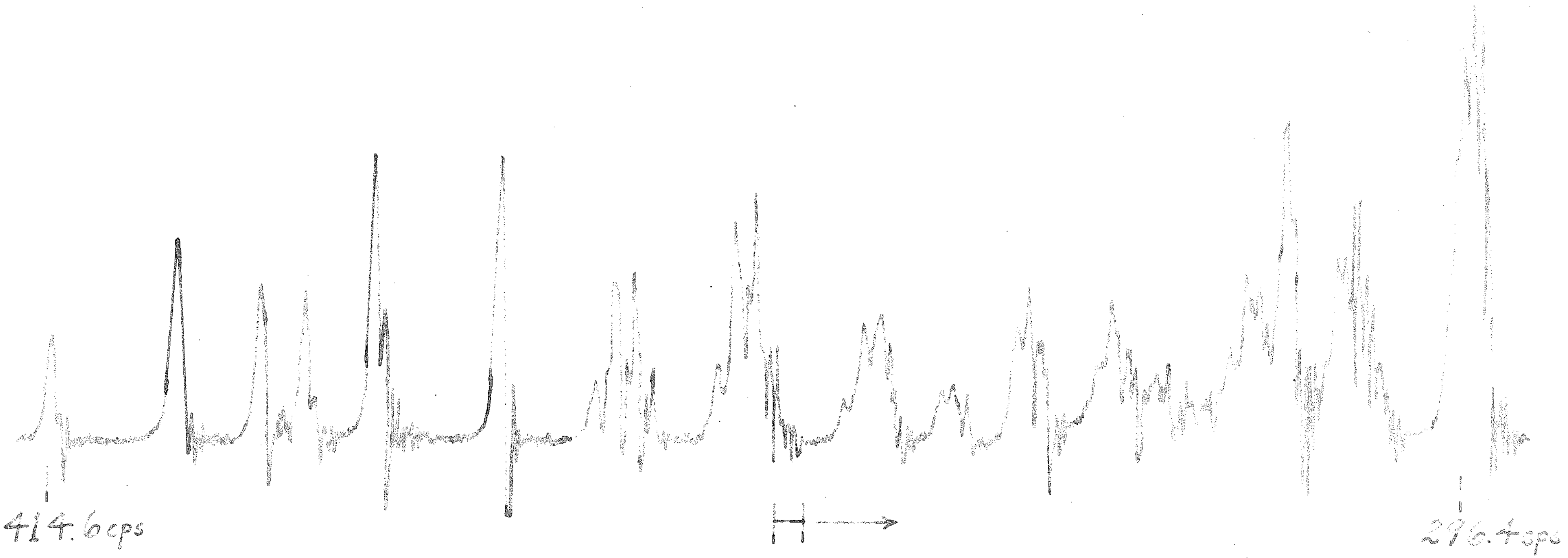
NUCLEAR MAGNETIC RESONANCE SPECTRA



N.M.R. Spectrum No. I

1-Dimethylamino-2,4-pentadiene (diene region)

Varian Associates V-4300 N.M.R. Spectrometer
60 Mc. Frequency
Flux Stabilized Field
Frequencies internally calibrated vs. $-N(CH_3)_2 = 0$

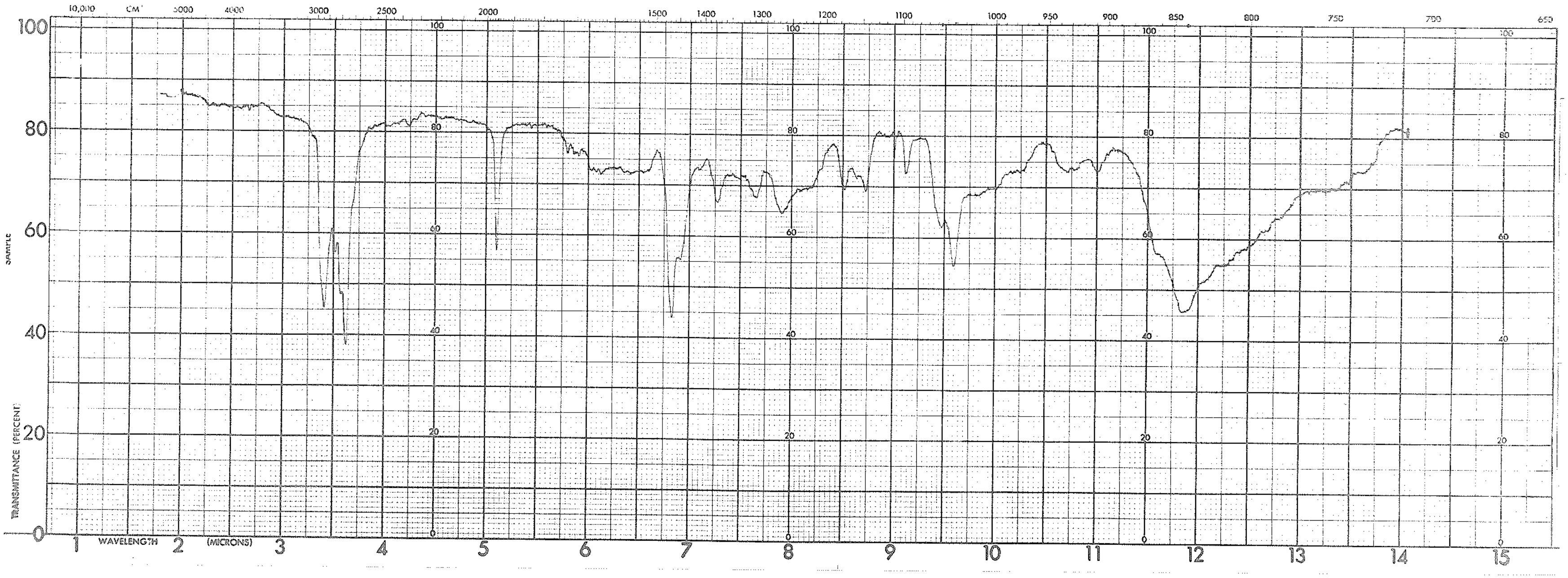


N.M.R. Spectrum No. II

<u>cis</u>-Piperylene (diene region)

Varian Associates V-4300 N.M.R. Spectrometer
60 Mc. Frequency
Flux Stabilized Field
Frequencies vs. Tetramethylsilane (internal standard)

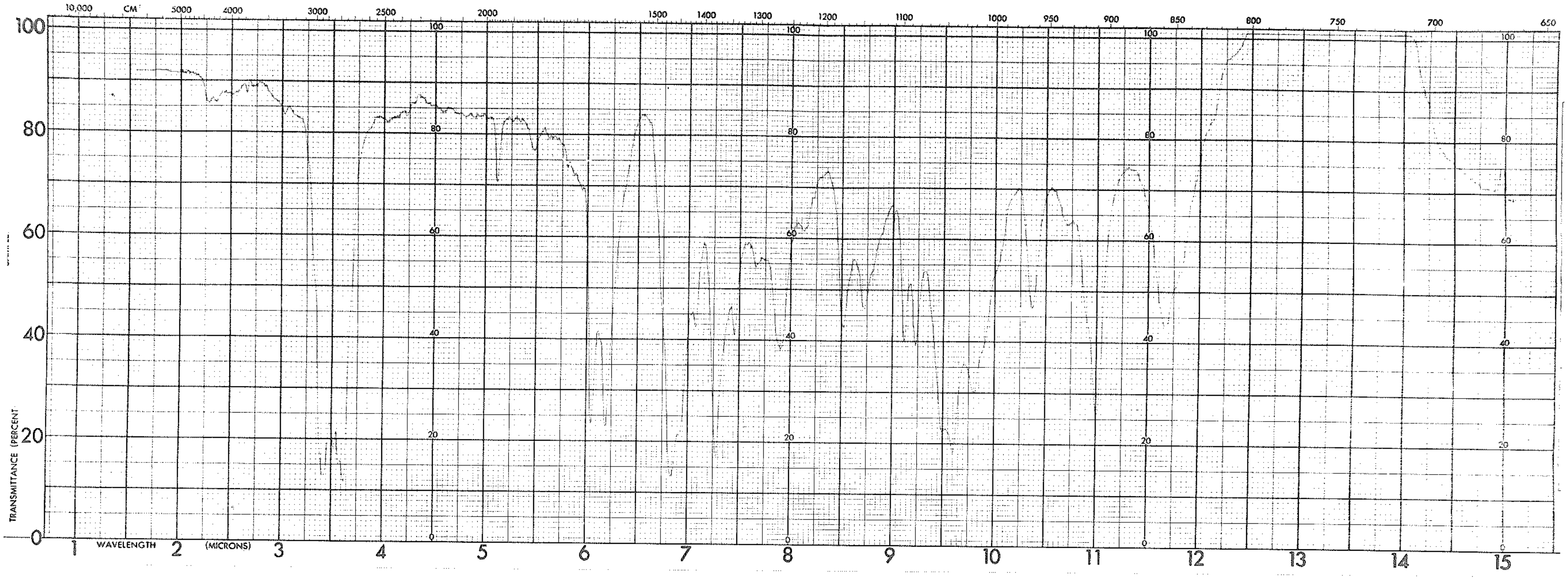
INFRARED SPECTRA



I. R. Spectrum #I

1-Dimethylamino-3, 4-pentadiene

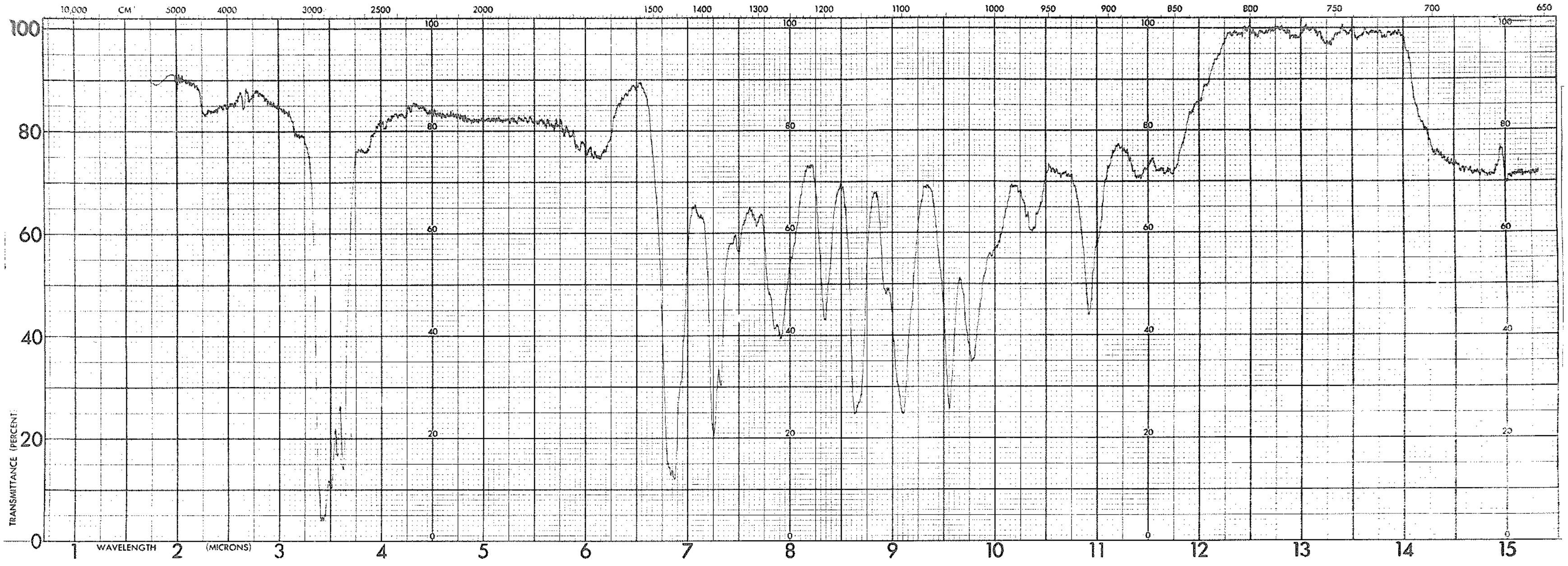
Solvent: carbon tetrachloride
Cell: 1 mm. NaCl prism



I. R. Spectrum #II

Total mixture of $C_7H_{13}N$ amines

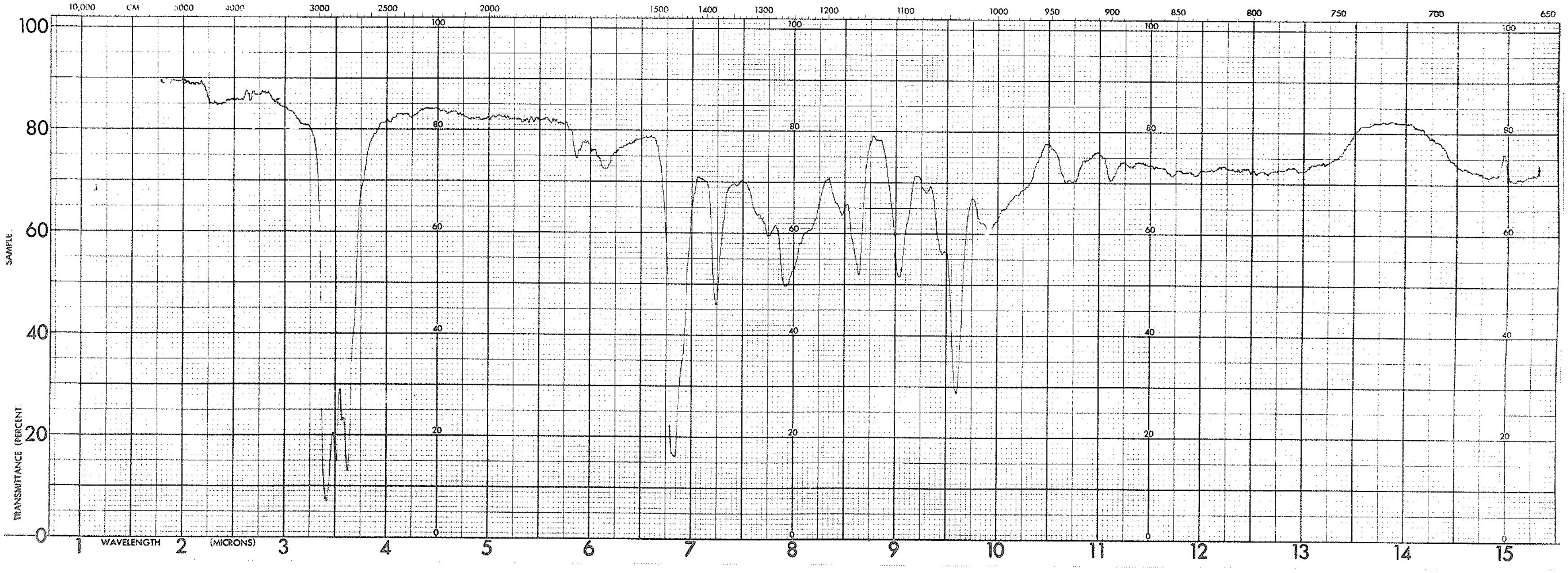
Solvent: carbon tetrachloride
Cell: 1 mm. NaCl prism



I. R. Spectrum #III

2-Dimethylaminopentane

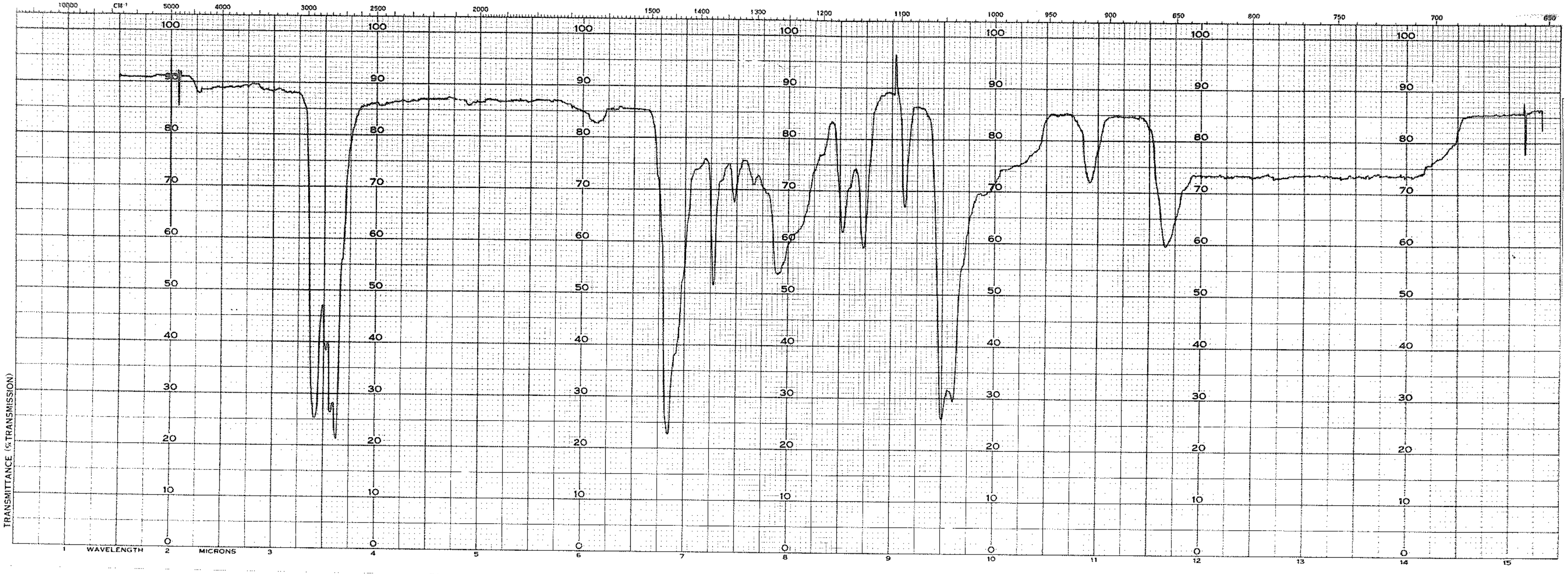
Solvent: carbon tetrachloride
Cell: 1 mm. NaCl prism



I. R. Spectrum #IV

1-Dimethylaminopentane

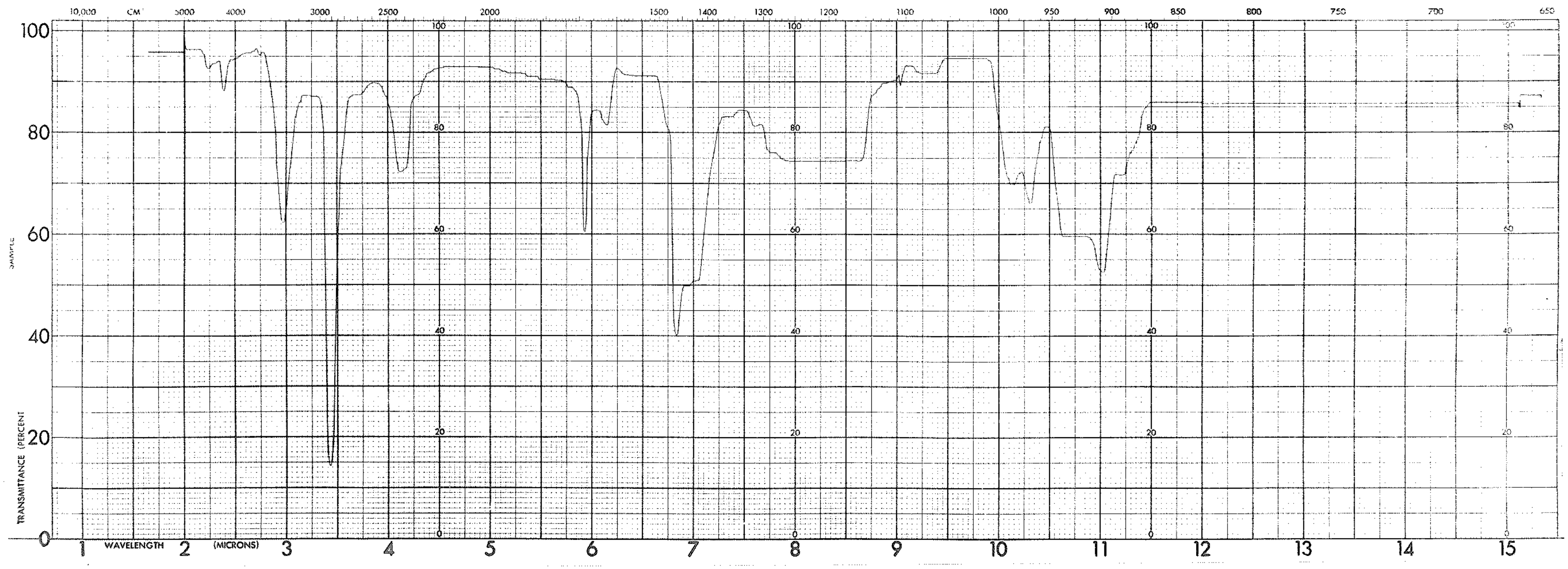
Solvent: carbon tetrachloride
Cell: 1 mm. NaCl prism



I. R. Spectrum #V

1-Dimethylamino-3-pentyne

Solvent: carbon tetrachloride
Cell: 1 mm. NaCl prism



I. R. Spectrum #VI

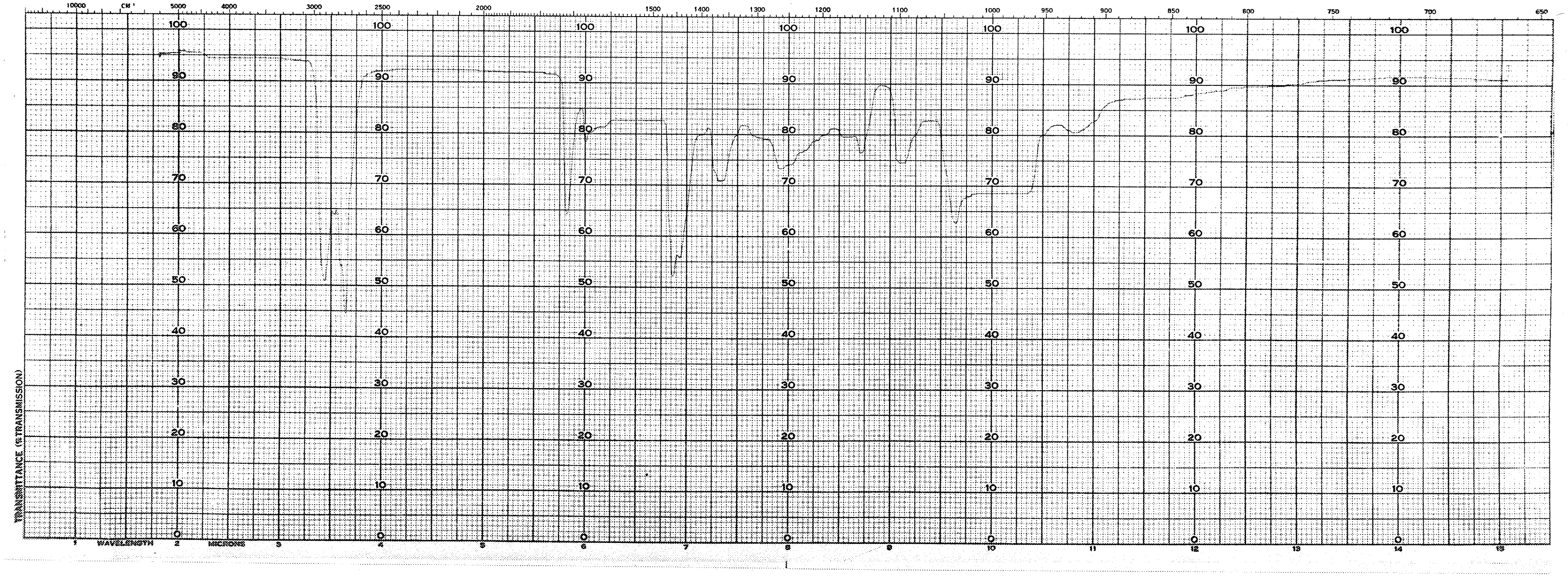
N, N-Dimethyl-α-methylenepyrrolidinium bromide

Solvent: chloroform
Cell: 1 mm. NaCl prism

I. R. Spectrum #VII

N, N-Dimethyl-α-methyl-Δ^2-pyrrolinium bromide

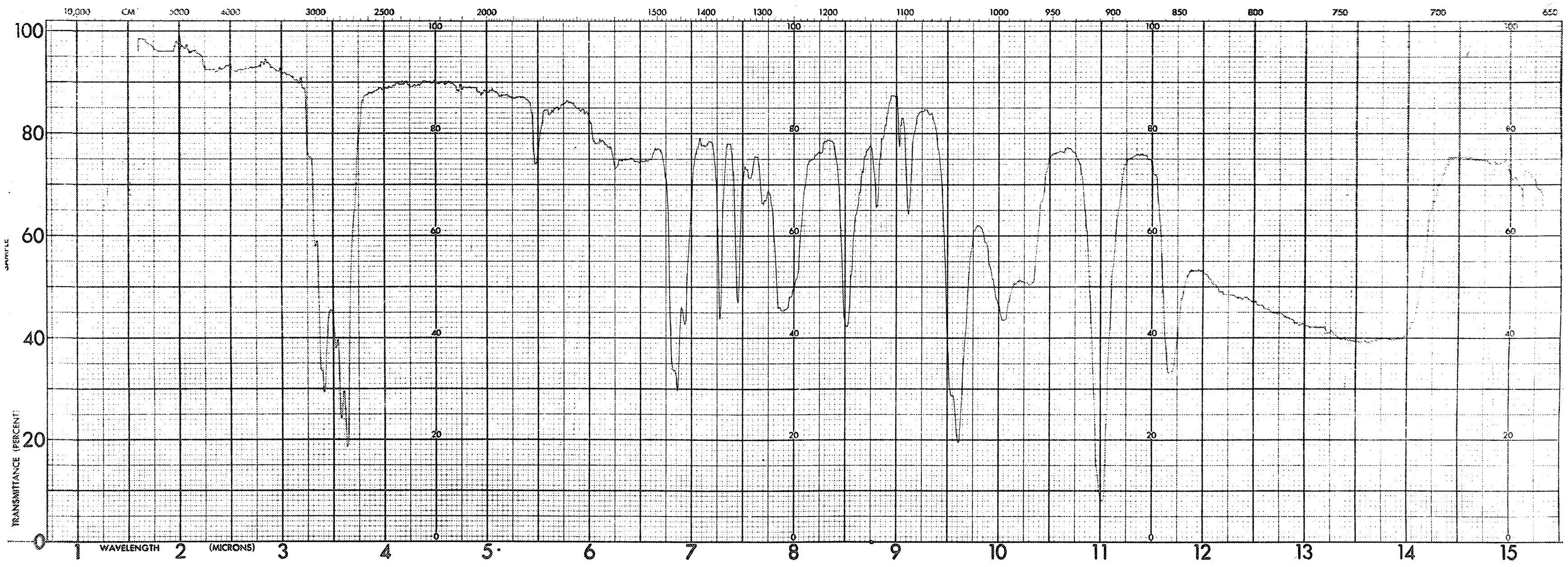
Solvent: chloroform
Cell: 1 mm. NaCl prism



I. R. Spectrum #VIII

Product from addition of HCl to 1-dimethylamino-3-pentyne

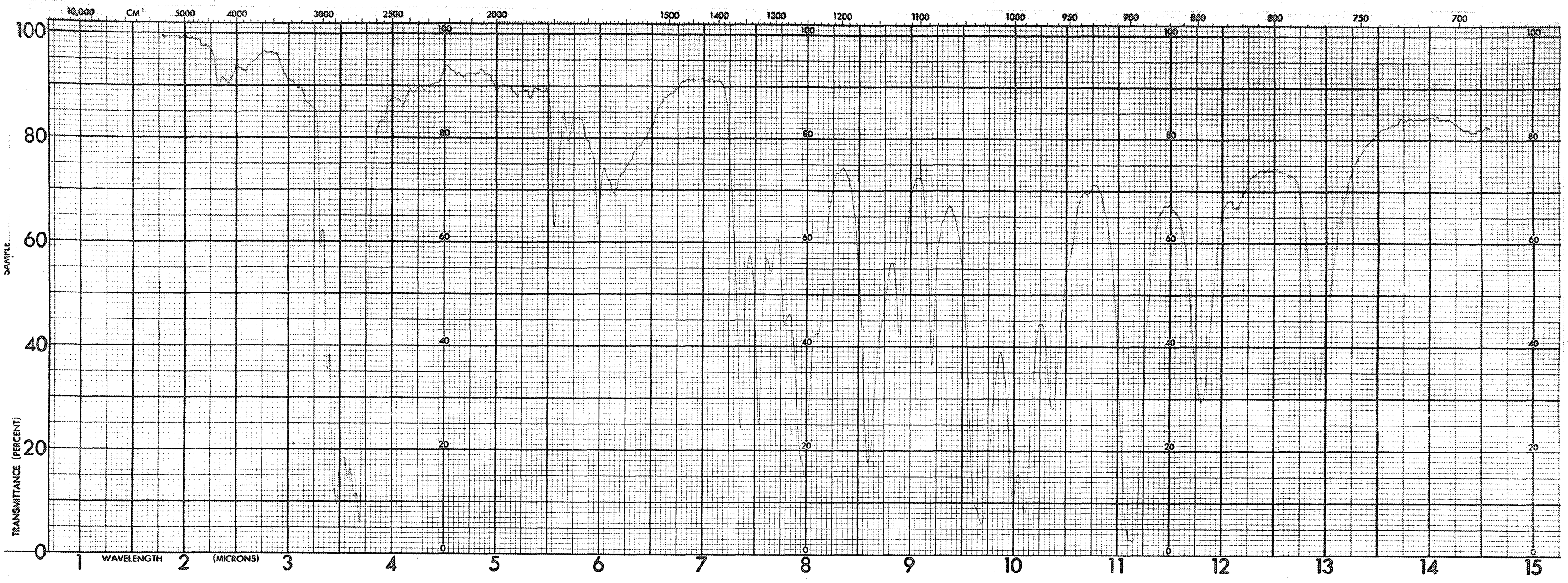
Solvent: carbon tetrachloride
Cell: 1 mm. NaCl prism



I. R. Spectrum #IX

1-Dimethylamino-2,4-pentadiene

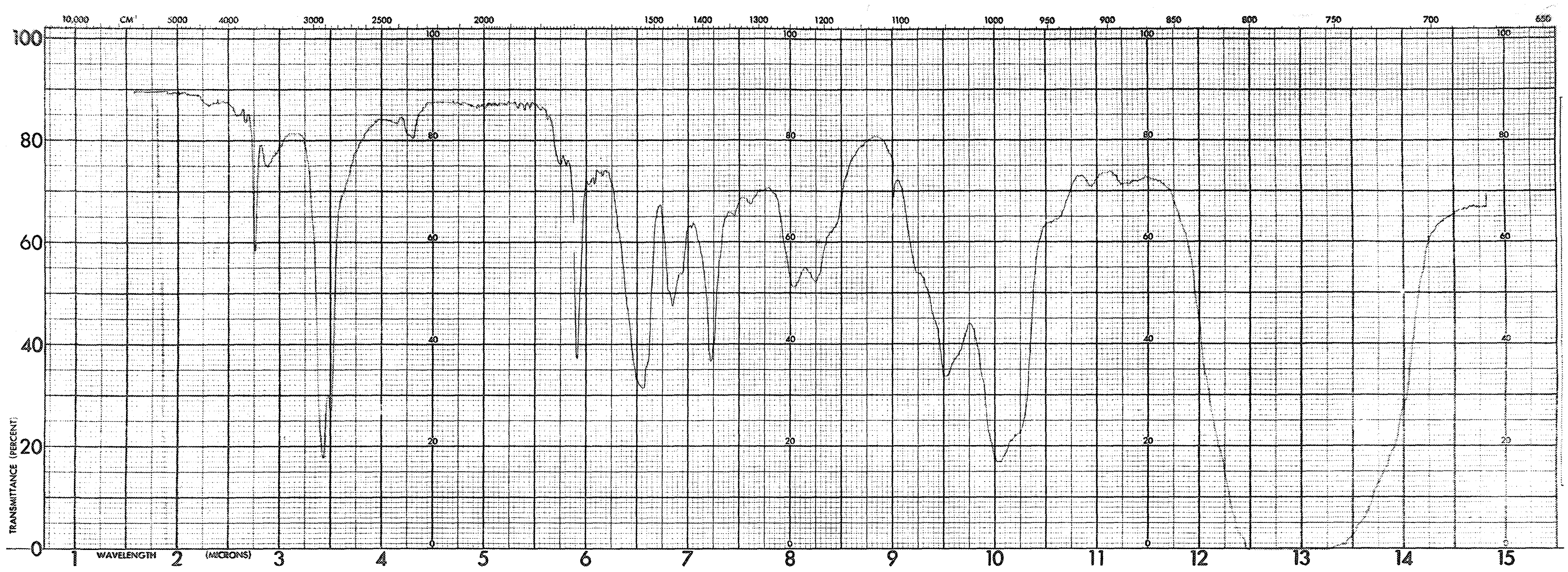
Solvent: carbon tetrachloride
Cell: 1 mm. NaCl prism



I. R. Spectrum #X

1-Dimethylamino-2, 4-pentadiene

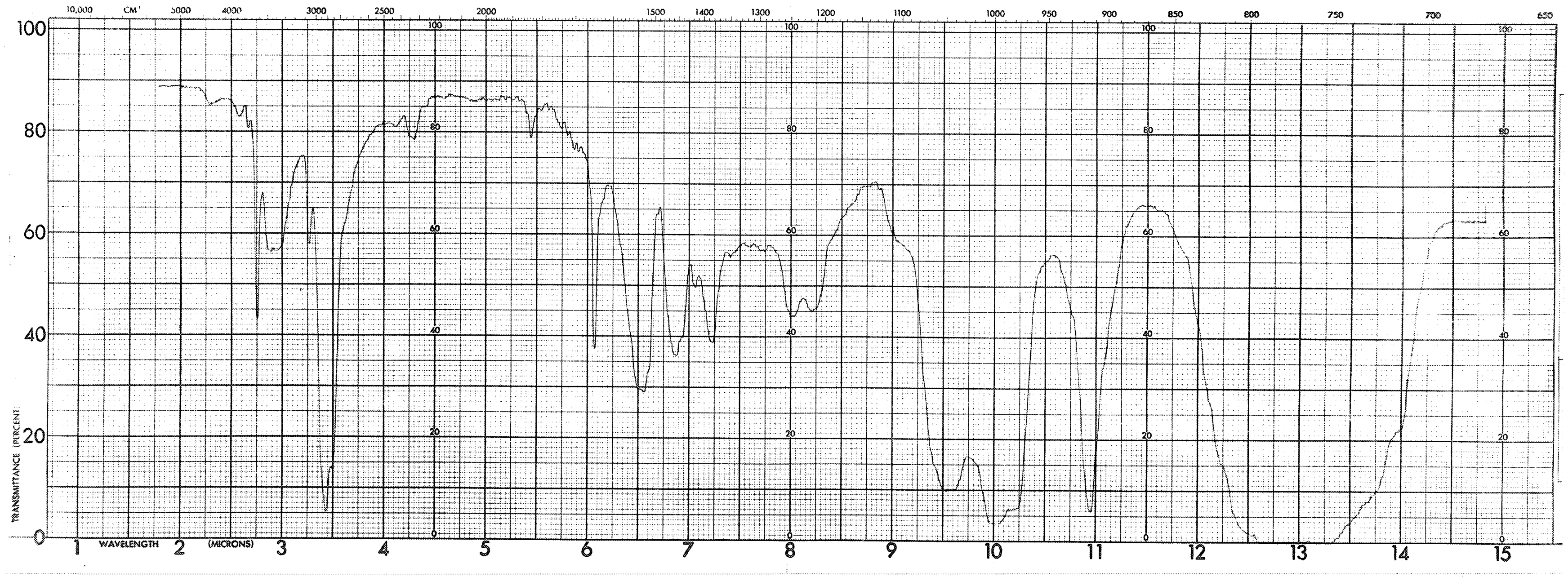
Solvent: carbon disulfide
Cell: 1 mm. NaCl prism



I. R. Spectrum #XI

Mixture of 1-hydroxy-2,4-pentadiene
and 2-pentenal

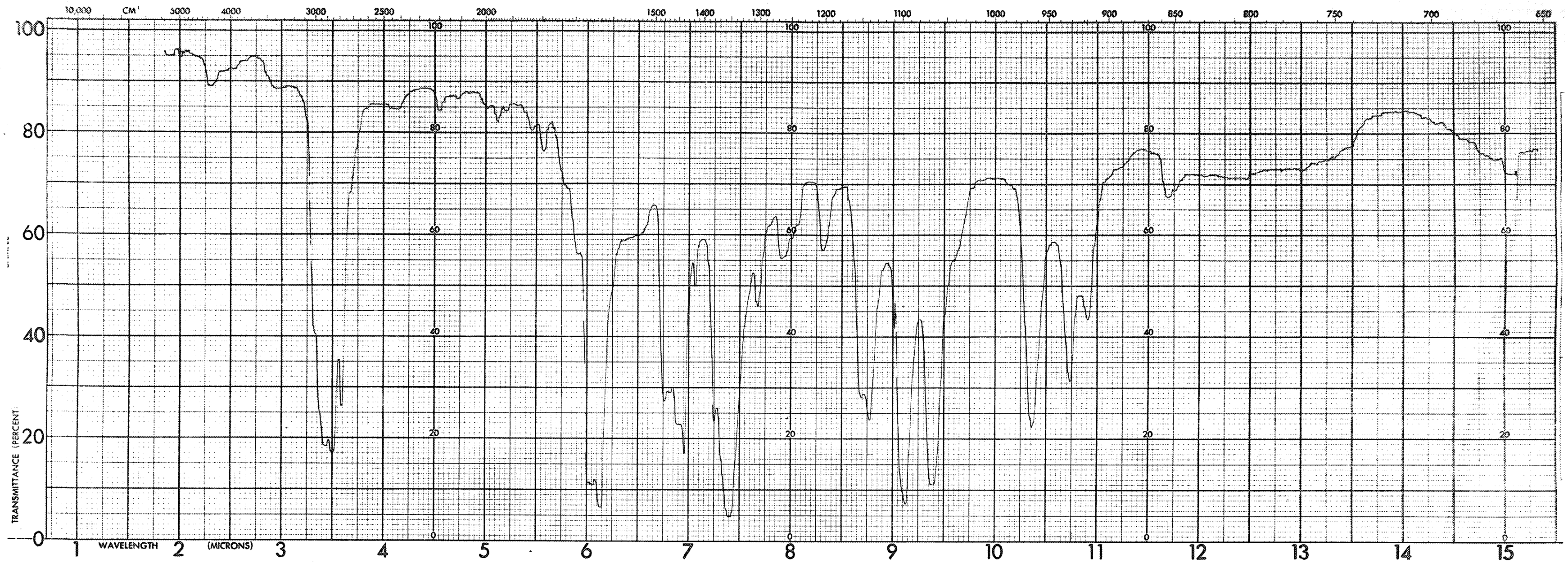
Solvent: carbon tetrachloride
Cell: 1 mm. NaCl prism



I. R. Spectrum #XII

1-Hydroxy-2, 4-pentadiene (impure)

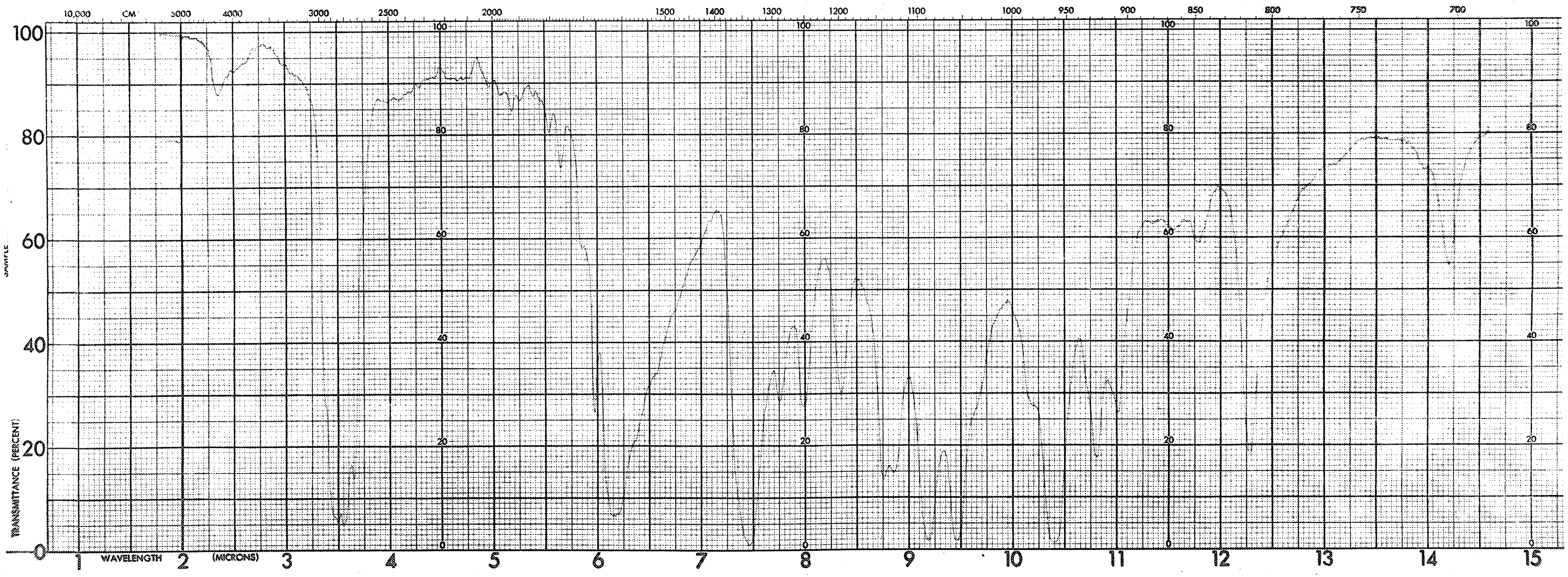
Solvent: carbon tetrachloride
Cell: 1 mm. NaCl prism



I. R. Spectrum #XIII

1-Dimethylamino-1, 3-pentadiene

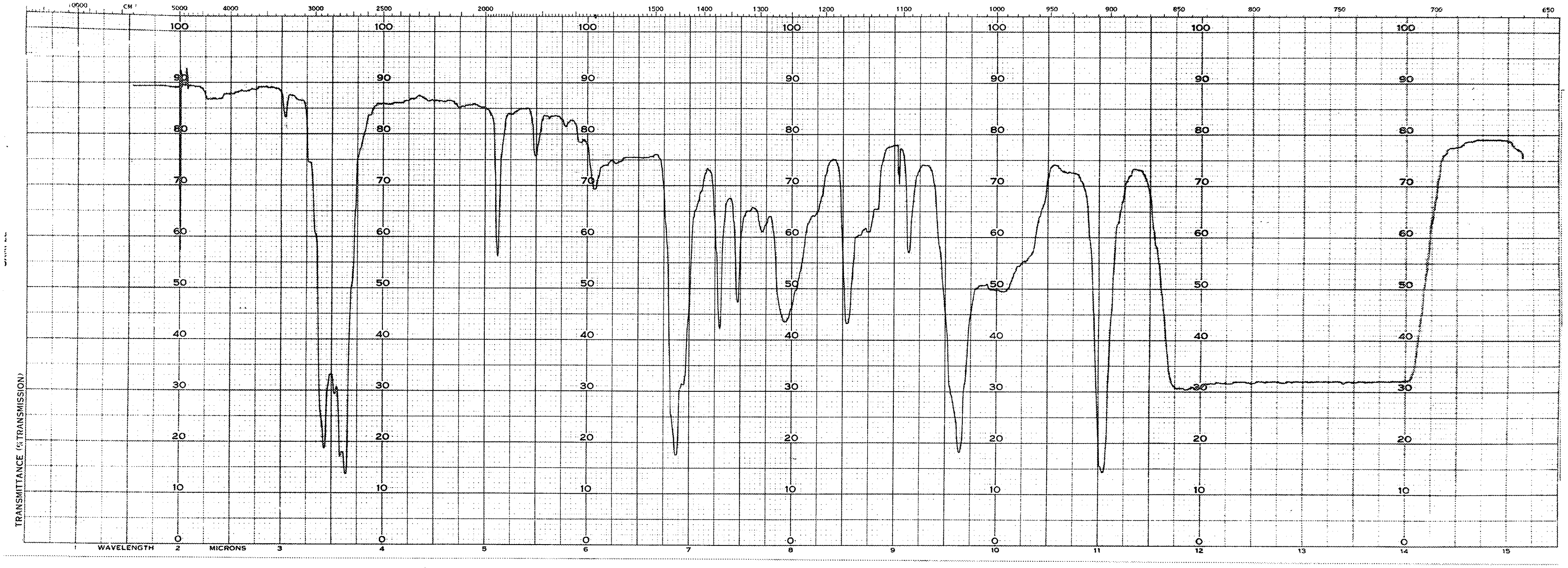
Solvent: carbon tetrachloride
Cell: 1 mm. NaCl prism



I. R. Spectrum #XIV

1-Dimethylamino-1,3-pentadiene

Solvent: carbon disulfide
Cell: 1 mm. NaCl prism



I. R. Spectrum #XV

Low boiling fraction of $C_7H_{13}N$ amine mixture
showing 3300 cm^{-1} absorption

Solvent: carbon tetrachloride
Cell: 1 mm. NaCl prism

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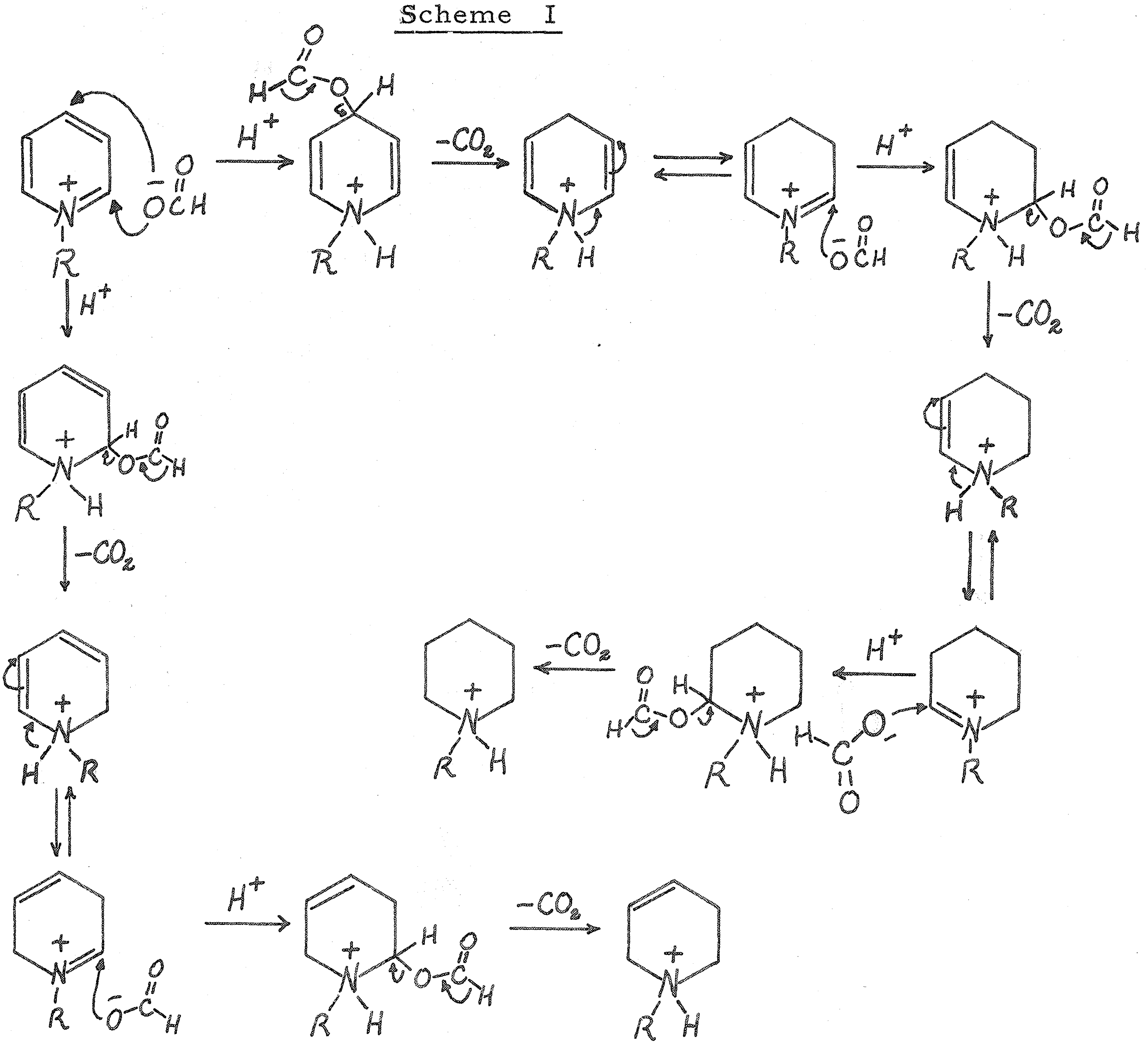
PROPOSITIONS

1. A mechanism is proposed for the reduction of N-alkylpyridinium salts by formic acid (Scheme I). Decker (1) performed this reduction as early as 1892, but it has received little attention as a synthetic method, except by Lukeš and co-workers in Czechoslovakia. Apparently no mechanistic studies of the reaction have been made.

Scheme I



Through a careful study, Lukeš (2) found that N-methylpyridinium salts were reduced to a mixture of N-methylpiperidine and N-methyl-1,2,5,6-tetrahydropyridine.

It is proposed (Scheme I) that a 1,2-dihydro intermediate is the precursor of the tetrahydro base and that a 1,4-dihydro intermediate is the precursor of the fully hydrogenated base.

The following are proposed as the rationale for the mechanism.

1) Positions 2 and 4 of the pyridinium ring are quite susceptible to electrophilic attack as shown by simple molecular orbital calculations (3). An analogy to the addition of formic acid is the addition of water to quaternary immonium salts (4).

2) The step involving tautomerization of an α,β-unsaturated quaternary ammonium salt to a quaternary immonium salt follows from the observation that no dihydropyridine has been isolated from the formic acid reductions (5).

3) In no case reported has tetrahydropyridine been isolated as the sole product. On the other hand, in some cases in which substituents are located in the 4-position (notably carboxyl (5c) and α-pyridyl (5d)) only a piperidine (hexahydropyridine) has been isolated. The substituents apparently deactivate positions meta to their positions.

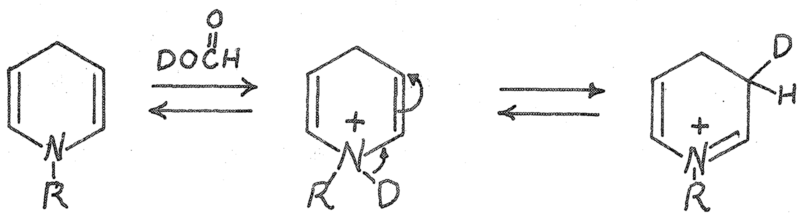
The following are proposed to either check or to offer some insight into the postulated mechanism.

1) N-Alkyldihydropyridinium salts have been prepared and it has been shown by Pullman, San Pietro and Colowick (6) that pyridinium salts on reduction by sodium hydrosulfite give the 1,4-dihydro compound. It is proposed that a 1,4-dihydropyridinium salt on reduction by formic acid would give only a fully hydrogenated pyridine (piperidine).

2) A 1,2-dihydropyridinium salt is not known with certainty (7a), so that a check cannot be made to see if it gives only the tetrahydropyridine on reduction. However, substituent studies can be made. Apparently the carboxyl group deactivates the 2-position when it is in the 4-position. Unfortunately, the 2-carboxypyridinium salt is decarboxylated during the reduction (5b). It would be interesting to study the products of reduction of 2- and 4-nitropyridinium salts.

3) It would be interesting to reduce a quaternary salt of compounds postulated to be Δ^2-tetrahydropyridines (7b). The Δ^3-isomer has been shown to not be reduced (2). In connection with this, the tautomerism of an α, β-unsaturated ammonium salt should be studied by deuterium exchange between $\mathrm{DO\overset{O}{\overset{\|}{C}}H}$ and a 1,4-dihydropyridinium salt (Scheme II).

Scheme II



4) A study of the pyrolysis of formates should be made using the conditions of the formic acid reduction.

2. It is proposed that the pK values for the cis- and trans-1,2-diaminocyclohexanes elucidate their configurations. A comparison is made with the 1,3-diaminocyclohexanes and with analogous aliphatic diamines. Postulations are made concerning the polar effects in the diamines and in aminocyclohexanecarboxylic acids and analogous aliphatic amino acids.

Tables I and II are compilations of the pK values which have been determined for the cis- and trans-1,2-, 1,3- and 1,4-diaminocyclohexanes and for the cis- and trans-2-, 3- and 4-aminocyclohexanecarboxylic acids, respectively. At the present time, the list is not complete. Table III gives the data for analogous aliphatic compounds.

TABLE I

pK Values for Diaminocyclohexanes

	pK_{a_1}	pK_{a_2}
cis-1,2 (8)	9.73	6.03
trans-1,2 (8)	9.60	6.24
cis-1,3 (9)	10.36	8.54
trans-1,3 (9)	10.30	8.29
cis-1,4	--	--
trans-1,4	--	--

TABLE II

pK Values for Aminocyclohexanecarboxylic Acids

	pK_1	pK_2
cis-1, 2	--	--
trans-1, 2 (10)	3.59	10.21
cis-1, 3 (11)	3.70	--
trans-1, 3 (11)	3.85	--
cis-1, 4 (10)	4.83	10.62
trans-1, 4 (10)	4.39	10.51

TABLE III (12)

	pK_1		pK_{a_2}
$H_3\overset{+}{N}(CH_2)_2COOH$	3.60	$H_3\overset{+}{N}(CH_2)_2\overset{+}{N}H_3$	6.97
$H_3\overset{+}{N}(CH_2)_3COOH$	4.23	$H_3\overset{+}{N}(CH_2)_3\overset{+}{N}H_3$	8.59
$H_3\overset{+}{N}(CH_2)_4COOH$	4.27	$H_3\overset{+}{N}(CH_2)_4\overset{+}{N}H_3$	9.31

The small difference in the pK values for the cis- and trans-1, 2-diaminocyclohexanes indicates that the trans-isomer has the diequatorial conformation. Ball-and-stick models show that electrostatic repulsion is probably not great enough to force the diprotonated species to assume the diaxial conformation, which is more unfavorable energetically due to steric repulsions from hydrogens across the ring.* Electrostatic repulsions are less in the 1, 3-diaminocyclohexanes and the cis-isomer would be expected to have the diequatorial conformation (9).

---

*It has been pointed out (13) that electrostatic repulsions in the dianion of the 1, 2-cyclohexanecarboxylic acids are serious and the trans-isomer can alleviate this by assuming the diaxial conformation.

Comparison of the pK_{a_2} values for the diaminocyclohexanes with the values for analogous aliphatic diamines shows that the 1,3-diaminocyclohexanes give the expected behavior, the lesser charge separation in the trans-isomer making it a stronger acid. The comparison clearly shows the electrostatic repulsive forces in both of the 1,2-diaminocyclohexanes. The cis-1,2-isomer is probably a stronger acid because due to ring inversion, the protonated amino groups are closer together.*

It is proposed that the 1,4-diaminocyclohexanes will have pK_{a_2} values very close to each other (the trans-isomer having the diequatorial conformation) and to the value for α,δ-tetramethylenediamine with the trans-isomer having a slightly higher pK_{a_2} value than the cis-isomer.

It is proposed that a comparison of the pK_1 value for trans-2-aminocyclohexanecarboxylic acid with the value for β-aminopropionic acid clearly shows that the former has the diequatorial conformation. It is further proposed that the cis-1,2-isomer will have a higher pK_1 value. The 1,4-aminocyclohexanecarboxylic acids have pK_1 values that agree with that for α,δ-aminovaleric acid and the greater charge separation in the trans-isomer has been used to explain its higher equilibrium constant (10). The 1,3-aminocyclohexanecarboxylic acids have similar pK values and this has been interpreted to mean that the cis-isomer

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*It has been pointed out (14a) that in cis- and trans-1,2-dimethylcyclohexanes the methyl groups are approximately equidistant (the trans having the diequatorial conformation). On the other hand, two adjacent polar substituents have a tendency to assume a diaxial conformation (14b).

has the diequatorial conformation (11). The difference between these values and the value for α, γ-aminobutyric acid probably shows the electrostatic effect.

3. Polyol complex formation with borates has been known for more than a century (15). In recent years other anions (or acids*) have been observed to form complexes with polyhydroxy organic compounds. Edwards and co-workers (16) have studied the borate, arsenite and tellurate ions in considerable detail. In a study of the equilibrium constants for complex formation, they found that the borate and arsenite ions gave good agreement with a series of polyols. These polyols are listed in Table IV. On the other hand, constants for complex formation

TABLE IV

Ethylene glycol
Propylene glycol
2, 3-Butanediol
Phenyl-1, 2-ethanediol
3-Methoxy-1, 2-propanediol
Glycerol
D-Mannose[1]

D-Glucose
L(+)-Arabinose
D(+)-Galactose
Fructose
Catechol[2]
Polyvinyl alcohol
Pentaerythritol[1]

[1] No complex formed with tellurate ion.
[2] Oxidized by tellurate ion.

---

*Edwards and co-workers (16) have postulated that the anion is the complexing species and this seems to be the accepted theory. However, further studies with other compounds (molybdic acid, e.g.) may reveal that the acid itself is capable of complexing with polyols.

with tellurate ion did not agree with expected values. Molecular models showed that some substituents induced a large steric effect (the sugar molecules, e.g.) in the octahedral tellurate complexes. The borate and arsenite complexes are tetrahedral and models showed that there was no steric crowding.

In the series of polyols studied by Edwards and co-workers (16), steric effects may play the predominant role in determining how strong the complex will be. It is proposed that, contrary to Edwards and co-workers' statement, the substituent groups on the polyols are not representative enough of electron-withdrawing and electron-releasing groups to rule out electronic factors as aids or hindrances to complex formation. Richardson (17) has studied complex formation of polyols with molybdic acid and observed that gluconic acid has a marked tendency to complex, whereas glucose has not. It is proposed that Richardson's dilemma over this is unfounded and that the important factor here is the electron-withdrawing power of the carboxyl group.* Steric effects are probably important here also; mannitol complexes, while inositol does not.

In order to get a clearer picture of this situation, the following are proposed.

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*The glucose undoubtedly exists mainly in its hemi-acetal form and not its aldehyde form (as stated by Richardson) and even if the gluconic acid existed as an internal structure (as stated by Richardson), the electron-withdrawing ability is not removed in the latter.

1) Study a series of polyols with varying numbers of hydroxyl groups to determine the importance of the number of sites available for complexing. (Richardson (17) reported that glycerol did not complex with molybdic acid, while erythritol did.)

2) Study the effect of electron-withdrawing and electron-releasing substituent groups located at the p-position of the benzene ring in 1-phenyl-1, 2-ethanediol.

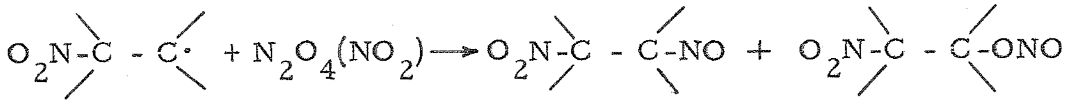
3) Study the effect of substituent groups such as acetyl in comparison to methyl.

4. Much interest has been given to the dinitrogen tetroxide addition to olefins since the work of Levy and co-workers (18) in which it was found that the products consisted mainly of dinitro compounds and nitro-alcohols (the latter being derived from nitronitrites). An ionic mechanism was at first proposed (18a, 19) for the reaction mainly on the basis of the finding that unsymmetrical olefins gave products having the nitro group substituted on the carbon with the greater number of hydrogen atoms. Later work has shown that methyl acrylate orients addition in the same direction as does propylene (20), that addition normally proceeds in a non-stereospecific manner (21) and that when the reaction is carried out in halogenocarbon solvents (such as bromotrichloromethane) none of the products of normal addition (with ethyl ether as a solvent, *e.g.*) are obtained (22); all of these results are inconsistent with an ionic mechanism.

A free radical mechanism has been postulated (20, 21, 22) for the reaction and is shown in the following equations.

$$N_2O_4 \rightleftharpoons 2NO_2$$ eq. 1)

eq. 2)

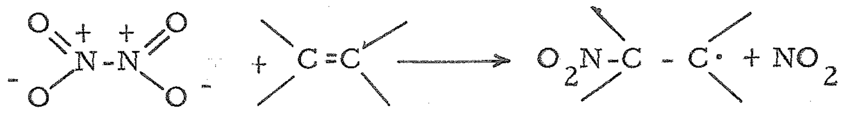


eq. 3)

With most authors being satisfied with a free radical mechanism for the dinitrogen tetroxide addition, current work has been concerned mainly with the stereochemistry of the products obtained from the addition (21b, 22).

The following are proposed.

1) It has been observed that the initial step of the addition always forms a C-N bond. This has been rationalized by one author (20) as being due to greater hyperconjugative stability of the nitroalkyl radical. It is proposed that the nitroalkyl radical is formed by attack of N_2O_4 and not NO_2 (eq. 4)).



eq. 4)

At the normal temperature (0° or below) at which the reaction is carried out, the equilibrium expressed by equation 1) is far to the left (dissociation of N_2O_4 into NO_2 at 0° is reported to be only 0.15% (20)).

Because of the greater electrophilic character of the nitrogen, initial formation of a C-N bond is reasonable.

2) Hydrolysis of nitrites has been demonstrated to proceed without inversion of configuration (23). Hydrolysis of nitrates, on the other hand, in neutral or acid medium has been observed to proceed by inversion of configuration (or by racemization) (24). It is proposed that some of the nitroalcohol comes from hydrolysis of the nitronitrate and that complete reliance cannot be placed on data used to formulate a mechanism in which only the nitroalcohol and not the dinitro compound is studied.

3) Mechanisms to explain the stereochemistry of observed products have been formulated (21b, 22) by considering the steric demands of the nitroalkyl radical. In systems in which no steric requirements are placed on the nitroalkyl radical, equal amounts of products from C-N and C-O bond formation in the final step have been found. It is proposed that this indicates the non-dependence of electronic factors in determining whether a C-N or C-O bond is formed in the final step. It is further proposed that in sterically hindered systems, not only the steric requirements of the nitroalkyl radical, but the steric requirements of the N_2O_4 (or NO_2) must be taken into account.

5. It is proposed that the following be investigated:

1) The addition of ammonia to a double bond with regard to the stereochemistry of the adduct;

2) the addition of nitramide to a double bond.

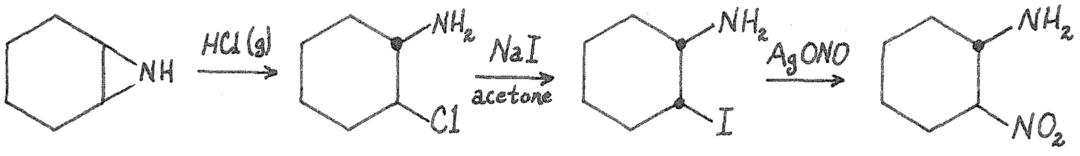
The addition of ammonia to 1-nitroalkenes has been observed (25) to lead to β-nitroalkylamines, but no study of the stereochemistry has been made. It is proposed that ammonia be added to the double bond of 1-nitrocyclohexene (18e) and that the configuration of the product be determined. This latter study might reveal something about the mechanism of addition.

Two possibilities are proposed for determining the stereochemistry of the product.

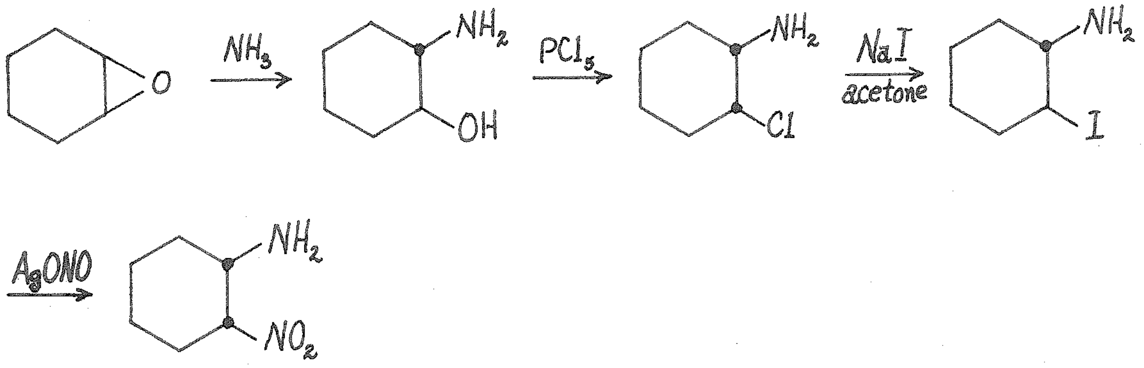
1) Stereospecific reduction (with retention of configuration) of nitro groups to amino groups by lead in acetic acid has been demonstrated (26a). Reduction of β-nitrocyclohexylamine by this stereospecific method and comparison of the product, 1,2-diaminocyclohexane, with authentic samples (27) is proposed as a possibility for determining the stereochemistry.

2) It is proposed that <u>cis</u>- and <u>trans</u>-β-nitrocyclohexylamine can be prepared as shown on the following schemes.

Scheme III



Scheme IV



trans-2-Chlorocyclohexylamine has been prepared by treatment of 1, 2-cyclohexenimine with HCl gas (Scheme III) (28). Displacement of a chloro group by reaction of an alkyl chloride with sodium iodide in acetone is known to occur with inversion of configuration (29). cis-2-Iodocyclohexylamine is unknown, but it is proposed that it can be formed as shown on Scheme III. Replacement of the iodo group with a nitro group is proposed to lead to trans-β-nitrocyclohexylamine.* This type of displacement has been shown to give inversion of configuration (26b).

cis-2-Chlorocyclohexylamine has been prepared as shown on Scheme IV (31). A displacement reaction with sodium iodide in acetone on this is proposed to lead to trans-2-iodocyclohexylamine. The latter has been reported (32), but no unequivocal proof of the configuration has been given. The trans-iodo amine on treatment with silver nitrite is proposed to give cis-β-nitrocyclohexylamine.

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*The nitroalcohol (formed by hydrolysis of the nitrite in work-up) can easily be separated by fractionation (30).

Comparison of the product from the addition of ammonia to the double bond of 1-nitrocyclohexene with authentic <u>cis</u>- and <u>trans</u>-β-nitrocyclohexylamines will show the configuration of the former.

The addition of nitramide (NH_2NO_2) to a double bond has never been reported. If it is successful, it would be a convenient route to β-nitroalkylamines. That the N-N bond in nitramide is strong has been demonstrated by its decomposition into N_2O and water (the N-N bond remaining intact) (33). The behavior of nitryl chloride may be used as an analogy for nitramide. The former has considerable ionic character (34) and adds to double bonds (35). It is proposed that the addition of nitramide to the double bond of cyclohexene be attempted. If the addition is successful and the product is β-nitrocyclohexylamine,* the configuration of the latter can be determined by one of the methods proposed above. This would offer insight into how the N-N bond is cleaved (homolytically or heterolytically).

6. It is proposed that a study be made of elimination in quaternary ammonium salts containing no hydrogens on a β-carbon.

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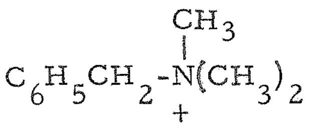
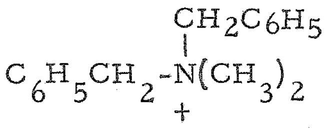
*The addition may proceed to give N-nitrocyclohexylamine similar to the addition of hydrazine to certain unsaturated linkages (36).

The behavior with certain basic reagents of the compounds shown on Scheme V has been studied (41). None of these compounds have hydrogens on a β-carbon.

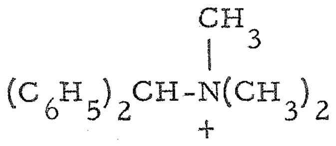
Scheme V



$C_6H_5CH_2\text{-}\overset{CH_3}{\underset{+}{N}}(CH_3)_2$



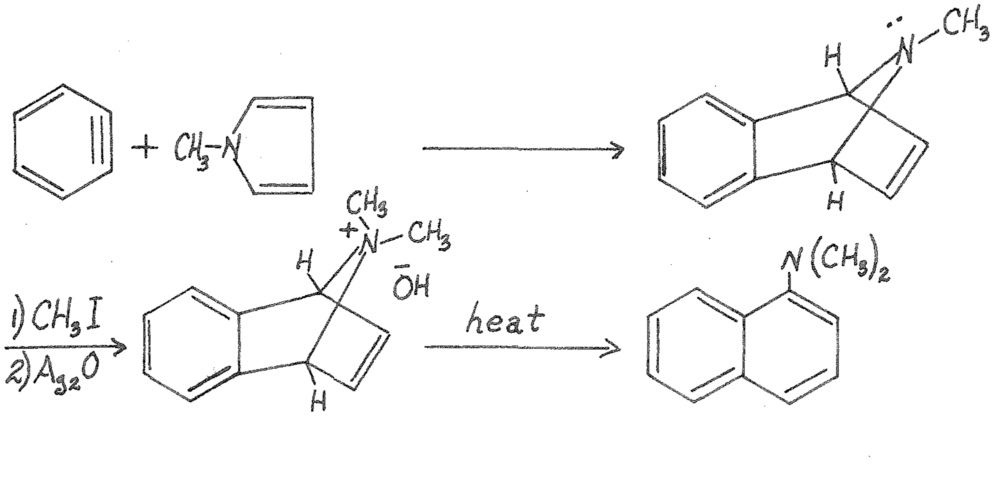
$C_6H_5CH_2\text{-}\overset{CH_2C_6H_5}{\underset{+}{N}}(CH_3)_2$



$(C_6H_5)_2CH\text{-}\overset{CH_3}{\underset{+}{N}}(CH_3)_2$

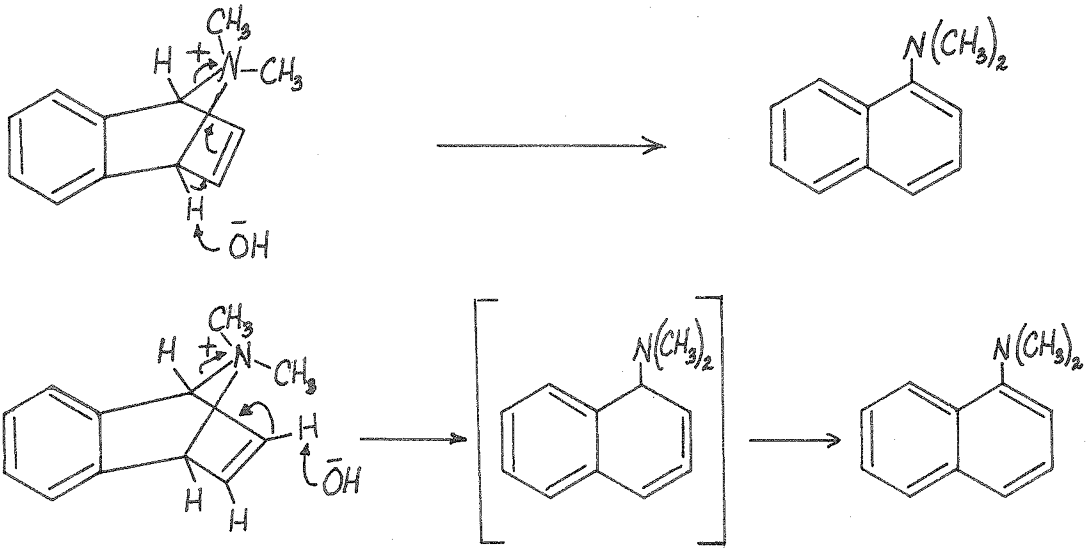
The tertiary amines isolated from the reactions had structures in which a 1, 2-shift of an alkyl or aralkyl group had occurred or a group had migrated into the ring. The normal β-elimination cannot occur. It has been observed (42) that benzyne reacts with N-methylpyrrole by a 1, 4-addition. Degradation of the adduct by pyrolysis of the quaternary hydroxide leads to α-dimethylaminonaphthalene.

Scheme VI



Two alternative mechanisms can be written for the Hofmann degradation. The first is removal of a proton from an α-carbon, with either a simultaneous allylic rearrangement or followed by an allylic rearrangement to the product. The second is by removal of a proton from a β-carbon with cleavage of the C-N bond in a single step.

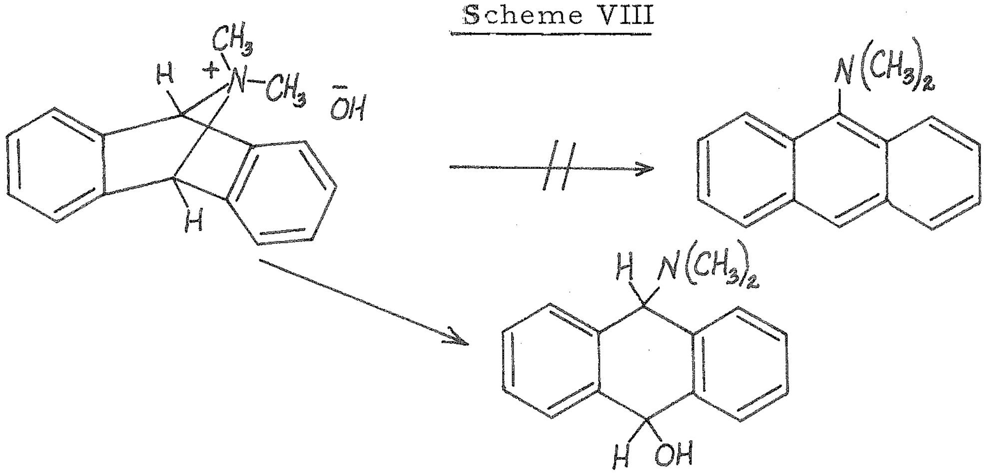
Scheme VII



The second mechanism is quite unlikely, because it involves the formation of an allenic linkage in a six-membered ring.

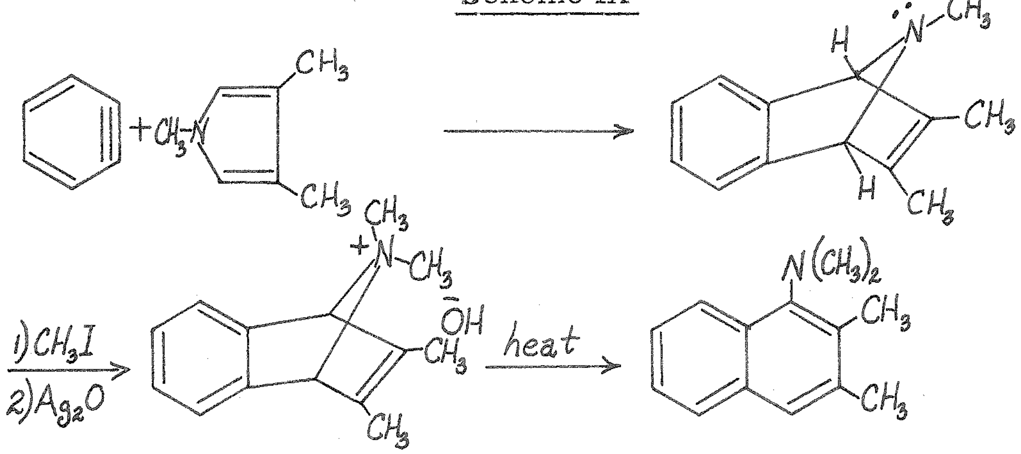
One system which has no hydrogens on a β-carbon and which can undergo a Hofmann-like elimination has been studied (42). On pyrolysis, the quaternary hydroxide gives a tautomeric product and not a product resulting from elimination.

Scheme VIII



It is proposed that the following reaction (Scheme IX) be carried out.

Scheme IX

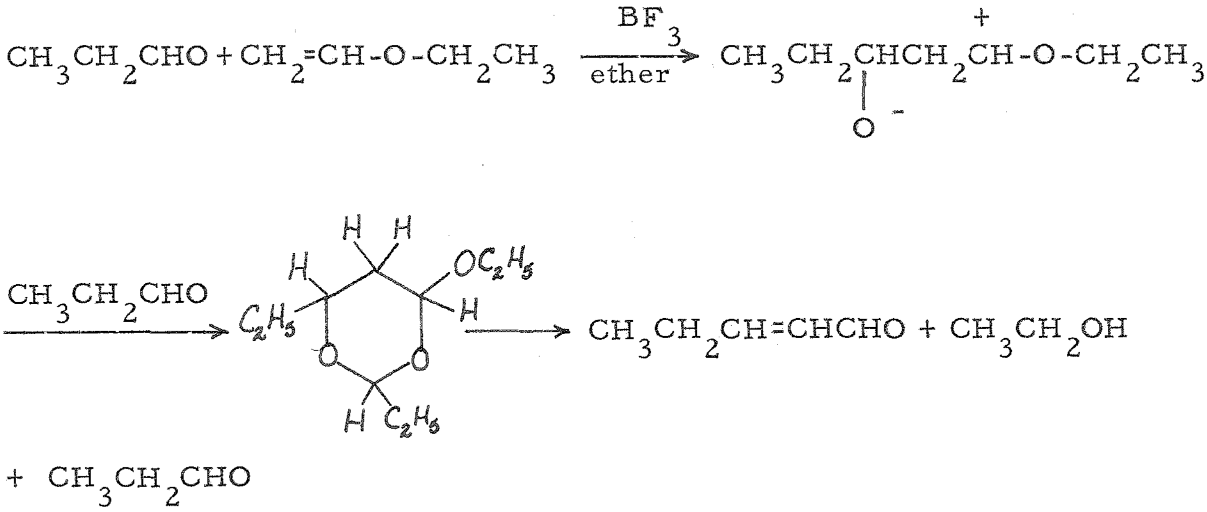


The proposal is that the double bond will assist removal of the proton from the α-carbon enabling an allylic rearrangement to take place.

7. It is proposed that the equilibrium between a vinyl alcohol and a saturated aldehyde in the presence of boron trifluoride determines the nature of the unsaturated aldehydes obtained.

It was postulated (43) that 2-pentenal was formed in the reaction of propionaldehyde with ethyl vinyl ether in the presence of boron trifluoride. The formation of a 1,3-dioxane intermediate was demonstrated (44).

Scheme X



Later work showed that the product from a similar reaction consisted of a mixture of tiglic aldehyde and α-methyl-2-pentenal (45). It is proposed that the products are determined by the following equilibrium.

Scheme XI

$$CH_3CH_2CHO + CH_2{=}CH\text{-}O\text{-}CH_2CH_3 \xrightarrow{BF_3} CH_3CH{=}CH\text{-}O\text{-}CH_2CH_3 + CH_3CHO$$

This equilibrium is analogous to the acid-catalyzed reaction of acetic anhydride with carbonyl compounds (46). When there is a large excess of propionaldehyde, the equilibrium should be displaced far to the right and the observed products should be tiglic aldehyde and α-methyl-2-pentenal, formed by reaction of acetaldehyde with ethyl propenyl ether and by reaction of propionaldehyde with ethyl propenyl ether, respectively.

The following are proposed to check the postulate.

1) On carrying out the reaction with propionaldehyde and a large excess of ethyl vinyl ether, the main products should be crotonaldehyde and tiglic aldehyde.

2) On carrying out the reaction with acetaldehyde and a large excess of ethyl propenyl ether, the main products should be 2-pentenal and α-methyl-2-pentenal.

It is proposed that the above procedures would be convenient synthetic preparations for the α,β-unsaturated aldehydes.

It is further proposed that the magnitude of the equilibrium constant can be determined by carrying out the reaction with equal amounts of propionaldehyde and ethyl vinyl ether or with equal amounts of acetaldehyde and ethyl propenyl ether. If the equilibrium constant is nearly one ($K = 1$), equal amounts of crotonaldehyde, 2-pentenal, tiglic aldehyde and α-methyl-2-pentenal should be formed.

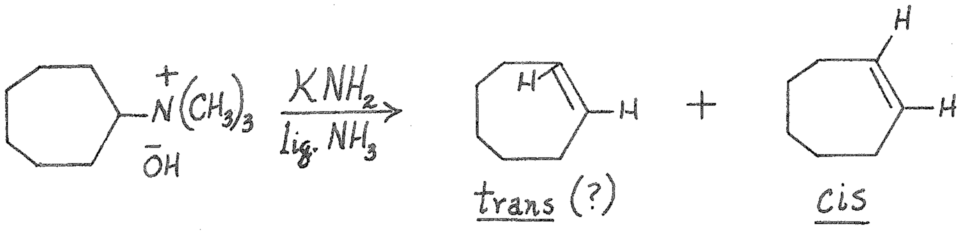
8. It is proposed that there be a reinvestigation and an extension of the studies of cycloheptene and 1,2-cycloheptadiene.

Both cis- and trans-cycloöctene are well-known (47). The latter is more unstable, but was prepared by a Hofmann degradation of the quaternary methohydroxide of N,N-dimethylaminocycloöctane. trans-Cycloheptene is expected to be much more unstable than cis-cycloheptene (47f, 47g). Molecular models show that there is considerable ring strain in the former. Deformation of the ring to relieve this strain brings the hydrogen in the ring in close proximity to a methylene group.

The physical properties reported for cycloheptene do not allow one to compare the product from various methods of preparation. It is not likely that the drastic conditions of the pyrolysis of the quaternary methohydroxide of N,N-dimethylaminocycloheptane would allow detection of any trans-cycloheptene.

It is proposed that the various methods used for preparation of cycloheptene be repeated and that the products be characterized. In particular, it is proposed that the following reaction (Scheme XII) be studied.

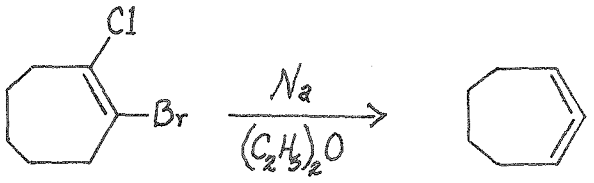
Scheme XII



The above conditions have been shown to give 85% trans-cycloöctene with the corresponding cycloöctyl ammonium bromide (48).

Also of interest is the doubly unsaturated seven-membered ring. The following has been reported (49).

Scheme XIII



This finding refuted a previous proposal (50) that the compound had an acetylenic linkage.

It is proposed that this reaction be repeated and that the product be checked for purity by vapor phase chromatography and for the allenic linkage by infrared absorption spectroscopy. The analogous reaction with the eight-membered ring has recently been shown to give a mixture containing a compound having an acetylenic linkage (51).

It is proposed that a study be made of the product(s) formed on base treatment of 1,2-cycloheptadiene. It is possible that the latter will give 1,3-cycloheptadiene on base treatment.* It has been reported that 1,3-dienes are not obtained from allenes (or acetylenes) in the aliphatic series on base treatment (52), except under the influence of substituent groups (such as $-N\begin{smallmatrix}R\\R\end{smallmatrix}$) (53). Apparently no studies of this type have been made in the alicyclic series.

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*Ball-and-stick models show that the great steric strain in cycloheptyne makes it an unlikely structure to survive this type of treatment.

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