The Synthesis of Potential Antimalarials

I. 1,3-Dimethylpiperidone-4.

II. Application of the Darzens-Claisen Reaction to a β-Dialkylaminoketone.

III. 6'-Methoxyrubanol-9.

IV. Synthesis of Some 2-Phenylquinolyl-4-α-Piperidylcarbinols.

V. 2,6-Diphenylpyridyl-4-di-n-butylaminomethylcarbinol.

VI. Preparation and Reduction of 9-Picolinylanthracene.

VII. Preparation and Reduction of α-Phenacylpyridine.

A New Guinea-Pig Test for Relaxin Activity.

Thesis by

David R. Howton

In Partial Fulfillment of the Requirements

for the Degree of Doctor of Philosophy

California Institute of Technology

Pasadena, California, 1946

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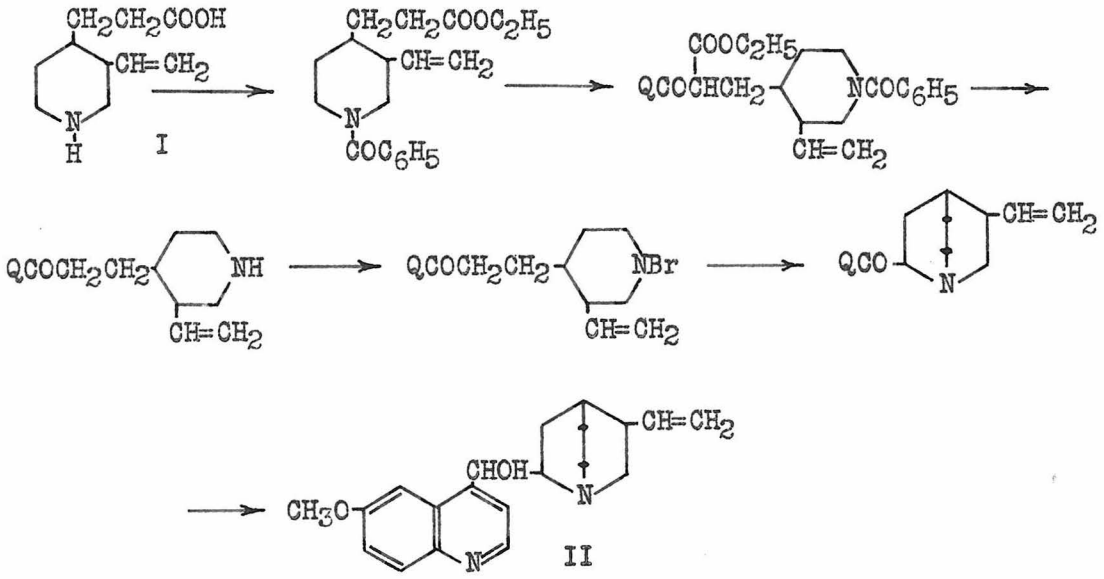
INTRODUCTION

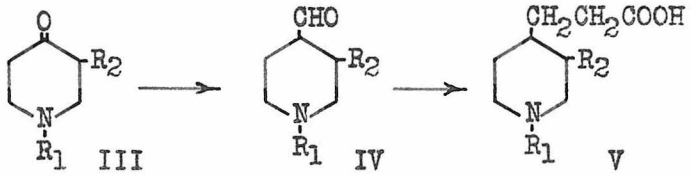
At the outbreak of the war with Japan in late 1941, it must have been apparent to many American organic chemists that the problem of synthesising quinine (an old one in terms of the comparative youth of organic chemistry) had ceased to be academic and had become a very practical one. So soon after the Pearl Harbor incident, we began an attack on this synthesis problem, which had engaged the attentions of such workers as Rabe for more than a quarter of a century.

The task resolved itself into that of preparing homomeroquinene (I), from which the path to quinine (II) could be followed by well-known methods:



The first step in one contemplated plan would involve the preparation of a 1,3-disubstituted piperidone-4 such as (III), where R_1 must be a group easily replaced by hydrogen, and R_2 vinyl or a group readily converted to vinyl; the second step might then employ the little-

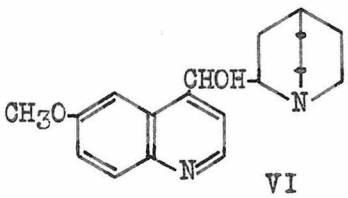
exploited Darzens-Claisen reaction to attach a formyl group to the ketonic carbon-atom of the piperidone-4. Classical methods could then be used to convert the aldehyde (IV) into the appropriately-substituted β-(piperidyl-4)-propionic acid (V) and the problem of synthesising homomeroquinene would be well on its way to solution.



We had prepared a model compound of type (III) and had successfully applied the Darzens-Claisen reaction to a model β-tertiaryaminoketone before being included in the plans of the Committee on Medical Research for a nationally-concerted attack on the urgent antimalarial problem. Then, because the Committee regarded the evolution of a quinine synthesis applicable to supplying large amounts of the drug as unlikely, our attentions were directed to less spectacular, though equally important, endeavors.

One of these was an investigation of the synthesis of the "vinyl-free quinines" (VI), which had been recently prepared by Rabe and by Prelog, but whose reported antimalarial activities were confusing and in need of further documentation.

Ainley and King published a paper in 1938 showing that relatively-easily prepared compounds (VII) having the α-piperidyl in place of the



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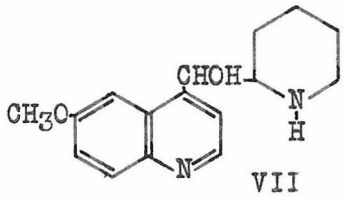
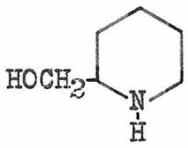


VII



VIII

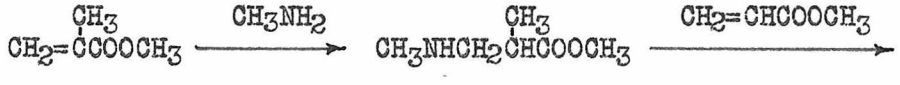
α-quinuclidyl grouping had activities approaching that of quinine. This opened a new field of investigation on the effects of various substituents in the quinoline-rest upon the physiological characteristics of these drugs. The evidence of Mead and Koepfli that quinine is degraded physiologically by an oxidative attack upon the α-carbon of the quinoline ring-system led to the synthesis of a number of Ainley-King-type compounds in which this vulnerable position was protected by a substituent phenyl-group. This protected-α-position idea also led to the synthesis of an α,α'-diphenylpyridyl-4-carbinol incorporating the discovery of King and Work that the α-piperidyl grouping could be replaced by certain dialkylaminomethyl groups without an important loss of antimalarial activity.

The rather surprising fact that α-piperidylcarbinol (VIII), which might be called the antimalarial nucleus of quinine, is not entirely devoid of activity, along with encouraging reports by other groups in the United States working on 9-phenanthrylcarbinolamines and carbinols derived from certain Mannich-type ketones, prompted investigations of the synthesis and activity of piperidylcarbinols which could be obtained from such starting materials as 9-picolinylanthracene and α-phenacylpyridine.

I. 1,3-DIMETHYLPIPERIDONE-4.

1,3-DIMETHYLPIPERIDONE-4

A piperidone-4 with a suitable alkyl substituent in the 3-position could conceivably function as starting material for a synthesis of homomeroquinene[+](2); no compound of this type has been reported in the literature (3). This paper describes the preparation of 1,3-dimethylpiperidone-4 (IV) by the steps outlined below; this type of synthesis has been employed extensively by McElvain and coworkers (4).



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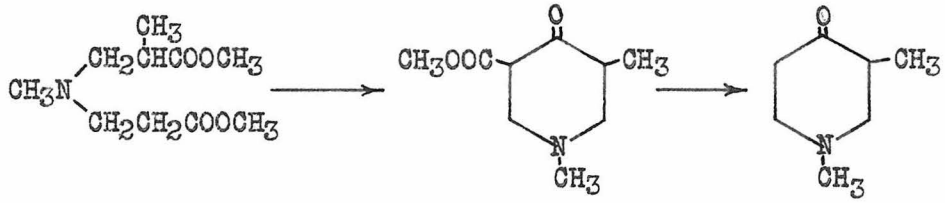

II III IV

The reaction between methyl methacrylate and methyl-(β-carbomethoxyethyl)-amine (compare (5)) was found not to afford a preparative route to methyl-(β-carbomethoxyethyl)-(β-carbomethoxy-n-propyl)-amine (II). (II) was, however, obtained in good yield by addition of methyl-(β-carbomethoxy-n-propyl)-amine (I) to methyl acrylate; (I) in turn was readily prepared by addition of methylamine to methyl methacrylate. The cyclization of (II) and hydrolysis of the product (III) to give (IV) were carried out by standard procedures (4a, d). (IV) has the

[+]The work reported here had been carried out before Woodward and Doering (1) published their synthesis of homomeroquinene.

expected properties, resembling 1-methylpiperidone-4 closely except that it does not show the pronounced tendency of the latter to condense with itself.

Unsuccessful attempts were made (6) to prepare a compound of the type (IV) by direct introduction of an alkyl group into 1-methyl-3-carbomethoxypiperidone-4.

Esters of acrylic acid exhibit a greater tendency to combine with primary and secondary bases than do the corresponding esters of methacrylic acid (see above). Aniline reacted with methyl acrylate (7) to give N-(β-carbomethoxyethyl)-aniline (but no diester), while under the same conditions no reaction was obtained with methyl methacrylate; similarly di-n-butylamine could be added to ethyl acrylate (8) but not to ethyl methacrylate.

The author wishes to acknowledge his indebtedness to Dr. E. R. Buchman for suggesting this problem and for guidance during the course of the investigation.

Experimental+

Methyldi-(β-carbomethoxyethyl)-amine (V) was prepared by the reaction between methylamine and methyl acrylate (methyl acrylate and methyl methacrylate employed in this research were stabilized with hydroquinone; a red crystalline byproduct, undoubtedly bis-(methylamine)-quinone (9), was occasionally encountered in the preparation of (V)) in methanol solution (10) employing the conditions given in Organic Syntheses (11) for

+All melting points are corrected; microanalyses by Dr. G. Oppenheimer and G. A. Swinehart.

the corresponding diethyl ester, b.p. 102–105° at 4 mm., (Cook and Reed (12) give b.p. 137–140° at 14 mm.), yield 84% (analysis for $C_9H_{17}NO_4$), picrate (all picrates described in this paper, unless otherwise stated, were prepared by adding to the base a saturated solution of picric acid in ethyl ether or in isopropyl ether) from methanol, well-formed yellow crystals, m.p. 113.6–114.1° (Cook and Reed (12) give m.p. 113°), analysis for $C_{15}H_{20}N_4O_{11}$.

Methyl-(β-carbomethoxyethyl)-amine (VI) (10) was encountered in the forerun from the preparation of (V), yield ca. 1%; equivalent amounts of methylamine and methyl acrylate in methanol, brought together as in Organic Syntheses (11), and allowed to stand for one week at room temperature gave an 8% yield of (VI). In another experiment, one equivalent of methyl acrylate in methanol was introduced slowly over a period of eighteen hours into two equivalents of methanolic methylamine maintained at about 10°; distillation of the product gave an 11% yield of (VI), 21% of (V), and a large residue. A sample of (VI) boiled at 43.3–43.8° at 8 mm. (lit. (10) b.p. 50° at 11 mm.); picrate, long yellow needles from isopropyl ether–ethanol, m.p. 113.1–113.6° (mixed m.p. with (V) picrate showed depression).

Anal. Calc'd for $C_{11}H_{14}N_4O_9$: C, 38.15; H, 4.08.

Found; C, 38.55; H, 4.26.

The acid oxalate (all oxalates described in this paper were prepared by adding to the base saturated ethereal or isopropyl–ethereal oxalic acid) crystallized in clusters of fine colorless needles from methanol, m.p. 135°.

Anal. Calc'd for $C_5H_{11}NO_2.C_2H_2O_4$: N, 6.76. Found: N, 6.62.

(VI) (12.7 g.) was allowed to stand for five days at room temperature with a slight excess of methyl methacrylate. On distillation 8.2 g. of (VI) was recovered and only 0.5 g. of higher boiling material was obtained (b.p. 101-104° at 4 mm.) (compare (5)).

Methyl-(β-carbomethoxy-n-propyl)-amine (I). To a solution of 62 g. (two moles) of methylamine in 225 g. of methanol was added with stirring and cooling during the course of one hour 302 g. (3 moles) of methyl methacrylate dissolved in 200 g. of methanol. The resulting solution was allowed to stand for three days after which the mixture was fractionated through a short packed column; (I) was obtained as a colorless oil, b.p. 48.8-49.5° at 8.5 mm., yield 203 g. (77%); yield of diester (see below) 31 g. (9%) (equivalent amounts of the reactants allowed to stand for seven days gave 41% of (I) and 11% of the diester). The picrate was oily; (I) plus isopropyl-ethereal 3,5-dinitrobenzoic acid gave an immediate colorless oily precipitate which crystallized on scratching, white bars or colorless parallelepipeds, m.p. 127.0-127.8° from isopropyl ether-ethanol.

Anal. Calc'd for $C_{13}H_{17}N_3O_8$: C, 45.48; H, 4.99; N, 12.24.

Found: C, 45.46; H, 4.91; N, 12.19.

The neutral oxalate crystallized from isopropyl ether-methanol in clusters of fine white needles, m.p. 145.2-145.8°.

Anal. Calc'd for $(C_6H_{13}NO_2)_2 \cdot C_2H_2O_4$: C, 47.71; H, 8.01; N, 7.95.

Found: C, 47.48; H, 7.96; N, 8.03.

The dilituratе, from equivalent amounts of the components, crystallized from aqueous ethanol in irregular clusters of white needles, m.p. 215° d.

Methyldi-(β-carbomethoxy-n-propyl)-amine was obtained (see above) as a colorless oil, b.p. 97-98° at 3 mm.

Anal. Calc'd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15.

Found: C, 57.41; H, 9.83.

The picrate, after recrystallization from isopropyl ether-methanol, melted at 127.1-127.5°, analysis for $C_{17}H_{24}N_4O_{11}$; the oxalate crystallized from isopropyl ether-methanol in colorless needles, m.p. 149-150°; an attempt to cyclize the diester by means of sodium led to no recognizable product.

Methyl-(β-carbomethoxyethyl)-(β-carbomethoxy-n-propyl)-amine (II). To 203 g. (1.55 moles) of (I) was added with cooling and swirling 134 g. (1.55 moles) of methyl acrylate during twenty minutes. After standing for four days at room temperature, the material was fractionated, yielding 34 g. of recovered (I) and 262 g. (77%) of (II) b.p. 105-107° at 4 mm.

Anal. Calc'd for $C_{10}H_{19}NO_4$: C, 55.27; H, 8.81; N, 6.45.

Found: C, 55.76; H, 8.83; N, 6.33.

The picrate was recrystallized from isopropyl ether-methanol, m.p. 88.4-88.9°; the acid oxalate crystallized from isopropyl ether-methanol in fine white needles, m.p. 108.0-108.2°.

Anal. Calc'd for $C_{10}H_{19}NO_4 \cdot C_2H_2O_4$: N, 4.56; Found: N, 4.54.

1-Methyl-3-carbomethoxypiperidone-4 (VII) was prepared by cyclization of (V) following the directions of McElvain (4a) for the carbethoxy compound. Crude (VII) hydrochloride (yield 86%) was recrystallized from ethanol-water; the recrystallized salt (yield 38%) melted at 180.5° dec.; Cook and Reed (12) give m.p. 165° dec.; Mannich and Veit (13c) who prepared

it by another method report the m.p. 173°. The free base was regenerated from the recrystallized hydrochloride (compare (4a)), yield from (V) 25%, b.p. 78.0-79.5° at 3 mm. (Cook and Reed (12) give b.p. 87-88° at 4.5 mm.).

Anal. Calc'd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18.

Found: C, 56.32; H, 7.65; N, 8.35.

(VII) gave a deep red color with ferric chloride; the picrate crystallized from ethanol-water in orange-yellow flat needles, m.p. 163.7-164.5°, analysis for $C_{14}H_{16}N_4O_{10}$. Alkylation of the potassium salt of (VII) with ethyl iodide was attempted (6) without success.

1-Methylpiperidone-4 (VIII). A solution of 5.9 g. of (VII) in 18 g. of 3 N hydrochloric acid was heated for twenty-four hours on the steam bath (compare(4d)) and then evaporated to dryness; (VIII) hydrochloride was obtained as well-formed crystals from ethanol, m.p. 94.7-95.2°; Bolyard and McElvain (4d) report m.p. 94-95°. After treatment of the salt with 50% aqueous potassium carbonate, the base (VIII) was taken up in chloroform, the extracts dried over potassium carbonate and distilled, yield 2.9 g. (74% from (VII)) of a colorless mobile liquid with a strong basic odor, b.p. 43.5-44.1° at 6 mm. (Prill and McElvain (4g) give b.p. 56-58° at 8 mm.).

On standing (VIII) was transformed to a viscous syrup; the picrate and oxalate were not found suitable for characterization. The dibenzal and the di-p-nitrobenzal derivatives were made from the free base by the method employed (4f) in the case of piperidone-4 hydrochloride. p-Nitrobenzaldehyde gave directly a crystalline derivative, as the hydrochloride,

minute yellow needles from ethanol-water, m.p. 252.3-252.8° dec.; benzaldehyde gave a corresponding derivative which was precipitated by isopropyl ether and recrystallized from ethanol, clusters of flat transparent needles, m.p. 240-241° dec. From the latter, the free base was liberated and recrystallized from isopropyl ether-ethanol, fine yellow flakes, m.p. 117.2-118.2°; analytical figures for carbon were consistently low.

Anal. Calc'd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84.

Found: C, 81.53; H, 6.52; N, 4.96.

(VIII) and methyl iodide reacted readily in isopropyl ether to give a precipitate which was recrystallized from methanol, minute white granules, m.p. 187.6-188.0° (capillary introduced into bath at 160°). The analysis indicates that the compound should be formulated as a hemiketal (compare (4d, e, f)).

Anal. Calc'd for $C_8H_{18}INO_2$: C, 33.46; H, 6.32; N, 4.88.

Found: C, 33.21; H, 6.50; N, 4.73.

1,3-Dimethyl-5-carbomethoxypiperidone-4 (III). Four and six-tenths grams (0.2 mole) of bird-shot sodium was prepared under 75 cc. of xylene, cooled to about 60°, and 43.5 g. (0.2 mole) of (II) added (compare (4a)); when the spontaneous gentle reaction subsided, the mixture, protected from moisture by a calcium chloride tube, was refluxed until all sodium particles had disappeared. The resulting dark red liquid was cooled and poured into 150 cc. of ice-water. The phases were separated and the xylene extracted with 50 cc. of ice-water. The combined aqueous phases were made acidic to Congo red paper by addition of concentrated hydro-

chloric acid and after washing with 50 cc. of isopropyl ether, were cooled, basified with potassium carbonate, and extracted eight times with 75 cc. portions of ethyl ether. The combined ethereal extracts were dried over potassium carbonate and treated with excess dry ethereal hydrogen chloride; (III) hydrochloride was filtered off and dried, yield 29.9 g. (67%). For analysis, a portion was recrystallized from methanol, colorless bars, melting with decomposition at 188-191°.

Anal. Calc'd for $C_9H_{16}ClNO_3$: C, 48.76; H, 7.28; N, 6.32.

Found: C, 49.34; H, 7.30; N, 6.43.

Three and four-tenths grams of the hydrochloride was treated with 10 cc. of 50% aqueous potassium carbonate and the liberated oil taken up in isopropyl ether and dried over potassium carbonate; distillation gave 1.88 g. (corresponding to 44% from (II)) of colorless oil, b.p. 89.0-89.5° at 3 mm.

Anal. Calc'd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56.

Found: C, 57.92; H, 8.52; N, 7.63.

(III) gave a vivid blood-red color with alcoholic ferric chloride; on long standing in an icebox, it became quite viscous and eventually precipitated a few colorless needles, presumably the isomeric 1,3-dimethyl-5-carboxypiperidone-4 methyl betaine (compare (4a)). The acid oxalate crystallized in fine colorless needles from isopropyl ether-methanol, m.p. 160.7-161.2°, dec.

Anal. Calc'd for $C_9H_{15}NO_3 \cdot C_2H_2O_4$: N, 5.09; Found: N, 5.14.

1,3-Dimethylpiperidone-4 (IV). A solution of 11.1 g. (0.05 mole) of recrystallized (III) hydrochloride in 60 cc. of 6 N hydrochloric acid

was heated on a water-bath (compare (4d)) for three hours, at the end of which time the initially vigorous carbon dioxide evolution had become negligible. The resulting solution was evaporated to dryness and dried in vacuo, yield of (IV) hydrochloride practically quantitative; a small portion was recrystallized from ethanol-ethyl ether, clusters of fine colorless needles, m.p. 194.9-195.3°.

Anal. Calc'd for $C_7H_{14}ClNO$: C, 51.37; H, 8.62; N, 8.56.

Found: C, 51.40; H, 8.47; N, 8.23.

The free base (IV) was obtained from the salt in the usual manner (compare (VIII)), yield 5.7 g. (89%) of a colorless oil, b.p. 43.0-43.4° at 5.5 mm.

Anal. Calc'd for $C_7H_{13}NO$: C, 66.09; H, 10.30; N, 11.01.

Found: C, 66.06; H, 10.18; N, 11.02.

After standing in an icebox for more than a year (IV) was apparently unaltered. (IV) picrate crystallized from ethanol-water in clusters of long orange needles, m.p. 191.9-192.2°, analysis for $C_{13}H_{16}N_4O_8$. The 2,4-dinitrophenylhydrazone hydrochloride was obtained (14) as small irregular clusters of orange needles from aqueous methanol, m.p. 230-232° dec., analysis for $C_{13}H_{18}ClN_5O_4$. The addition of 4 N sodium hydroxide to a solution of this salt in hot aqueous ethanol precipitated the free base, clusters of light orange granules from acetonitrile, m.p. 151.4-151.7°, analysis for $C_{13}H_{17}N_5O_4$.

<u>N-(β-Carbomethoxyethyl)-aniline</u>. Methyl acrylate (86 g. = 1.0 mole) was added to 46.5 g. (0.5 mole) of aniline in 125 cc. of methanol and the solution allowed to stand for ten days at room temperature; distillation

yielded 34.7 g. of unreacted aniline and 13.4 g. (14%) of faintly colored oil, b.p. 125–126° at 3 mm., which solidified on standing, white micaceous crystals from methanol–water, m.p. 37.6–38.3°.

Anal. Calc'd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82.

Found: C, 67.42; H, 7.21; N, 7.75.

N-(β-carbomethoxyethyl)-aniline gave an acid oxalate which crystallized from isopropyl ether–methanol in white flakes, m.p. 143.1–143.9°.

Anal. Calc'd for $C_{10}H_{13}NO_2 \cdot C_2H_2O_4$: N, 5.20. Found: N, 5.42.

No higher boiling fraction was obtained; when the reaction was carried out at higher temperatures, refluxing both with and without solvent, large amounts of aniline were recovered and apparently acrylic ester polymers constituted the chief product.

From a solution of 45.5 cc. (0.5 mole) of aniline and 100 g. (1.0 mole) of methyl methacrylate in 125 cc. of methanol which had stood at room temperature for 13 days, 42.5 g. of aniline was recovered and no higher boiling volatile product was obtained.

Ethyl β-(di-n-butylamino)-propionate. Ethyl acrylate (156 g. = 1.56 moles) was added over a period of fifteen minutes to 202 g. (1.56 mole) of di-n-butylamine cooling meanwhile by means of an ice bath. The solution was allowed to stand stoppered at room temperature for eleven days and then distilled at 1 mm.; 334 g. (93%) was obtained boiling in the range 90–94°. Weisel, Taylor, Mosher, and Whitmore (15) report preparing this ester in essentially the same way, using a slight excess of the amine and heating with steam for 44 hours, yield 60% of product boiling at 136–137° at 16 mm.

Anal, Calc'd for $C_{13}H_{27}NO_2$: C, 68.07; H, 11.87; N, 6.11.

Found: C, 68.26; H, 11.92; N, 6.26.

The base formed no ether insoluble picrate (Whitmore et al. (15) report the picrate as an oil); the methiodide was obtained as an oil. The diliturate was obtained from equivalent amounts of the components in ethanol, irregular clusters of light yellow needles from ethanol, m.p. 167.0-167.2° (analysis for $C_{17}H_{30}N_4O_7$).

A mixture of 25.8 g. (0.2 mole) of di-n-butylamine and 22.8 g. (0.2 mole) of freshly distilled ethyl methacrylate was allowed to stand for sixteen days at room temperature; on distillation under reduced pressure the reactants were recovered essentially unchanged (distillation residue 1.5 g.).

Summary

A representative 3-alkylsubstituted piperidone-4, the 1,3-dimethyl derivative, has been prepared by standard methods.

Acrylic esters combine much more readily than methacrylic esters with primary and secondary bases.

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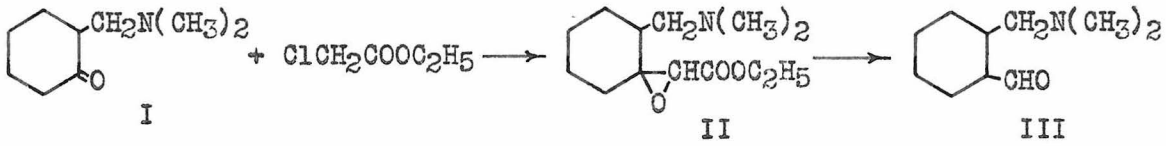
II. APPLICATION OF THE DARZENS-CLAISEN REACTION TO A β-DIALKYLAMINOKETONE.

APPLICATION OF THE DARZENS–CLAISEN REACTION TO A β-DIALKYLAMINOKETONE.

Interest in attaching functional sidechains to the ketonic carbon of certain γ-piperidones (1) prompted us to investigate the applicability of the method of Darzens (2a) and Claisen (2b). We have now shown that 2-dimethylaminomethylcyclohexanone (I) condenses with ethyl chloroacetate according to this method, giving a mixture from which two glycidic esters (II) were isolated, both of which can be converted to the same o-dimethylaminomethylhexahydrobenzaldehyde (III).



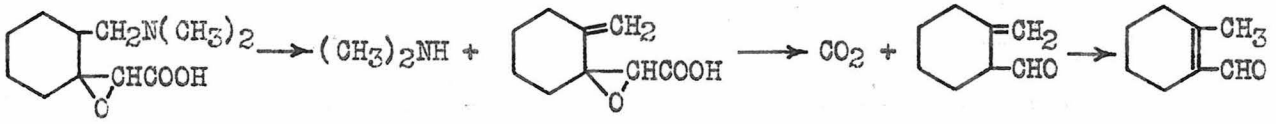
I II III

Clemo, Ramage, and Raper (3) obtained a glycidic ester from an α-tertiaryaminoketone, but were not able to prepare the aldehyde from it.

The well-known Mannich reaction provides easily-available β-aminoketones, from which (I), derived from cyclohexanone, was selected because of the good yields obtained in its preparation, the simplicity of carrying out rather large-scale runs, and the stability of the product. Although considerable work has been done toward improving the conditions of the Darzens–Claisen condensation (see (4)), we obtained very satisfactory results using the directions originally given by Darzens (2a): one mole of freshly-prepared sodium ethoxide was slowly added to an equimolar mixture of the ketone and the chloroester at about room temperature; the yields of the ester mixture (II) were consistant and good (43–57%).

A glycidic ester derived from an asymmetrically-substituted cycloalkanone contains two new centers of asymmetry and hence could consist of four diastereoisomeric racemates; by a slightly different type of Darzens reaction (5) (condensation of a ketone with an α,α-dihalogenoaliphatic ester by means of a magnesium amalgam and subsequent treatment with alkali), Miescher and Kägi (6) obtained and characterized four isomeric glycidic acids derived from dehydroandrosterone; Yarnall and Wallis (4) apparently obtained two of these four acids by application of the Darzens-Claisen reaction to the same ketone. By fractional recrystallization of the dilituratesformed from the crude glycidic ester (II), it was shown to be a mixture from which only two isomers could be isolated.

The aldehyde (III) was obtained most conveniently by refluxing the ester (II) for one-half hour with concentrated hydrochloric acid. On exposure to atmospheric oxygen, (III) is slowly oxidized to the corresponding acid, o-dimethylaminomethylhexahydrobenzoic. (III) was also identified among the products of the thermal decomposition of the glycidic acid (IV) derived from the esters by hydrolysis with barium hydroxide, but the main product of this reaction was a non-basic aldehyde (probably (VII)) formed by the loss of dimethylamine and carbon dioxide from (IV).



IV V VI VII

(IV) bears a certain structural resemblance to the β-aminoketones, whose tendency to split into amines and vinyl ketones has been well-

documented (7). This similarity suggests that in its thermal decomposition, dimethylamine is lost from (IV), giving first the unsaturated glycidic acid (V), which would lose carbon dioxide and rearrange, via (VI), to (VII), in which the two centers of unsaturation are in the more stable conjugated configuration. The deep scarlet color of the aldehyde's 2,4-dinitrophenylhydrazone is in agreement with the postulated conjugated configuration of (VII) (8).

Experimental[+]

2-Dimethylaminomethylcyclohexanone (I) was prepared by the method of Mannich and Braun (9), used also by Dimroth, Resin, and Zetzsch (10), in yields which seemed to depend on the size of the run; a one mole experiment gave 71%, three moles 64.3%, and 6.13 moles 55.2% of colorless, mobile oil boiling at 96-97° at 11.5 mm. (Dimroth et al. (10) give b.p. 93-94° at this pressure). Although Mannich and Braun state that the base (I) "schon binnen 8 Tagen bilden sich reichlich höher siedende Produkte", we noted no indications of instability and found that of a sample redistilled after standing for almost three years at room temperature, almost 75% boiled at 70-77° at 5 mm.

The hydrochloride of (I), recrystallized once from ethyl acetate and again from isopropyl ether-ethanol, formed small, glistening, white flakes melting at 139.9-140.6° when heated very slowly; the melting point was somewhat higher (145.5°) when the bath temperature was raised more rapidly (Mannich and Braun (9) give m.p. 152°)(analysis).

[+]All melting points are corrected. We are indebted to Dr. G. Oppenheimer and her staff for microanalyses.

Mannich and Braun (9) state that "Das Jodmethylat der Ketobase [I] ist so unbeständig, dass es nicht rein erhalten werden konnte"; Dimroth and his coworkers (10) prepared the salt in ether solution under nitrogen and report it stable in the pure crystalline form, m.p. 136-137°, followed by resolidification and decomposition from 200°. We prepared the salt using no special precautions and obtained a product forming clusters of colorless pyramids in square patterns from ethanol, m.p. 152-153°, resolidifying at about 160°.

Anal. Calc'd for $C_{10}H_{20}INO$: C, 40.41; H, 6.78; N, 4.71.
Found: C, 40.78; H, 6.83; N, 4.80.

Prepared by adding isopropyl-ethereal picric acid to a solution of (I) in the same solvent, the picrate formed minute yellow needles from isopropyl ether-ethanol, m.p. 147.0-147.2° (Mannich and Braun (9) give m.p. 149°).

Attempts to apply the Reformatsky reaction (with zinc and methyl bromoacetate) to (I) were apparently complicated by quaternary salt formation, giving only traces of starting material and negligible amounts of higher-boiling basic substances.

Dimethylaminomethylacetone was obtained in yields of 3.6 to 13% following the directions of Mannich (11); careful fractional distillation was required to purify the base, b.p. 50-51° at 13 mm., in agreement with Mannich (11). 0.159 mole of this material subjected to the Darzens condensation (see details below) gave 6.1% of the starting material and 4.7% of a pale yellow viscous oil boiling at 78-91° at 3 mm. An attempt to condense the ketone with ethyl dichloroacetate in the

presence of a magnesium amalgam, using the conditions set forth by Darzens and Lévy (5), gave only a negligible yield of high-boiling material.

2-Carbethoxy-4-dimethylaminomethyl-1-oxaspiro[2.5]octane (II). A mixture of 77.6 g. (0.5 mole) of (I) and 61.25 g. (0.5 mole) of ethyl chloroacetate was cooled in a three-necked 500-cc. flask equipped with a mercury-sealed Hershberg stirrer, a water-cooled Allihn condenser protected by a calcium-chloride tube and containing a thermometer dipping into the mixture, and a small conical flask attached to the third neck of the reaction vessel by a piece of large-bore rubber tubing and containing 34.0 g. (0.5 mole) of freshly-prepared, dry, alcohol-free sodium ethoxide (12). The ethoxide was slowly added at such a rate that the temperature of the mixture did not exceed 20°, requiring about one-half hour. After stirring overnight at room temperature, the light brown paste was heated in a boiling water bath for three hours, during which time it first thickened, then became more mobile and somewhat lighter in color. This paste was cooled in ice, dissolved in 160 cc. of cold 6 N hydrochloric acid, washed with 200 cc. of ethyl ether, carefully basified with 100 g. of potassium hydroxide pellets, and the liberated red-brown oil extracted with two 200-cc. portions of ethyl ether; dried over sodium sulfate and stripped of ether, the product was distilled at 0.025 mm., yielding 64.4 g. (53.3%) of light-yellow oil, b.p. 101-110°. A 1.0 mole run in which the temperature of the mixture was kept under 0° during the addition of the ethoxide gave a 53.8% yield of (II), b.p. 110-115° at 1 mm. Other experiments gave

yields ranging from 43.5% to 57.5%. For analysis, a sample of (II) was redistilled at 3 mm., b.p. 127-129°.

Anal. Calc'd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.81.

Found: C, 64.45; H, 9.60; N, 6.03.

2-Carboxy-1-oxaspiro[2.5]octane was obtained in 90% yield by an aqueous-potassium-hydroxide saponification of the corresponding ethyl ester, prepared from cyclohexanone in 76% yield by the method of Darzens and Lefébure (13). The ester was a colorless oil boiling at 106-112° at 6 mm. (Darzens and Lefébure give b.p. 128-129° at 17 mm.). The acid, after three recrystallizations from warm water, formed clusters of short, colorless needles, m.p. 125.0-125.7°.

Anal. Calc'd for $C_8H_{12}O_3$: C, 61.51; H, 7.75.

Found: C, 61.39; H, 8.00.

Separation of Isomeric Esters (II) with Dilituric Acid. One-tenth mole (24.1 g.) of the above ester mixture was dissolved in 300 cc. of absolute ethanol and 22.7 g. (0.1 mole) of dilituric acid trihydrate was added; the mixture was brought to a boil and water added dropwise as long as solid continued to dissolve; a trace of difficultly-soluble white solid was filtered off. On cooling, 24.7 g. of the α-form of (II) dilituric crystallized out as small, compact clusters of light yellow plates; this crop was filtered off, washed with ethanol and isopropyl ether and air-dried. After standing for about a week, the mother liquors deposited 7.1 g. more of the same material. Spontaneous evaporation of a small portion of the first-crop mother liquors gave seed crystals of the β-dilituric, which were added to the mother liquors

from the second crop of the α-dilituratе, yielding 3.8 g. of the β-form, compact, white needle-clusters. Evaporation of the filtrate from this crop to dryness left 13.3 g. of material whose melting point could not be raised above 133-134° by repeated recrystallizations from ethyl acetate-ethanol, but which gave pure β-(II) in poor yield, identified by the methiodide and dilituratе (see below).

The α-(II) dilituratе, recrystallized from ethanol-water, melted at 188.6-188.8° with decomposition to a red liquid. After several recrystallizations from ethanol, the β-(II) dilituratе formed clusters of colorless needles with a greenish tinge, decomposing at 177.2-178.0° to a red liquid.

Anal. Calc'd for $C_{17}H_{26}N_4O_8$: C, 49.27; H, 6.33; N, 13.52.

Found (α-form): C, 49.60; H, 6.25; N, 13.32.

(β-form): C, 49.63; H, 6.46; N, 12.76.

Characterization of Pure α-(II). After grinding to a fine powder, 10.4 g. of α-(II) dilituratе was dissolved in 50 cc. of warm water and the solution was cooled in ice and treated with 7.51 g. (one equivalent) of freshly-distilled anhydrous ethylene diamine (see (14)); the resulting slurry was centrifuged, giving a layer of white solid, a colorless oil, and a yellow aqueous phase, α-(II) being apparently more dense than water. The ester was extracted with ethyl ether, dried over potassium carbonate, and distilled at 1 mm., yield 3.54 g. (60%) of colorless, very viscous oil boiling at 95-98°. Similarly, an aqueous solution of α-(II) dilituratе basified with 4 N sodium hydroxide and extracted with ligroin gave 75.5% of the pure ester, undistilled.

Anal. Calc'd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.81.

Found: C, 64.61; H, 9.68; N, 5.58.

The acid α-(IV) was obtained by boiling 1.21 g. of pure α-(II) with 50 cc. of saturated aqueous barium hydroxide for 15 minutes, a clear solution being obtained in 5. Careful precipitation of the barium with 6 N sulfuric acid followed by evaporation to dryness gave 1.00 g. of colorless solid which, after washing with acetone, melted with decomposition at 188-190°. One recrystallization from acetonitrile-methanol gave very tiny colorless granules, m.p. 202-203° decomp.

Anal. Calc'd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57.

Found: C, 61.83; H, 8.71; N, 6.42.

Addition of one equivalent of methyl iodide to the ester α-(II) or a concentrated ethanolic solution of it gave the α-(II) methiodide, which crystallized in either of two forms of different melting point. One form emerged from ethanol in massive clusters of colorless prisms with pyramidic terminations or as diamond-shaped plates thickening into rhomboid figures, m.p. 186.9-187.3°. The other, also recrystallized from ethanol, formed colorless, irregularly-faced acute pyramids melting at 217.3-218.1°; from ethyl acetate-ethanol, feathered pyramids of m.p. 220.1-220.4° were noted. The form obtained in the absence of seed crystals seemed to be a matter of chance; an ethanolic solution of the lower-melting form seeded with the other gave the higher-melting salt.

Anal. Calc'd for $C_{14}H_{26}INO_3$: C, 43.87; H, 6.84; N, 3.65.

Found (187°): C, 44.09; H, 6.87; N, 3.17.

(218°): C, 44.26; H, 6.71; N, 3.56.

Prepared in the same way, the ethiodide of α-(II) crystallized from ethyl acetate–ethanol in beautiful clusters of colorless, stubby needles, m.p. 187.6–188.0°. A mixture of this salt with the low-melting methiodide (above) had m.p. 186–195°.

Anal. Calc'd for $C_{15}H_{28}INO_3$: C, 45.34; H, 7.10; N, 3.53.
Found: C, 45.47; H, 7.52; N, 3.35.

Treatment of α-(II) with isopropyl–ethereal oxalic acid gave a colorless oil which solidified on standing; after four recrystallizations from isopropyl ether–ethanol, the white puffballs so formed melted at 140.9–141.7° and analyzed as the acid-oxalate.

Anal. Calc'd for $C_{13}H_{23}NO_3 \cdot C_2H_2O_4$: C, 54.36; H, 7.60; N, 4.23.
Found: C, 54.15; H, 7.60; N, 4.46.

Addition of isopropyl–ethereal solutions of picric and 3,5-dinitrobenzoic acids to α-(II) gave oils which did not solidify.

Characterization of Pure β-(II). By the ethylene-diamine method detailed above, 3.8 g. of the crude β-(II) diliturate yielded 1.01 g. (48%) of pure β-(II), very viscous, colorless oil, b.p. 93–94° at 1 mm. Liberation of the free base with aqueous sodium hydroxide gave a yield of 43%, undistilled.

Anal. Calc'd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.81.
Found: C, 64.88; H, 9.62; N, 5.63.

By the method described above, β-(IV) was obtained in quantitative yield, crude m.p. 196° with decomposition.

β-(II) methiodide formed clumps of colorless granules from ethanol, m.p. 173.4–173.6°.

Anal. Calc'd for $C_{14}H_{26}INO_3$: C, 43.87; H, 6.84; N, 3.65.

Found: C, 43.37; H, 7.21; N, 3.53.

Recrystallized from isopropyl ether or ethyl acetate–ethanol, the ethiodide of β-(II) formed clusters of fine colorless needles or blades with a micaceous luster, m.p. 134.9–135.3°.

Anal. Calc'd for $C_{15}H_{28}INO_3$: C, 45.34; H, 7.10; N, 3.53.

Found: C, 45.37; H, 6.97; N, 3.13.

The picrate of β-(II) was obtained as a red oil which could not be induced to crystallize.

o-Dimethylaminomethylhexahydrobenzaldehyde (III). One eighth of a mole (30.2 g.) of the ester mixture (II) was treated with 104 cc. of 12 N hydrochloric acid and refluxed for one-half hour, giving a deep wine-red, slightly cloudy solution and a small amount of dark green oil. After cooling in ice, the solution was basified by the slow addition of about 200 cc. of 30% aqueous potassium hydroxide, the solution turning yellow at about the neutral point. The product was extracted with two 100-cc. and four 50-cc. portions of freshly-distilled isopropyl ether, dried over potassium carbonate, and distilled at 1 mm., yielding 3.20 g. (15.2%) of colorless liquid boiling at 61.6–62.3°; about an equal amount of brown oil remained in the boiler after the distillation of the product. The aldehyde (III) had a characteristic terpene-like odor, was insoluble in water, and seemed fairly stable, for a few days at least, when kept under nitrogen.

Anal. Calc'd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28.

Found: C, 71.11; H, 11.30; N, 8.32.

Small amounts (2.2 g. and 1.1 g., respectively) of the pure esters α-(II) and β-(II) subjected to this same procedure gave the same aldehyde (III), identified in the case of the α-ester as the picrate, in that of the β-ester as the air-oxidation acid; these derivatives are described below.

A hydrolysis of another eighth-mole of the mixed esters (II) with 500 cc. of 1.68 molar sulfuric acid, refluxed overnight, gave 0.79 g. (3.7%) of (III).

On cooling a solution of the picrate of (III) in hot ethanol-acetonitrile, the salt emerged first in dendritic, bright-yellow needle-clusters, which slowly changed into larger, darker-yellow, flat needles; both forms had the same melting point (168.6-169.4°), which was not depressed by admixture.

Anal. Calc'd for $C_{16}H_{22}N_4O_8$: C, 48.23; H, 5.57; N, 14.06.

Found: C, 48.30; H, 5.82; N, 13.68.

The methiodide of (III), prepared in ethanol and recrystallized from ethyl acetate-acetonitrile, formed irregular clusters of colorless bars, m.p. 213.8-214.0°; this melting point was somewhat higher when the heating was rapid.

Anal. Calc'd for $C_{11}H_{22}INO$: C, 42.45; H, 7.13; N, 4.50.

Found: C, 42.58; H, 7.07; N, 4.27.

One millimole each of (III) and 2,4-dinitrophenylhydrazine were placed in 5 cc. of 95% ethanol and 6 N hydrochloric acid was added dropwise at the boiling point until a clear solution resulted; a lightening of the solution's color was also noted. On cooling and scratching, a

light-yellow, finely-divided solid separated out; one recrystallization from acetonitrile gave beautiful clusters of light-yellow or orange-yellow needles, m.p. 221.5-221.8° with decomposition. The analysis of this substance showed it to be the hydrochloride of (III)-2,4-dinitrophenylhydrazone.

Anal. Calc'd for $C_{16}H_{24}ClN_5O_4$: C, 49.81; H, 6.27; N, 18.16.
Found: C, 50.36; H, 6.50; N, 18.44.

The free 2,4-dinitrophenylhydrazone was obtained from an aqueous solution of the salt above by basifying with 4 N sodium hydroxide; from acetonitrile, it formed beautiful clusters of light orange rods melting at 146.9-147.4°.

Anal. Calc'd for $C_{16}H_{23}N_5O_4$: C, 55.00; H, 6.63.
Found: C, 55.28; H, 6.36.

Attempts to prepare the semicarbazone of (III) were unsuccessful.

o-Dimethylaminomethylhexahydrobenzoic acid separated from (III) within a few minutes after exposure to air as colorless bobbin-clusters which increased in amount over two or three weeks until the whole sample became an oily solid; washed with ligroin or isopropyl ether and recrystallized from ethyl acetate-ethanol, this compound melted at 154.0-155.0°; it was readily soluble in water, giving a weakly basic solution (pH about 8).

Anal. Calc'd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56.
Found: C, 64.24; H, 10.37; N, 7.60.

When this acid was stirred with an ethereal solution of diazomethane at 0°, nitrogen was slowly evolved, the acid slowly dissolved, and a white flakey solid separated from the solution; this solid redissolved

on warming to room temperature and was not obtained from the colorless oil left on evaporation of the ether and excess diazomethane. Treatment with isopropyl-ethereal picric acid gave a red oil which solidified on standing and scratching; recrystallized from isopropyl ether-ethyl acetate, the picrate of the methyl ester formed rugged orange bipyramids, m.p. 114.2-115.1° after some softening from 112°.

Anal. Calc'd for $C_{17}H_{24}N_4O_9$: C, 47.66; H, 5.65; N, 13.08.
Found: C, 48.05; H, 5.59; N, 12.55.

Thermal Decomposition of (IV). After washing with acetone and drying, 0.62 g. of the glycidic acid (IV) obtained from the mixed esters (II) was heated to 200° in a vessel evacuated to 1 mm.; when the evolution of gases had ceased, the contents of the reaction flask were extracted with isopropyl ether and treated with picric acid in the same solvent; the picrate thus obtained was identified as that of (III) by m.p. and mixed m.p.

In a similar experiment with 0.83 g. of acetone-washed α-(IV), about 0.4 cc. of a light yellow-green liquid was trapped out with dry ice; redistillation of this distillate gave 0.2 cc. of colorless oil, b.p. about 80° (bath temperature) at 4 mm. Analysis of this material gave values different from those calculated for (III) and approaching those for (VII).

Anal. Calc'd for (III): C, 70.96; H, 11.31.
for (VII): C, 77.37; H, 9.74.
Found: C, 75.23; H, 10.09

A portion of this product heated with an equivalent of 2,4-dinitrophenylhydrazine in 95% ethanol gave a dark red solid on addition of a

little 6 N hydrochloric acid; this derivative formed deep scarlet needles from acetonitrile, m.p. 192.4–192.7° and analyzed as the 2,4-dinitrophenylhydrazone of the tetrahydro-o-tolualdehyde (VII).

Anal. Calc'd for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41.

Found: C, 55.45; H, 5.13; N, 18.88.

Another portion of this redistilled product gave a picrate, yellow needles from isopropyl ether–ethanol, m.p. 147.8–148.1°, in amount too small for analysis.

The crude product from another thermal decomposition of 0.55 g. of α-(IV) was treated with isopropyl-ethereal picric acid; the crude picrate was recrystallized from isopropyl ether–ethanol, giving a mixture of yellow needles and red blades which was separated mechanically. The yellow needles crystallized in clusters from ethanol, m.p. 193.4–193.9° to a black liquid, analysis: C, 49.49, 49.71; H, 5.07, 5.37; N, 15.80, 15.66%. The red blades formed orange lattices from ethanol, m.p. 159.9° after some sintering from 155°, unaffected by admixture with an authentic sample of dimethylamine picrate (Jerusalem (15) gives m.p. 158–159°).

Anal. Calc'd for $C_8H_{10}N_4O_7$: C, 35.04; H, 3.68; N, 20.43.

Found: C, 35.30; H, 3.73; N, 20.21.

A 0.47 g. sample of β-(IV) thermally decomposed in this way and the volatile product redistilled gave 0.07 g. of a colorless oil having a strong terpene-like odor and boiling at 66–76° at 10 mm., analysis: C, 74.93; H, 9.97%. The picrate of this oil could not be induced to crystallize, but the 2,4-dinitrophenylhydrazone formed deep scarlet needles or bars from acetonitrile, m.p. and mixed m.p. identical with the derivative obtained from α-(IV) (see above), presumably of (VII).

Summary

The Darzens–Claisen reaction has been successfully applied to the conversion of a typical β-dialkylaminoketone into a mixture of two basic glycidic esters which have been separated as their dilituratesand degraded to the same basic aldehyde.

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III. 6'-METHOXYRUBANOL-9.

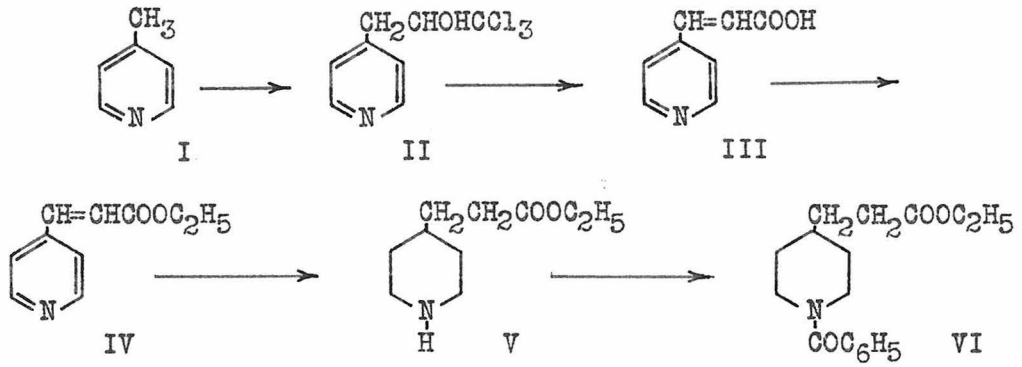
6'-METHOXYRUBANOL-9+

The synthesis of 6'-methoxyrubanol-9 was reported in 1941 simultaneously by Rabe and coworker (1) and by Prelog and coworkers (2); a further publication by Rabe which appeared in 1943 (3) also dealt with this subject. Still more recently, Kleiman and Weinhouse in Chicago have prepared this substance and the results (4) of their as yet unpublished work have been made available to us.

The general plan for synthesis of 6'-methoxyrubanol-9 which we have followed was essentially that of Rabe who used as a model his classical dihydroquinine synthesis (5). Certain modifications were introduced and a more careful study was made of certain of the reactions involved so that, on the whole, our knowledge concerning the synthesis has been considerably extended and the derived carbinol has been made more easily accessible than formerly. The synthesis may be considered as consisting of two parts, the preparation of ethyl β-(N-benzoylpiperidyl-4)-propionate (6), and the conversion of this intermediate to the methoxyrubanol.

Preparation of Ethyl β-(N-Benzoylpiperidyl-4)-propionate (VI). Rabe (6a, 1, compare 4) prepared this substance starting from γ-picoline (I). Condensation of (I) with chloral gave 1,1,1-trichloro-3-(γ-pyridyl)-propanol-2 (II) which on alkaline hydrolysis (8) gave a 70% yield of

+The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.



β-(γ-pyridyl)-acrylic acid (III) (6b). This was reduced (8) directly to β-(piperidyl-4)-propionic acid (6b) and esterified to the ester (V) (6c) (70% yield from III)). Benzoylation (6a) gave a 92% yield of (VI). In the present work it was found convenient to carry out these same steps except that esterification of (III) preceeded reduction.

The preparation of (II), the so-called γ-picoline chloral, has been described by numerous investigators (7, 8, 6, 9, 10, 1, 4, 11); the yields reported vary from a few percent (8) up to 70% (4). Undoubtedly the yield is very largely dependent on the quality of (I) (compare 1); in the present investigation, γ-picoline from three sources—Barrett Division of Allied Chemical and Dye Corporation, Koppers Company, and Reilly Tar and Chemical Corporation—proved satisfactory. Equimolecular amounts of (I) and of chloral, allowed to react in the absence of condensing agent and solvent at 25–40° for periods up to one week, gave a better than 60% yield of (II); higher temperatures gave lower yields due to increased tar formation. When the reaction was carried out using an excess of (I) as solvent and in the presence of anhydrous zinc chloride and maintaining at 40° for two days (solvent removed at water bath

temperature), the yield based on chloral was better than 75%.

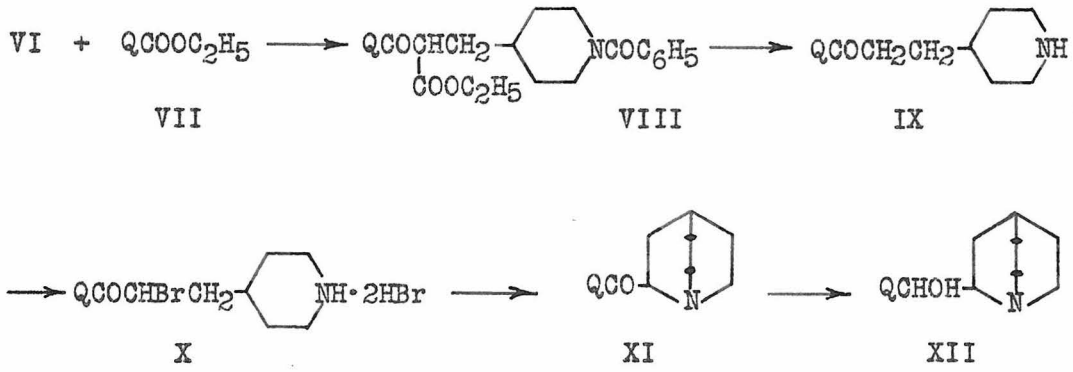
The preparation of (III) has been previously described (8, 6b, 6c, compare 4). Its esterification has been carried out at this Institute (11) by Niemann and Brown+, who characterized (IV) as a nicely crystalline solid melting at 64°. In the present work (IV) was obtained (in 52% yield from (II)) directly from the hydrolysis mixture from (II) without isolating the intermediate (III). Further the preparation of (IV) from the crude γ-picoline-chloral condensation product without isolation of either (II) or (III) was investigated; the overall yield of (IV) obtained starting from equimolecular amounts of (I) and of chloral was 33-37%. This yield compares favorably with that obtained under the most favorable conditions and it is possible to recommend the simplified procedure because of the relative ease of obtaining (IV) by this method.

The catalytic reduction (using Raney nickel at 100°) of (IV) to β-(γ-pyridyl)-propionic ester has been successfully carried out by Niemann and Brown (11). We found that the latter ester may be further reduced at high pressures and temperatures with Raney nickel to give (V) but, although considerable time was expended on the method, no completely satisfactory procedure could be evolved. On the other hand, hydrogenation of (IV) as the hydrochloride at atmospheric pressure and room temperature in the presence of Adams' catalyst and benzoylation

+We are very much indebted to Dr. Carl Niemann, who placed at our disposal unpublished notes of Mr. David H. Brown relating to the preparation of (II), (III), (IV), and β-(γ-pyridyl)-propionic ester.

(compare 6) of the crude crystalline reaction product in the presence of anhydrous pyridine gave the desired (VI) in excellent yield (92%). The overall yield of (VI) based on (I) and/or chloral is 30-34%.

Preparation of 6'-Methoxyrubanol-9 (XII) from (VI). The steps indicated below were used by previous workers (1,2,4) as well as by ourselves to convert (VI) to (XII). Q = (6'-Methoxyquinolyl-4)-



The condensation of (VI) with quininic ester (VII) has been effected with sodium ethylate (6,1,4, compare 2) and with sodium (2). We used sodamide which had been recommended for this type of synthesis (12, compare 13) and obtained N-benzoyl-6'-methoxy-8-carbethoxyrubatoxanone-9 (VIII) as a crystalline solid, m.p. 144°--previously reported only as an oil--in average yield of 43.5%; powdered sodium as a condensing agent gave a 29% yield.

The hydrolysis (6, 1, compare 2) of (VIII) to 6'-methoxyrubatoxanone-9 (IX) as well as the bromination (1, 2) of the latter to 6'-methoxy-8-bromorubatoxanone-9 dihydrobromide (X) was accomplished by literature methods. Bromine in the form of bromine vapor was used for the bromination as suggested by Rabe (1, compare 12); however, subsequent

results obtained in this laboratory in analogous cases indicate that the use of bromine dissolved in concentrated hydrobromic acid (1, 2, 4) may be preferable. (X), which had not previously been reported pure, was obtained as an easily purified solid melting with decomposition at 194°, overall yield from (VIII) 68.5%.

The ring closure of (X) to 6'-methoxyrubanone-9 (XI) was accomplished as described by Rabe (1, compare 2); crude (XI) was obtained as a non-crystallizing oil in average yield of 78%. Purification was achieved by conversion to the crystalline dihydrochloride of (XI) from which pure (XI), m.p. 90.5° (compare 1, 2) was easily regenerated, yield 58-62% from (X). Pure (XI) was shown to be quite stable toward air, even in the presence of alkali; unpublished work from this laboratory (14, compare 13) had shown that simpler ketones of the type QCOC-N are very susceptible to autoxidation.

Reduction of (XI) was carried out by Rabe in aqueous hydrochloric acid in the presence of palladium black (1, compare 5) and by Prelog (2, compare 4) in methanol in the presence of reduced platinum oxide. Making use in the present investigation of a method developed by Sargent (13) on a somewhat analogous case, (X) was ring-closed with sodium carbonate in aqueous methanol and the resulting solution, without isolation of (XI), reduced after addition of Adams' catalyst; the yield of (++) (−−) 6'-methoxyrubanol-9 (XII) was 38-41%. When pure (XI) was reduced under comparable conditions, the yields of (++) (−−) and of (+−) (−+) racemates were respectively 55% and 9%; the remaining products of the reaction were not identified. When crude (XI) (see above) was reduced

with aluminum isopropylate, the (++) (--) and (+-) (-+) racemates were obtained in yields based on (X) of 38% and 22% respectively. In this work the two racemates were separated as monohydrochlorides (isolation of the (++) (--) form as the monohydrochloride (3) proved superior to use of the free base hydrate (1) or of the dihydrochloride). On the basis of the above data, one would choose the Sargent method as the more direct for preparation of the (++) (--) isomer; the isopropylate reduction, on the other hand, gives far better yields of (+-) (-+) base which can be converted (3) to the (++) (--) form. The overall yield of (++) (--) (XII) was 11-12% from (VI).

The catalytic reduction of (XI) monohydrochloride in methanol in the presence of Adams' catalyst was also studied; after one mole-equivalent of hydrogen had been absorbed, the product isolated was shown to be (IX) monohydrochloride formed by reductive splitting of the quinuclidine ring (compare 15). It was further found that reduction of crude (XI) free base in methanol and with Adams' catalyst gave erratic results so that this method is not suitable for quantity production of (XII); also under these conditions considerable amounts of (IX) could be detected in the product.

Although it was noted that 6-methoxyquinolyl-4 ketones could be distinguished from the corresponding carbinols by their brilliant yellow color in aqueous hydrochloric acid as well as by their lack of the fluorescent properties so characteristic of the quinine type, the difficulty of differentiating between (IX), (XI) and (XII) by means of distinctive derivatives or by elementary analyses made a study of the ultraviolet

absorption spectra of these compounds very valuable. Manta (16) showed that quinine and quinidine exhibited the characteristic absorption spectrum of 6-methoxylepidine. We found that solutions of the isomeric carbinols (XII), like quinine, show three maxima near 230, 280 and 330 mμ; at a pH of about 3, a bathochromic shift of all three maxima moves them to ca. 250, 320 and 350 mμ. The characteristics of the spectra of the ketones (IX) and (XI) appear also in analogous cases (17). The quinuclidyl ketone (XI) at pH ca. 6 shows a single broad absorption maximum which is shifted (from 359 mμ to 336 mμ) when the pH is raised to about 10. In contrast, (IX) has a single maximum near 340 mμ which is not appreciably affected by pH change. Particularly characteristic of these ketonic compounds is a more or less pronounced discontinuity at ca. 260 mμ in the otherwise smooth steep curve defining the decreasing light absorption between 220 and 285 mμ. Graphs of these spectra are shown in Figures 1, 2, 3, and 4.

The resolution of (++) (- -) (XII) as described by Rabe (1,3) necessitates the use of l-tartaric acid to separate the laevorotatory base. We found that the readily available l-malic acid was not only suitable for this purpose but can apparently be used with advantage for separation of the dextrorotatory isomer also. The (++) and (--) bases agreed in physical properties with the Rabe description (1, 3).

According to Prelog et al. (18), (++) (--) (XII) dihydrochloride has an action in bird malaria equivalent to that of quininehydrochloride. Rabe and collaborators (19), who employed a comparable physiological test, reported that neither (--) (XII), the analog of quinine, nor

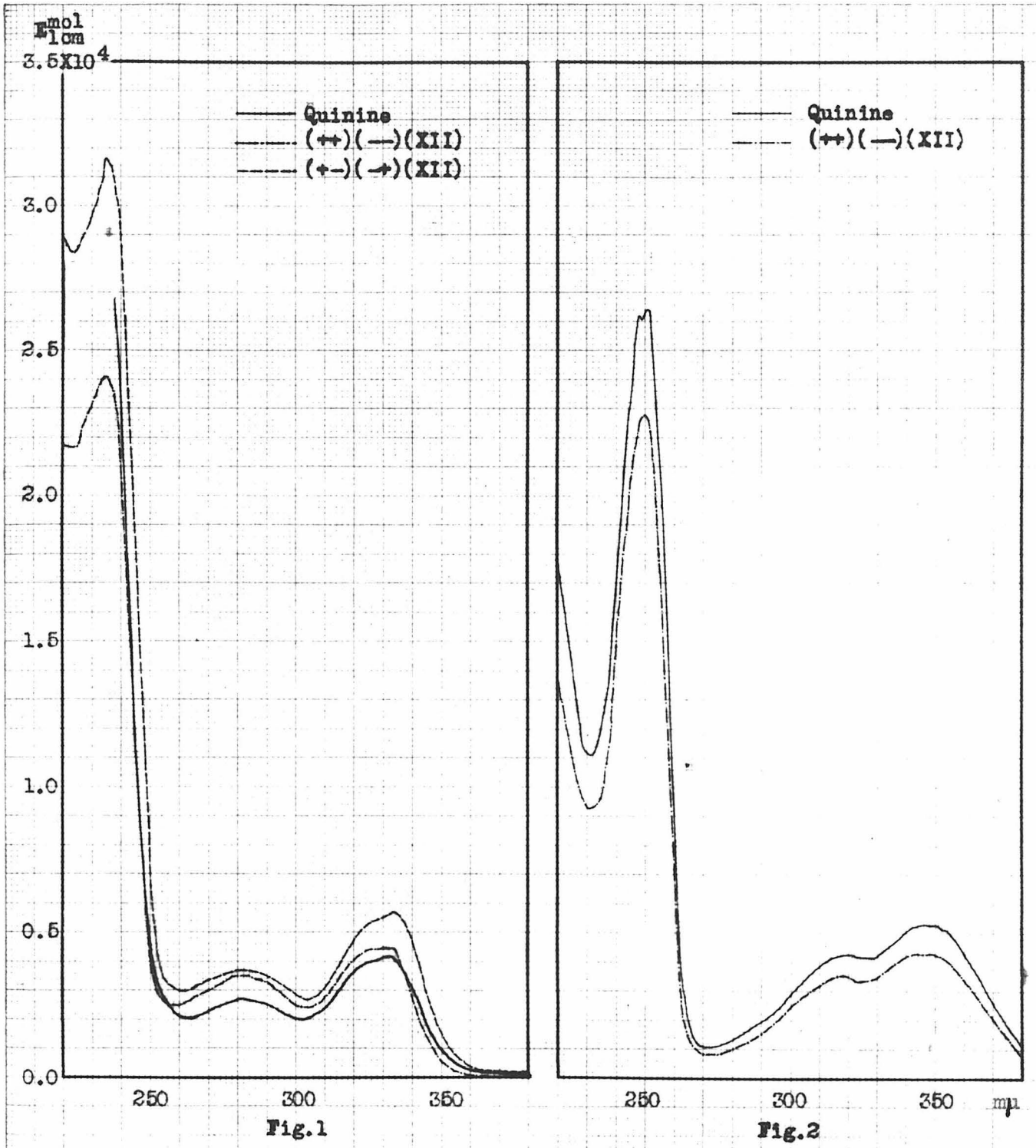


Fig.1 Fig.2

Fig.1: 1.55 mg. of anhydrous quinine in 3 drops of 6 N HCl diluted to 100 cc. with water, then treated with 5 drops of 4 N NaOH, pH 11.07.
1.30 mg. of (+-)(-+)(XII)·HCl in 100 cc. of water, pH ca. 6.
1.20 mg. of (++)(—)(XII)·HCl·1 1/2 H_2O in 100 cc. of water, pH 6.36.

Fig.2: 1.55 mg. of anhydrous quinine in 3 drops of 6 N hydrochloric acid diluted to 100 cc. with water, pH 2.18.
1.30 mg. of (++)(—)(XII)·HCl·1 1/2 H_2O and 0.02 cc. of 6 N HCl in 100 cc. of water, pH 3.86.

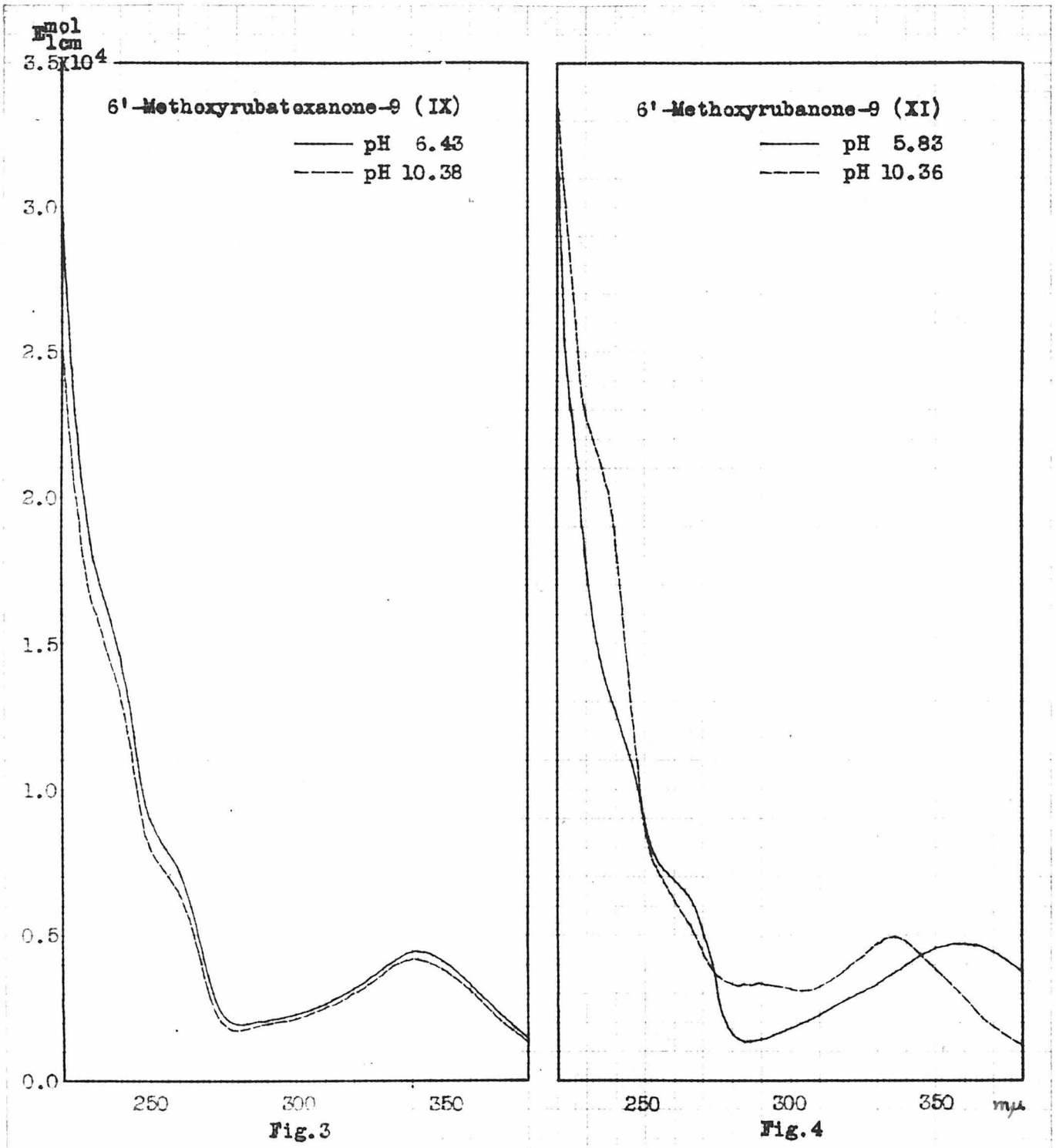


Fig.3 Fig.4

Fig.3: 1.70 mg. of (IX)·HCl·H_2O in 100 cc. of water, pH 6.43.
Same solution treated with 2 drops of 1 N sodium hydroxide, pH 10.38.

Fig.4: 1.40 mg. of (XI)·HCl in 100 cc. of water, pH 5.83.
Same solution treated with 1 drop of 1 N sodium hydroxide, pH 10.36

any of the other three optically active carbinols (XII) showed any sign of antimalarial activity. In Rabe's most recent publication (3) on the subject, new figures are cited which uphold the previous claim that (--) (XII) hydrochloride has no curative effect on canaries infected with Plasmodium relictum; on the other hand, the Prelog claim that the (++) (--) racemate has activity is verified. A further substantiation is found in the Kleiman and Weinhouse Report (4); using chicks infected with Plasmodium gallinaceum, an activity for the racemate dihydrochloride of between one-fourth and one-half of that of quinine was found. Our own compounds were tested by Dr. E. K. Marshall, Jr. and his staff[+] who used as test objects ducks infected with Plasmodium lophurae. In these tests (20), the (++) (--) (XII) monohydrochloride gave a quinine equivalent of one-half, the (++) (XII) d-tartrate an equivalent of one-quarter and the (--) (XII) l-malate an equivalent of one-half; the (+-) (-+) monohydrochloride was inactive at these concentrations and proved toxic at higher dosage levels. The (++) and (--) forms of (XII) as well as the (++) (--) racemate may therefore be regarded (20) as having essentially the same antimalarial activity.

Experimental[++]

1,1,1-Trichloro-3-(γ-pyridyl)-propanol-2(II).[+++] Chloral was

[+]We are greatly indebted to Dr. Marshall for the results of his tests.

[++]All melting points are corrected. Microanalyses by Dr. G. Oppenheimer. Spectrophotometric measurements by Mrs. M. Howton.

[+++]The assistance of J. A. Seneker in large runs of (II) is acknowledged.

prepared as follows: One kilogram of USP chloral hydrate in a 3 l. round-bottom flask was covered with 500 g. of concentrated sulfuric acid; after the endothermic dehydration, the chloral was distilled off through an all-glass apparatus into a separatory funnel protected from moisture. The colorless distillate was shaken with two 100-cc. portions of the same sulfuric acid, then redistilled, yielding 817 g. (91.5%) of anhydrous chloral.

When equimolecular amounts of chloral and γ-picoline (I) were mixed[+] at room temperature, the temperature rose spontaneously to 40-50° and after about 6 hours standing, crystals appeared in the mixture. After standing for one week, the product was recrystallized from ethanol, 60% yield; an experiment allowed to stand for two weeks gave 62%. The product (II) melted at 165.8-166.2° which agrees with the literature values; the picrate was prepared by dissolving in dilute hydrochloric acid and adding aqueous sodium picrate, clusters of long, jagged orange

[+]Note: Due caution should be exercised in carrying out this reaction; it is advisable to use the hood. In two cases in the hands of a technician of limited experience the reaction led to an explosion which, although not sufficiently violent to shatter the containing flask, scattered the material over a wide area and necessitated considerable cleaning up. In the one case anhydrous chloral (1720 g.) plus an equivalent amount of (I) were allowed to stand at room temperature; the temperature after mixing rapidly rose to 100°, dropping after 4 hours to 40°. About 6 hours after mixing, the mixture suddenly blew up. The product formed by the explosion was a hard, black, porous, water-soluble material. In the other case, 825 g. of chloral, 40 g. of fused zinc chloride and 2200 cc. of (I) were heated at 40° for 2 1/2 days and, while excess (I) was being removed by heating in vacuo from a boiling water bath, the explosion took place. The product was insoluble in ethanol and soluble in water. Since a great number of preparations of (II) have been carried out without incident, it is probable that the explosions were due to the presence of undetected impurity.

blades, m.p. 152.6-153.2° from ethanol (analysis). 50 g. of anhydrous chloral and 31.5 g. of (I) were mixed and kept for 44 hours in a bath at 40°; recrystallization of the product from ethanol gave two crops, 51.5 g. (63%) of (II). Equivalent amounts of chloral and (I) heated in a water bath at 85-100° for 4 hours gave a 45% yield of (II).

A 2200-cc. portion of (I) contained in a 5-l. flask was dried by distilling off a small forerun at atmospheric pressure, treated with 40 g. of freshly fused zinc chloride and 817 g. of anhydrous chloral. The temperature of the mixture rose to about 40°, where it was maintained for 46 hours. Using an aspirator and steam bath, the excess picoline was distilled off overnight, leaving a hard, flakey, crystalline mass weighing 1284 g., m.p. 157-159°. This was divided into four portions, each dissolved in about 800 cc. of absolute ethanol, norited, and let crystallize. Three crops gave 951.2 g. of light brown flakes (77.3% based on chloral); in similar experiments yields up to 80.6%+ have been obtained.

Ethyl β-(γ-Pyridyl)-acrylate (IV (11)). In a 5-l. three-neck flask equipped with reflux condenser, Hershberg stirrer, and 1-l. separatory funnel, 230 g. of potassium hydroxide pellets was dissolved in 1450 cc. of boiling absolute ethanol. A warm solution of 162 g.

+These experiments indicate that the best yields of (II) based on chloral may be obtained when an excess of (I) is used. It suggests itself that it might be advantageous to condense chloral with excess of (I) for 2 days at 40°, then to filter off the product (II), which crystallizes from the reaction mixture, and to utilize the mother liquors by adding them to the next batch consisting of equivalent amounts of chloral and of (I). A semi-continuous process for preparing (II) would result; data on yields are not yet available.

(0.0673 mole) of (II) in 725 cc. of absolute ethanol was then added slowly from the funnel, which was finally washed out with 50 cc. of boiling alcohol. After refluxing for an hour, 217 cc. of CP concentrated sulfuric acid was added from the funnel during 25 minutes, and the resulting mixture refluxed overnight. Inorganic solids were filtered off on a Buchner funnel and washed thoroughly with hot ethanol. The red-brown filtrate was stripped of ethanol under suction and the residual syrup cooled in ice, covered with 500 cc. of ether, and basified by the addition of an ice - potassium-carbonate slurry. The solids were filtered off an a large Buchner and the filtrate separated; the filter-cake and the aqueous phase of the filtrate were extracted with five additional 500-cc. portions of ether. After drying over sodium sulfate, the ether was stripped from the extracts; on cooling the residual oil overnight in an icebox, 46.5 g. of massive colorless or light yellow crystals were obtained, the mother liquors yielding a further 15.5 g. to made a total yield of 52.0%. When the crude product was distilled instead of crystallizing directly, a distillate boiling at 100-110° at 1 mm. was collected, representing crude yields of up to 78%, only about two-thirds of which, however, could be obtained crystalline[+].

[+]The non-crystalline material obtained as a byproduct in the preparation of (IV) was hydrogenated in ethanol solution in the presence of Raney nickel at about 100° and under a hydrogen pressure of about 4000 lbs./in.^{2} After separation from catalyst and removal of solvent, the residue was fractionated at 1 mm. using a 25 cm. Vigreau column. From 32.6 g. of the oil were obtained 0.4 g. of a colorless oil, b.p. 45-50°, 18.6 g. of light yellow oil boiling from 73° to 92°, and 8.6 g. of colorless oil, b.p. 102°. From the first fraction, a picrate was obtained melting at 92.5-93.0°, long, light yellow, flakey needles from ethanol (Anal. Found: C, 47.43; H, 4.65; N, 13.66). The last fraction (b.p. 102° at 1 mm.) gave a picrate, short, flat, bright yellow needles from ethanol, m.p. 101.1-101.8° (Anal. Found: C, 47.74; H, 4.62; H, 12.44).

The crystalline product (IV) formed massive colorless granules from isopropyl ether, m.p. 64.6-64.9°, this value agreeing with that given by Niemann and Brown (11). (IV) colors on long standing and becomes oily. The 3,5-dinitrobenzoate formed clusters of very light tan needles from isopropyl ether-ethanol, m.p. 124.2-124.4° (analysis). After three crystallizations from ethanol-water, the picrate melted at 163.2-164.1°, bright orange-yellow micaceous flakes (analysis). From ethanol-water, the hydrobromide formed colorless rhombs, m.p. 206.8-207.6° with gas evolution (analysis for $C_{10}H_{11}O_2N \cdot HBr$). The methiodide was an oil which could not be induced to crystallize.

A 750-g. portion (5.09 moles) of anhydrous chloral was added to 495 cc. (5.09 moles) of (I); the temperature of the mixture rose spontaneously to about 50°, then was maintained at 40° for 66 hours. The crude solid product dissolved in 4 l. of absolute alcohol was added to a hot solution of 1740 g. of potassium hydroxide in 11 l. of ethanol over a period of two hours. After refluxing an additional two hours, 1640 cc. of concentrated sulfuric acid was added, and the mixture refluxed with stirring for three hours. Worked up as described above, 280 g. of (IV) crystallized from the oil obtained. An additional 25 g. was obtained by distillation of the mother liquors, raising the overall yield from chloral and (I) to 33.8%; a similar experiment carried out on a smaller scale gave a yield of 37%.

Ethyl β-(N-Benzoylpiperidyl-4)-propionate (VI). In a one and one-half liter bottle, 98.4 g. (0.556 mole) of crystalline (IV) was dissolved in 400 cc. of absolute ethanol and treated with 250 cc. of the same solvent containing 21.3 g. (1.0 g. more than the theory) of anhydrous

hydrogen chloride. An Adams' catalyst (which could be used repeatedly) containing 1.6 g. of platinum was added to the white crystalline slurry and the mixture hydrogenated at room temperature and atmospheric pressure. An initially rapid rate of hydrogen absorption was maintained for one and one-half hours, when about one mole-equivalent had been taken up; the rate then tapered off to about one-seventh that initially and finally became negligible after about 44 hours, when 55.0 out of a theory of 57.8 l. of moist hydrogen had been absorbed. The catalyst was filtered off, and the filtrate stripped of ethanol in vacuo, leaving a white crystalline mass weighing 145.7 g. (theory 123.2 g.). This was dissolved in 465 cc. of anhydrous pyridine (distilled off barium oxide) in a 2-l. flask and treated with 120 cc. of benzoyl chloride (theory and enough to esterify the residual 22.5 g. of ethanol associated with the crude ester hydrochloride). After heating on the steam bath for one hour, the excess pyridine was distilled off in vacuo, 250 cc. of water added, the mixture acidified with 6 N hydrochloric acid, and the product taken up in 250, 100, and 50 cc. of isopropyl ether, each extract being washed with 60 cc. of 15% potassium hydroxide. The combined ether extracts were dried over sodium sulfate and distilled from a low-take-off Claisen flask, yielding a forerun (ethyl benzoate) of 61.7 g. and 148.6 g. (92.3%) of the desired product, a colorless, viscous oil, b.p. 185-193° at 1 mm. Rabe and coworkers (6) give b.p. 240° at 8 mm.

High Pressure Catalytic Reduction of (IV)[+]. An ethanolic solution

[+]D. R. V. Golding and J. A. Seneker helped in the investigation of this process.

of (IV) in the presence of Raney nickel readily took up one mole of hydrogen at 100° (11); at higher temperatures ethyl β-(N-ethylpiperidyl-4)-propionate was formed (compare 21). Ethyl β-(γ-pyridyl)-propionate could be reduced further to (V) in dioxane by raising the temperature to 200° but the yields were at best moderate and the product was contaminated with starting material; furthermore, runs on a large scale were far less satisfactory than those on a smaller scale. Poor results were also obtained on carrying out the one-step reduction of (IV) to (V) in dioxane.

Following the directions of Niemann and Brown (11), 29.0 g. (0.164 mole) of (IV) was dissolved in 100 cc. of absolute ethanol, 2 cc. of Raney nickel in ethanol (22) added, and the mixture sealed in a high-pressure hydrogenation bomb. Under an initial hydrogen pressure of 3320 lb./in^2, the bomb was heated up to 93° with shaking, the theoretical pressure drop for one mole-equivalent of hydrogen being taken up in less than one hour. The catalyst was centrifuged off and the solution distilled, yielding 26.7 g. (92%) of ethyl β-(γ-pyridyl)-propionate, a colorless liquid, b.p. 88-90° at 1 1/2 mm. (Niemann and Brown give b.p. 158° at 30 mm.) congealing readily when cooled with dry-ice, and melting again at -30° to -27°. The picrate formed bright yellow, feathered needles from ethanol, m.p. 117.2-117.6° (analysis). The hydrobromide was formed by adding equivalent amounts of the ester and 48% aqueous hydrobromic acid, cooling, and removing the water in vacuo; the resulting syrup solidified on addition of acetone and crystallized from isopropyl ether-ethanol as large, colorless, well-formed rhombs, m.p. 112.3-113.1° (analysis for $C_{10}H_{14}BrNO_2$). Formed by mixing equivalent amounts of the reactants, the 3,5-dinitrobenzoate emerged from isopropyl ether-ethanol as

long, light tan needles, m.p. 86.9-87.3° (analysis). The benzoate was obtained as a byproduct in the preparation of (VI) from crude (V); it formed long colorless blades, m.p. 45.6-46.5° from ligroin-isopropyl ether, boiled at about 110° at 1 mm. and analyzed for $C_{17}H_{19}NO_5$.

Ethyl β-(N-ethylpiperidyl-4)-propionate was obtained by hydrogenating 32.6 g. (0.184 mole) of (IV) in 50 cc. of absolute ethanol over 4 cc. of Raney nickel catalyst at an initial pressure of 2500 lb./in.^{2} of hydrogen and temperatures up to 197°. After shaking an hour and one-half, the mixture was cooled and worked up, yielding 33.7 g. of a colorless oil boiling at 85-89° at 1 mm., insoluble in water.

Anal. Calc'd for $C_{12}H_{23}NO_2$: C, 67.56; H, 10.87; N, 6.57.

Found: C, 67.62; H, 10.96; N, 6.36.

From ethanol-water, the picrate of the base formed long, thin, yellow needles, m.p. 164.8-165.8° (analysis). The methiodide could be obtained only as an oil.

In a representative experiment, 26.7 g. (0.149 mole) of ethyl β-(γ-pyridyl)-propionate was dissolved in 100 cc. of 1,4-dioxane purified according to Fieser (23) and 7.5 cc. of Raney nickel catalyst was added from which the ethanol had been washed with dioxane (catalyst stored under dioxane gave poor results). At an initial pressure of 3000 lb./in.^{2} of hydrogen, the reaction mixture was heated, starting the shaking mechanism at 110°; after 4 1/2 hours, the temperature was 184° and 93% of the theory of hydrogen (three mole-equivalents) had been taken up; 96% had been absorbed after the bomb had cooled overnight. Removal of the catalyst and distillation gave 20.5 g. (74.3%) of crude (V), a colorless, water-soluble oil, b.p. 78-83° at 1 mm. (Rabe and Kindler (8) give b.p. 145° at 15

mm., Prelog and Cerkovnikov (24) b.p. 142-143° at the same pressure, and Webb and Corwin (6c) b.p. 76-80° at 1-2 mm.). The picrate formed long yellow needles from isopropyl ether-ethanol, m.p. 158.3-158.8° (analysis). The 3,5-dinitrobenzoate crystallized from isopropyl ether-ethanol as light tan, bobbin-shaped crystals, m.p. 141.4-141.7°. When larger runs were attempted, the rate of hydrogenation fell off before complete hydrogenation had been accomplished; thus starting with 64 g., only 88% of the theory was taken up after 18 hours, and working up yielded only 25.4 g. (38.3%) of the desired product, extensive polyamide formation apparently having taken place, since an additional quantity (6.9 g.) of volatile base was obtained by refluxing the large non-volatile distillation residue with aqueous hydrochloric acid and re-esterifying the hydrolysate (compare (5) footnote on page 2496).

Benzoylation of 116.3 g. (0.63 mole) of crude (V) obtained as above, using essentially the method of Rabe and coworkers (6a) except that pyridine was substituted for potassium carbonate, gave 145.7 g. (80.2%) of (VI), b.p. 168-188° at 1 mm. Foreruns of benzoic acid and of ethyl β-(γ-pyridyl)-propionate benzoate were troublesome.

N-Benzoyl-6'-methoxy-8-carbethoxyrubatoxanone-9 (VIII). Sodamide (0.643 mole) was prepared in a 2 l. three-neck flask from 800 cc. of liquid ammonia, 14.8 g. of metallic sodium, and a pinch of anhydrous ferric chloride. After evaporation of the excess ammonia, the grey residue was broken up with a stirring rod, and a solution of 146.0 g. (0.633 mole) of ethyl quininate and 146.5 g. (0.506 mole) of (VI) in 280 cc. of thiophene-free, anhydrous benzene added. The flask was fitt-

ed with a short water-cooled Allihn condenser protected by a sodalime tube and with a Hershberg stirrer sealed by a long, close-fitting bearing sleave. A glycerin bath was used to heat the stirred mixture slowly to about 85° during three hours; much ammonia was evolved and a ring of brown solid formed about the inner periphery of the flask. After sixteen more hours stirring at this temperature, the mixture had become a brown paste, which was allowed to cool to room temperature and then shaken with ice until it was entirely dispersed. The red-brown aqueous phase was drawn off, washed with two 100-cc. portions of benzene, and the combined benzene phases extracted with two 100-cc. portions of water. Added to 560 cc. of chloroform in a two liter conical flask, the aqueous phases were treated with the carbon dioxide from one pound of dry-ice. In some experiments, a colorless, crystalline solid separated at this point; it was filtered off and identified by m.p. and mixed m.p. with an authentic sample of quininamide. After further extracting the aqueous phase with two 75-cc. portions of chloroform, the combined extracts were dried over sodium sulfate and freed of chloroform in vacuo, leaving 242 g. of viscous, red-brown oil, which was taken up in 80 cc. of absolute ethanol, treated with 160 cc. of ether, and set in the ice-box, giving 123.0 g. of light yellow-brown granules. Concentration and cooling of the mother liquors raised the yield to 128.1 g. (53.3%). From the discarded benzene and aqueous phases, 29.5 g. of quininic acid was recovered. An average yield of 43.5% was obtained from five such condensations with sodamide; with powdered sodium, five experiments gave an average yield of 29.0%. Recrystallized from iso-

propyl ether–ethanol, the compound, (VIII), formed colorless granules, m.p. 143.7–144.3°.

Anal. Calc'd for $C_{28}H_{30}N_2O_5$: C, 70.86; H, 6.37; N, 5.91.

Found: C, 70.78; H, 6.60; N, 5.83.

The compound did not form an ether-insoluble picrate nor did it give any notable coloration with ferric chloride; its solution in 6 N hydrochloric acid was intensely yellow; its ultraviolet absorption spectrum showed maxima at 230 mμ and 335.5 mμ in ethanol.

6'-Methoxyrubatoxanone-9 (IX) was prepared by refluxing a solution of 43.8 g. of crystalline (VIII) in 475 cc. of 6 N hydrochloric acid for 6 hours. On cooling overnight, a large quantity of benzoic acid separated, which was taken up in 250 cc. of ether; a little red solid was filtered off. The aqueous phase was drawn off into a 2 l. conical flask, 300 cc. of chloroform added, and, with stirring and cooling, 30% potassium hydroxide added until no more oil precipitated from the aqueous phase, which was then further extracted with 150 and 75 cc. of chloroform. Dried over sodium sulfate, the extracts were freed of chloroform on the steam cone in vacuo (first on water aspirator and finally on the oil pump), leaving a viscous, dark red-brown oil which was cooled in ice and dissolved at once in 245 cc. of chilled 48% aqueous hydrobromic acid. This solution was brominated immediately, as described below. The monohydrochloride of (IX) was prepared (see below) by reduction of 6'-methoxyrubanone-9 (XI) in acid media; it forms bulky clusters of long, light tan, micaceous needles, m.p. 164.4–164.8° from ethanol. Prepared from either the crude free base or from the monohydrochloride by adding 6 N hydrochloric acid, evaporating, and crystallizing the residue from

ethanol, the dihydrochloride of (IX) forms small clusters of bright yellow granules, m.p. 216-217° after some fusion at about 160°. The analysis indicates one molecule of water in the salt:

Anal. Calc'd for $C_{18}H_{22}N_2O_2 \cdot 2HCl \cdot H_2O$: C, 55.53; H, 6.73; N, 7.20.

Found: C, 55.71; H, 6.83; N, 7.30.

The picrate was made by dissolving the 164° monohydrochloride in water and adding aqueous sodium picrate; it crystallized from acetonitrile as orange swords twinned or in clusters, m.p. 231.9-232.5° with decomposition. The absorption spectrum of (IX) was taken in water; at pH 6.43, the maximum was at 340 mμ; at pH ca. 11, it was at 341.5 mμ (see Figure 3).

6'-Methoxy-8-bromorubatoxanone-9 Dihydrobromide (X). The above described solution of crude (IX) in 245 cc. of 48% hydrobromic acid was warmed in a bath maintained at 50°, stirred vigorously, and treated with 14.8 g. (0.0924 mole) of bromine vapors blown in with nitrogen over a period of three and one-half hours. On cooling, clusters of short yellow needles separated, weighing 36.6 g.; evaporation and cooling of the mother liquors yielded further amounts of the solid, raising the crude yield to 53.2 g. Seven similar experiments gave an average crude yield of 91.3%. The compound recrystallized nicely from 10% aqueous ethanol in yields varying from 61 to 90% (average 68.5%), depending upon the quality of the crude material. Attempts to simplify this procedure by hydrolyzing the ketoester (VIII) with 6 N hydrochloric and hydrobromic acids and brominating directly without isolation of the crude rubatoxanone (IX) led to poorer yields of (X). The salt (X) crystallizes from aqueous

ethanol in clusters of bright yellow diamonds, m.p. 194–195° with decomposition.

Anal. Calc'd for $C_{18}H_{23}Br_3N_2O_2$: C, 40.10; H, 4.30; N, 5.20.

Found: C, 40.29; H, 4.74; N, 5.29.

The ultraviolet absorption curve has one maximum at 345 mμ in water.

In one experiment, starting from 156.4 g. of the keto-ester (VIII), the bath temperature accidentally rose to 70° during the bromination; there resulted 44.1 g. (24.8%) of the desired monobromo salt (X) plus 77.3 g. (37.9%) of a new product, identified by analysis and reactions (see below) as 6'-methoxy-8,8-dibromorubatoxanone-9 dihydrobromide. It is less soluble in alcohol-water than (X) and forms clusters of pale yellow needles, melting with gas evolution at 211.2–211.6°.

Anal. Calc'd for $C_{18}H_{22}Br_4N_2O_2$: C, 34.98; H, 3.59; N, 4.53.

Found: C, 34.28; H, 3.75; N, 4.46.

The absorption spectrum of the dibromoketone dihydrobromide was taken in water, λmax. 338 mμ.

6'-Methoxyrubanone-9 (XI). In a one-liter bottle, 27.0 g. (0.050 mole) of recrystallized (X) was dissolved in 390 cc. of water, the solution covered with 343 cc. of ether, the air displaced from the bottle with nitrogen, and 192 cc. of 14% aqueous sodium carbonate added, precipitating a brown oil from the aqueous phase. After shaking for one-half hour, the ether phase no longer clouded on standing. The aqueous phase was further extracted with four 50-cc. portions of ether and combined bright yellow ether extracts dried over potassium carbonate and freed of ether at room temperature by means of an aspirator, leaving 12.4 g. (83.7% crude

yield) of bright yellow, viscous oil, which could not be induced to crystallize at this point. Varying the time of shaking gave crude yields which could not be correlated with this variation in the reaction conditions; the yields ran from 68 to 88%, with an average of 78% for ten experiments. The lowest yield was obtained starting with unrecrystallized (X). The above crude ketone (12.4 g.) was dissolved in 40 cc. of boiling absolute ethanol and treated with a solution of 4.0 g. of anhydrous hydrogen chloride in an additional 20 cc. of ethanol. On cooling, the red solution deposited 10.7 g. of bright yellow flakes; concentration and cooling raised the yield to 11.5 g. (59.2% from (X)). In a similar experiment, 64.0% was obtained. This dihydrochloride forms narrow diamond wafers from ethanol-water, m.p. 238.5° decomposition.

Anal. Calc'd for $C_{18}H_{22}Cl_2N_2O_2 \cdot H_2O$: C, 55.82; H, 6.25; N, 7.23.

Found: C, 56.09; H, 6.63; N, 7.50.

Three and eighty-seven hundredths grams (0.01 mole) of this dihydrochloride was dissolved in water and the free base liberated into 25 cc. of ether with 6 N sodium hydroxide and further extracted with five 10-cc. portions of ether. After drying the combined extracts with potassium carbonate, they were stripped of ether at room temperature as before, leaving a viscous, bright yellow oil which slowly and completely crystallized in large, well-formed, colorless rhombs, 2.91 g. (98%), m.p. 90.5-90.9°, not appreciably raised by recrystallization from isopropyl ether or aqueous ethanol. (Rabe and Hagen (1) give m.p. 89°; Prelog and coworkers (2) give m.p. 90-91°). Shaking a methanolic solution of (XI) in communication with a eudiometer containing oxygen showed

the ketone to be surprisingly stable toward oxidation, even after aqueous sodium carbonate had been added; no appreciable oxygen-uptake was noted after five and one-half hours of such treatment. Upon adding one equivalent of 12 N hydrochloric acid to a solution of the ketone in alcohol, the monohydrochloride precipitated. Recrystallized from ethanol-water, it formed clusters of stubby, light tan needles, m.p. 253.0-253.3° with decomposition.

Anal. Calc'd for $C_{18}H_{21}ClN_2O_2$: C, 64.95; H, 6.36; N, 8.42.

Found: C, 64.74; H, 6.62; N, 8.09.

By adding picric acid in ethyl ether to a solution of the free ketone in ether-ethanol, or by addition of aqueous sodium picrate to a solution of the monohydrochloride in water, the same picrate was formed, clusters of yellow needles from acetonitrile, m.p. 212.0-212.7°. (Prelog and co-workers (2) report a monopicrate having m.p. 211 to 211.5°). The absorption of the ketone was taken in aqueous solution; at pH 5.83, λmax. 359 mμ; at pH 10.36, λmax. 336 mμ (secondary maxima at 332 mμ, 289 mμ, and 284 mμ) (see Figure 4).

Ring-Closure of 6'-Methoxy-8,8-dibromorubatoxanone-9 Dihydrobromide was carried out as described above for (X), using 6.18 g. (0.01 mole) of the recrystallized salt in 80 cc. of water covered with 66 cc. of ether and treating with 40 cc. of 14% aqueous sodium carbonate. After shaking for one hour and 45 minutes, the ether phase clouded only very slowly. A little tar was removed with "Cellite 535" and the aqueous phase further extracted with three 25-cc. portions of ether; the combined ether extracts were dried over potassium carbonate and freed of ether

as before, leaving 3.07 g. (82% crude yield) of orange oil. This was taken up in 50 cc. of methanol and hydrogenated over 0.05 g. of $PtO_2 \cdot 2H_2O$, one mole-equivalent of hydrogen being absorbed rapidly (11 minutes); the catalyst was then centrifuged off and the solution evaporated to a red-brown, viscous oil which crystallized partially on standing. The oil was washed out with acetone, leaving 0.49 g. of material crystallizing from aqueous ethanol in clusters of pale greenish-yellow needles, m.p. 260-261° with decomposition, which was shown to be (XI) monohydrobromide (analysis and mixed m.p.'s of picrate and dihydrochloride).

6'-Methoxyrubanol-9's (XII). As described above, crude (XI) (10.2 g., 88% yield) was prepared from 21.1 g. (0.0391 mole) of recrystallized (X); the ketone was placed in a 2 l. flask with 80 g. (10-fold excess) of aluminum isopropylate (purified by distillation) and 1 l. of anhydrous isopropanol (distilled from sodium). A ten centimeter helix-packed column was attached and the mixture heated in a glycerin bath to maintain slow distillation, the bulk of the pink solution in the boiler being maintained by addition of isopropanol from time to time. After four days, consistent negative tests for acetone in the distillate with a fresh 2,4-dinitrophenylhydrazine reagent (25) were obtained; two days later, solvent was distilled off rapidly until about 100 cc. remained and then ice (discharging the pink color), 100 cc. of chloroform, and a solution of 50 g. of sodium hydroxide in 75 cc. of water were added. The liberated bases were further extracted with 100-, 50-, and 25-cc. portions of chloroform, the combined extracts dried over potassium car-

bonate, then stripped of solvent in vacuo on a steam bath, leaving 13.3 g. of viscous brown oil. The crude product was taken up in 40 cc. of absolute ethanol, centrifuged, and treated with 2.88 cc. (one equivalent) of CP 12 N hydrochloric acid; 5.03 g. of the (++) (--) monohydrochloride separated out at once, crude m.p. 237°. Spontaneous evaporation of the mother liquors brought about deposition of crystalline (+ -) (- +) monohydrochloride. Further concentrations and coolings gave totals of 5.42 g. of (++) (--) and 2.88 g. of (+ -) (- +) (XII) monohydrochloride, or 60.5% of the total possible yield from (X).

In a 300-cc. bottle was placed 10.8 g. (0.02 mole) of (X), 100 cc. of methanol was added, the air was swept from above the solution with nitrogen, and 46 cc. of 14% aqueous sodium carbonate was added. After shaking for one hour, 0.05 g. of $PtO_2 \cdot 2H_2O$ was added, and the mixture hydrogenated at room temperature and atmospheric pressure, 507 cc. of a theory of 591 cc. of moist hydrogen being taken up after two hours, when the rate had become negligible. Inorganic solids were filtered off and the filtrate freed of methanol in vacuo on a steam bath until an oil precipitated; this was extracted with 20, 10, and 5 cc. of chloroform, the combined extracts freed of solvent on a steam bath, finally in vacuo (oil pump). The remaining viscous brown oil was taken up in 22 cc. of ethanol and treated with 1.77 cc. of CP 12 N hydrochloric acid (one equivalent), giving 3.00 g. (41.3% yield) of the (++) (--) monohydrochloride, crude m.p. 230-231°. In experiments of the same size, shaking during ring closure for two hours gave 2.67 g. (36.0%) of the (++) (--) salt, and 0.25 g. of the (+ -) (- +); shaking for one-half

hour, 2.81 g. (38.7%) (++) (--). Experiments in which (++) (--) (XII) was isolated as the dihydrochloride or as the crystalline free base hydrate were difficult to work up and gave lower yields.

Twelve and four tenths grams (0.02 mole) of recrystallized 6'-methoxy-8,8-dibromorubatoxanone-9 dihydrobromide was treated exactly as the monobrom salt (X) above; shaking during ring closure was continued for two hours. Eighty three percent of the theoretical two mole-equivalents of hydrogen was absorbed in seven hours. Working up the product gave 2.24 g. (31.0%) of the (++) (--) monohydrochloride.

Three and twenty-seven hundredths grams (0.00843 mole) of (XI) dihydrochloride was added to 42 cc. of methanol, the air above the mixture swept out with nitrogen, 20 cc. of 14% aqueous sodium carbonate and 0.15 g. of $PtO_2 \cdot 2H_2O$ added, and the mixture hydrogenated as above, 306 cc. (theory 258 cc.) being absorbed in two and one-half hours. Working up the product gave 1.70 g. of (++) (--) and 0.28 g. of (+-) (-+) monohydrochlorides—total yield 66.0%.

The (++) (--) monohydrochloride is fairly insoluble in cold water and crystallized from ethanol-water in characteristic clusters of colorless plates, m.p. 239.8-240.5°, varying somewhat with the period and rate of heating. Rabe and Schuler (3) obtained from water a monohydrochloride trihydrate melting with decomposition at 240° after losing water at 120°.

Anal. Calc'd for $C_{18}H_{23}ClN_2O_2 \cdot 1\ 1/2\ H_2O$: C, 59.67; H, 7.24; N, 7.74.
Found: C, 59.28; H, 7.14; N, 7.96.

On cooling a concentrated solution of the monohydrochloride in 6 N hydrochloric acid, the (++) (--) dihydrochloride separated out as clear, colorless bars of rectilinear outline, m.p. 246-247° with gas evolution. (Rabe and Schuler (3) give m.p. 242°, Prelog and coworkers (2) m.p. 239-240°, and Kleiman and Weinhouse (4) m.p. 238-239°). The (++) (--) dipicrate separated when aqueous solutions of either the mono- or the dihydrochloride were treated with equivalent quantities of 10% aqueous sodium picrate; the salt was difficultly soluble in aqueous ethanol, from which it separated in sparse clusters of well-formed, light yellow prisms, m.p. 252.1-252.4°, turning black and evolving gases (analysis). The free (++) (--) (XII) base liberated from an aqueous solution of the monohydrochloride into chloroform with sodium hydroxide crystallized as the hydrate from aqueous ethanol or methanol in stars of colorless, stout needles, melting unsharply at 96-100°. (Rabe and Hagen (1) describe a trihydrate melting ca. 100° and Rabe and Schuler (3) a monohydrate, m.p. 94-95°).

More soluble in cold water and with less crystallizing power, the (+-) (-+) monohydrochloride emerges slowly from ethanol containing a trace of water in tiny colorless needle clusters, m.p. 246.3-246.4°, mixed melting point with the diastereoisomeric monohydrochloride 228-230°.

Anal. Calc'd for $C_{18}H_{23}ClN_2O_2$: C, 64.56; H, 6.92; N, 8.37.
Found: C, 64.74; H, 7.08; N, 8.48.

When a crystal of the (+-) (-+) monohydrochloride was added to 6 N sulfuric acid in ultraviolet light, a brilliant pastel blue fluorescence was exhibited. Prepared from an aqueous solution of the mono-

hydrochloride by addition of one equivalent of 10% aqueous sodium picrate, the (+ –) (–+) picrate formed clusters of light yellow, irregular, pointed blades from aqueous ethanol, m.p. 235.0–235.3°, brown melt. (Prelog and coworkers (2) report a (+–) (–+) (XII) monopicrate, m.p. 226°.) The free (+ –) (–+) carbinol could not be induced to crystallize.

The ultraviolet absorption spectra of both racemic carbinols (XII) are compared with those of quinine in the following table; all readings were made on aqueous solutions (see Figures 1 and 2).

(++) (––) (XII)			(+ –) (–+) (XII)			Quinine		
pH	λmax	$E^{mol}_{1\ cm} \times 10^{-4}$	pH	λmax	$E^{mol}_{1\ cm} \times 10^{-4}$	pH	λmax	$E^{mol}_{1\ cm} \times 10^{-4}$
6.36	235 282 332	2.410 0.275 0.422	ca. 6	235 282 333	3.165 0.377 0.570	11.07	231 281 332	2.960 0.352 0.460
3.86	250 317.5 344	2.280 0.359 0.433				2.18	251 320.5 347.5	2.640 0.428 0.530

Catalytic Reduction of (XI) Monohydrochloride with Adams' Catalyst. When 0.88 g. (0.00264 mole) of the ketone (XI) monohydrochloride in 30 cc. of methanol was shaken with 15 mgm. of Adams' platinic acid catalyst and hydrogen, one mole-equivalent of hydrogen was absorbed in seven minutes. Centrifuging off the catalyst and boiling off the methanol left a crystalline residue which recrystallized from ethanol in bulky, micaceous needle-clusters, m.p. 162–165°. The identity of this reduction product with (IX) was indicated by the ultraviolet spectrum and was established by melting points and mixed melting points of the dihydrochloride, picrate, and of (X) prepared from the reduction product.

The catalytic reduction of (IX) monohydrochloride was carried out with a solution of 0.71 g. of the recrystallized substance in 30 cc. of methanol, using 25 mgm. of $PtO_2 \cdot 2H_2O$; the theoretical amount of hydrogen was slowly absorbed (four hours) but no crystalline derivatives of the oily product could be obtained.

Catalytic Reduction of Crude (XI) with Adams' Catalyst. Fifteen and nine-tenths grams of crude (XI) from 33.9 g. of (X) was dissolved in 60 cc. of methanol and hydrogenated over 0.50 g. of $PtO_2 \cdot 2H_2O$; the hydrogenation was stopped when the theoretical volume of hydrogen had been absorbed. After removal of the catalyst and the solvent, the crude product was taken up in ethanol and treated with one equivalent of 12 N hydrochloric acid. Concentration and cooling gave 8.0 g. of a product melting over a range (125-130°) with gas evolution. After recrystallization from ethanol-water, 5.5 g. was obtained, m.p. 193-196° decomposition; that this material was still contaminated by a considerable admixture of ketone was indicated by its ultraviolet absorption spectrum. Regeneration of the free base from a small portion gave crystalline (++) (--) (XII) hydrate in ca. 45% yield and after a second recrystallization reasonably pure (++) (--) (XII) monohydrochloride, m.p. 233°, resulted. In another experiment on a somewhat larger scale, the lower-melting material which comprised the bulk of the reduction product was isolated by extraction with warm absolute ethanol (in which the (XII) monohydrochloride is relatively insoluble) and identified as (IX) monohydrochloride by m.p. and by conversion to the characteristic (IX) dihydrochloride, m.p. and mixed m.p.

Resolution of the (++) (--) (XII). The free (++) (--) carbinol was liberated from an aqueous solution of 16.87 g. (0.0465 mole) of the monohydrochloride into chloroform by addition of sodium hydroxide. After stripping off the solvent, 6.90 g. (theory 6.98 g.) of d-tartaric acid and 63 cc. of water were added to the viscous brown oil, and the mixture heated gently to obtain a clear solution. Cooling in the icebox over the weekend gave 8.04 g. of large, light tan blades in clusters; these were recrystallized once from 16 cc. of water, giving 7.40 g. of fine white needles, m.p. 155-158° after fusion at 100°, $(\alpha)_D^{24.3}$ + 138° (α = +1.33°, c = 0.01985 g./2.051 cc. of aqueous solution). Rabe and Hagen (1) describe the (++) mono-d-tartrate as melting at 150-155° with decomposition after previous sintering at 115°, $(\alpha)_D^{15}$ +124.1° in ethanol. Obtained from the pure d-tartrate, the free (++) carbinol crystallized in clusters of stout, irregular, colorless needles from aqueous methanol, m.p. 184.5-185.1° after losing water at 114-122°, $(\alpha)_D^{24.5}$ +164° (α = +0.5350°, c = 0.00670 g./2.051 cc. of ethanolic solution); correction for one molecule of water of hydration (see analysis below) gives $(\alpha)_D$ (in ethanol) +173.8° for the anhydrous carbinol.

Anal. Calc'd for $C_{18}H_{22}N_2O_2 \cdot H_2O$: C, 68.33; H, 7.65; N, 8.86.
Found: C, 68.27; H, 7.62; N, 8.91.

After removal of the above (++) (XII) mono-d-tartrate, the residual bases were isolated as before and treated with 4.00 g. (theory 4.08 g.) of l-malic acid and ethanol-water to give a homogeneous solution. Concentrations and coolings gave a first crop (0.90 g.) of dextrorotatory solid and two subsequent crops totaling 4.74 g. of laevorotatory solid.

Recrystallization of the first crop to constant rotation gave white needle-clusters, m.p. 209.1-210.0° and $(\alpha)_D^{24.1}$ +146° (α = +0.505°, c = 0.00710 g./2.051 cc. aqueous solution).

Anal. Calc'd for $C_{18}H_{22}N_2O_2 \cdot C_4H_6O_5$: C, 61.10; H, 6.53; N, 6.48.

Found: C, 61.32; H, 6.56; N, 6.68.

This (++) (--) mono-l-malate gave a free carbinol, m.p. 183.9-184.2°, $(\alpha)_D^{24.3}$ +172° (α = +0.570°, c = 0.00680 g./2.051 cc. of ethanolic solution).

Recrystallization of the laevorotatory solids from ethanol-water gave fine, light tan needles in sheaves, m.p. 193.9-194.2°, $(\alpha)_D^{24.3}$ -121° (α = -0.385°, c = 0.00655 g./2.051 cc. of aqueous solution).

Anal. Calc'd for $C_{18}H_{22}N_2O_2 \cdot C_4H_6O_5$: C, 61.10; H, 6.53; N, 6.48.

Found: C, 60.89; H, 6.47; N, 6.40.

From the pure (--) (XII) mono-l-malate the free carbinol was obtained, recrystallizaing from water-methanol in clusters of large, irregular, colorless needles; on slow heating, the compound fuses at 106°, begins to resolidify at 116°, and finally melts at 184.8-185.3°; it has $(\alpha)_D^{23.9}$ -163° (α = -0.735°, c = 0.00925 g./2.051 cc. of ethanolic solution).

Equivalent quantities of the (++) (--) carbinol and β-d-camphor sulfonic acid gave beautiful clusters of colorless bars, m.p. 257-258° from ethanol, $(\alpha)_D^{24}$ +15.5° (α = +0.275°, c = 0.03635 g./2.051 cc. of aqueous solution), but the free base liberated from this salt was devoid of optical activity.

Summary

The two racemic 6'-methoxyrubanols-9 (vinyl-free quinines) have been prepared by improvements on known methods and intermediates in the synthesis further characterized.

The (++)(——) racemate and the antipodes obtained from it by resolution with l-malic acid have been shown to have antimalarial activities comparable with that of quinine; the (+—)(—+) racemate was found to be inactive.

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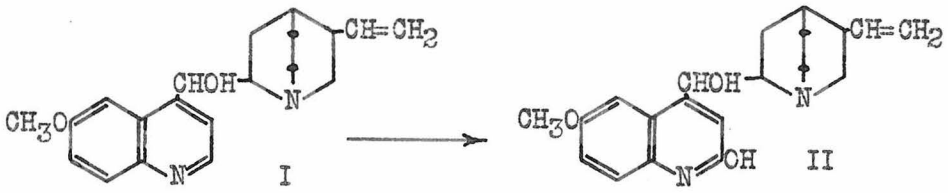
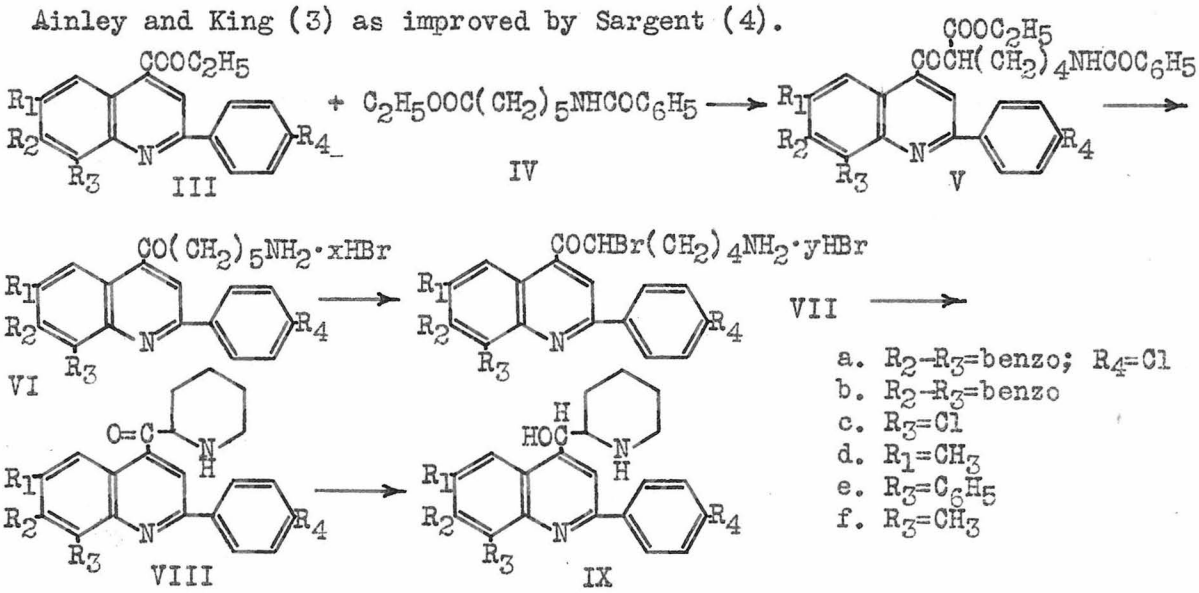
IV. SYNTHESIS OF SOME 2-PHENYLQUINOLYL-4-α-PIPERIDYLCARBINOLS.

SYNTHESIS OF SOME 2-PHENYLQUINOLYL-4-α-PIPERIDYLCARBINOLS[+]

Mead and Koepfli (1) have presented evidence that the crystalline product obtained (2) by the in vitro action of rabbit liver on quinine (I) has the structure represented by (II):



This work, together with the proven antimalarial efficacy of the simpler quinolyl-4-α-piperidylcarbinols of Ainley and King (3), suggested the synthesis of such carbinols in which the 2-position of the quinoline rest is protected by a phenyl group against this type of oxidative attack. The preparation of these compounds (IX) followed the method of Ainley and King (3) as improved by Sargent (4).



In this scheme, undesignated R's are understood to be hydrogens.

[+]The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

The esters (III) whose syntheses are described in this paper were prepared from acids made by the method of Doebner (5) from appropriately-substituted aromatic amines, aldehydes, and pyruvic acid in the moderate yields typical of this reaction. These esters were then condensed with ethyl ε-benzamidocaproate (IV) by means of sodamide. The crude β-keto-esters (V) were not isolated, but hydrolyzed directly with 50-60% sulfuric acid to the amino-ketones, isolated as the hydrobromides (VI). Treatment of solutions of these salts (VI) in aqueous hydrobromic acid with an equivalent quantity of bromine in the same solvent gave the α-bromoketone hydrobromides (VII), which were shaken with aqueous-ethanolic sodium carbonate to yield the α-piperidyl ketones (VIII); these were catalytically reduced without isolation, yielding the desired carbinols (IX) in overall yields (from (III)) of 13.6% (IXa), 35.4% (IXb), 24.7% (IXc), 22.8% (IXd), 20.4% (IXe), and 29.1% (IXf); taking into account the varying amounts of unreacted cinchoninic acids (corresponding to (III)) recoverable after the hydrolysis of the crude Claisen-condensation mixture, the yields were considerably greater; thus, in the case of (IXf), the yield on this basis was 52.0%.

In the preparation of modified quinolyl-4-α-piperidylcarbinols with the quinoline-2-position unsubstituted, Ainley and King (3), Sargent (4), Golding (6), and Howton (7) have isolated and characterized both forms of the carbinols predicted because of the two adjacent asymmetrically-substituted carbon atoms in the molecule; in compounds of this type with the 2-phenyl substituent, however, no appreciable amounts of diastereoisomeric carbinols have been detected.

Experimental[+]

Series a

2-p-Chlorophenyl-7,8-benzocinchoninic Acid.[++] A 22-l. flask was charged with a mixture of 572.8 g. (4.0 moles) of α-naphthylamine, 562.4 g. (4.0 moles) of p-chlorobenzaldehyde, 704.0 g. (4.0 moles) of 50% aqueous pyruvic acid, and 10 l. of denatured alcohol; on refluxing, a yellow crystalline precipitate began separating after about twenty minutes. After boiling overnight, the mixture was cooled to about 4° C., the product filtered off on a large Buchner funnel, washed with cold 95% ethanol, and air-dried—yield 670 g. The filtrate on standing deposited two more crops totaling 76.2 g. and representing, in all, a crude yield of 55.9%. This crude product had a rather indefinite melting point extending up to about 280°, and was almost insoluble in all the ordinary solvents except boiling glacial acetic acid; two recrystallizations from this solvent gave yellow microneedles melting at 308-309° to a dark-brown liquid.

Anal. Calc'd for $C_{20}H_{12}ClNO_2$: N, 4.20.

Found: N, 4.19.

Ethyl 2-p-Chlorophenyl-7,8-benzocinchoninate (IIIa) was prepared from the above crude acid by refluxing it for 41 hours with a mixture of 9 l. of absolute ethanol and 400 cc. of concentrated sulfuric acid.

[+]For the microanalyses included in this paper, we are indebted to Dr. G. Oppenheimer and her staff. All melting points are corrected.

[++]The assistance of J. A. Seneker in large-scale preparations of this acid and its ester is acknowledged.

The resulting solution was evaporated in vacuo (heating on a steam bath) to about 2 l. and the remaining thick sirup extracted with 3 1/2 l. of benzene. These benzene extracts were washed with 1 l. of cold 1 N sodium hydroxide, dried over sodium sulfate, and evaporated as before leaving a thick oil which was taken up in 600 cc. of boiling absolute ethanol and allowed to stand over the weekend; a mixture of crystalline material and tar resulted, which was redissolved in a hot mixture of 940 cc. of ethanol and 610 cc. of benzene. On cooling, 167.3 g. of (IIIa) was deposited, m.p. 124-126°, a yield of 21.9% from the crude acid or 12.3% from α-naphthylamine. Recrystallized from ethanol-benzene, (IIIa) formed dense tufts of tan bars, m.p. 127.4-127.8°.

Anal. Calc'd for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87.

Found: C, 72.86; H, 4.76; N, 3.89.

ε-(2-o-Chlorophenyl-7,8-benzocinchoninyl)-n-amylamine Hydrobromide (VIa). About 1 l. of liquid ammonia was collected in a 3-l. round-bottomed flask and 13.8 g. (0.6 mole) of metallic sodium and a pinch of anhydrous ferric chloride added. When the blue color had disappeared, small deposits of sodium on the walls of the vessel were rinsed down with the remaining ammonia, which was then boiled off by placing the flask in a pan of stirred alcohol. Meanwhile, 173 g. (0.478 mole) of (IIIa) and 126 g. (0.478 mole) of ethyl ε-benzamidocaproate (IV)+ were dissolved in 368 cc. of thiophene-free benzene, about 80 cc. of the solvent was boiled off at atmospheric pressure, and the solution allowed to cool

+Some samples of (IV) used in these syntheses were supplied by R. C. Elderfield of Columbia University and by C. C. Price of the University of Illinois.

protected by a potassium-hydroxide tube; it was then added to the above-prepared sodamide and the reaction vessel was equipped with a sleeve-sealed Hershberg stirrer (8) turned by a slow, powerful electric motor and a water-cooled Friedrichs condenser protected from moisture by a potassium-hydroxide tube. On heating at 90-95° in a glycerin bath for 24 hours, the mixture first turned to a white paste with the evolution of ammonia, then to a dark-brown sirup. After cooling to room temperature, this sirup was treated with a cold mixture of 250 cc. of concentrated sulfuric acid and 357 cc. of water and the benzene boiled off, heating cautiously at first because of extensive foaming. On refluxing over a free flame for 42 hours, the resulting insoluble, tan gum slowly turned to a solid and largely dissolved; the still-warm reaction mixture was next poured onto about 5 l. of ice, covered with 800 cc. of benzene, vigorously stirred, and basified with a solution of 430 g. of sodium hydroxide pellets in 1440 cc. of water. There resulted a colorless aqueous phase and a brown benzene phase containing a large amount of suspended yellow solid; after addition of about 1 l. of "Cellite 535", solids were filtered off on a large Buchner and washed with hot benzene. The combined benzene extracts, totaling about 3 l., were dried over sodium sulfate, filtered, and evaporated on a steam bath under an aspirator vacuum, leaving 134.7 g. of dark brown sirup; this was transferred to a 1 l. wide-mouth conical flask with 260 cc. of hot isopropyl alcohol and 50 cc. of acetone, treated with 90.3 g. (one equivalent) of 48% hydrobromic acid, warmed until homogeneous, and allowed to cool and stand. The solution soon set to a mass of fine needle-clusters, which was filtered off on a sintered-glass funnel,

washed with a suitable mixture of isopropyl alcohol, acetone, and ether, then with ether alone, and air-dried; this first crop of bright yellow solid weighed 42.0 g. and melted at 264-265° to a dark-brown liquid. Mother liquors and washings were collected with about 100 cc. of hot ethanol, evaporated to about 150 cc., and diluted with 150 cc. of benzene (other ordinary solvents caused separation of an oil); this solution yielded an additional crop of 34.7 g. melting at 245-247°. In the same way, a third crop of 22.7 g., m.p. 242-247°, was obtained, making a total of 99.4 g. or 43.0% of crude (VIa) calculated anhydrous. A small sample of the first crop recrystallized from a little warm glacial acetic acid in clusters of fine bright-yellow needles, which turned gummy and heterogeneous on drying; from aqueous acetic acid, more-tractable tan flakes of high crystallizing power were obtained, melting at 190-191° when heated slowly from 184°; this melting point varied with the rate and period of heating; the analysis indicated this solid to be a hydrated form of (VIa):

Anal. Calc'd for $C_{25}H_{24}BrClN_2O \cdot 1/2H_2O$: C, 60.92; H, 5.11; N, 5.69.

Found: C, 60.44; H, 5.54; N, 5.78.

The free base from (VIa) was obtained in a crystalline form from the first crop of the salt (see above) by suspending a small amount in water, basifying with 4 N sodium hydroxide, extracting with benzene, drying over potassium carbonate, freeing of benzene, and scratching with a mixture of isopropyl alcohol and ligroin; the base crystallizes very slowly even when seeded and scratched; after solution in ethanol, noriting, and evaporation to dryness, the solid melted at 132-135°.

The free base from the second crop behaved similarly and melted at 134-136°.

Since the histories of the three crops of (VIa) in the conversions VIa ⟶ VIIa and VIIa ⟶ IXa are different, typical runs of these steps will be described, followed by the detailed description of the treatment of the separate crops.

ε-Bromo-ε-(2-p-chlorophenyl-7,8-benzocinchoninyl)-n-amylamine Dihydrobromide (VIIa). Six-tenths of a mole (29.1 g.) of (VIa) was suspended in 120 cc. of boiling 48% hydrobromic acid and treated with a solution of 9.60 g. (one equivalent) of bromine in 12 cc. of the same solvent, heating and swirling during the addition. After some cooling, 120 cc. of isopropyl alcohol was slowly added, then 100 cc. of "Cellite 535", and the hot solution filtered through sintered glass and cooled in a refrigerator; the crop of bright-yellow solid was filtered off on the same sort of funnel, washed with isopropyl-alcohol-ether, then with ether alone, and air-dried--yield, 25.4 g. of crude (VIIa) melting with decomposition from 160° to 190°. Recrystallized from a rather large amount of boiling glacial acetic acid, the salt (VIIa) formed microscopic, rough, bright-yellow bobbins melting with decomposition at 189° and analyzing as a dihydrobromide monohydrate.

Anal. Calc'd for $C_{25}H_{24}Br_3ClN_2O \cdot H_2O$: C, 45.38; H, 3.96; N, 4.23.

Found: C, 45.63; H, 4.07; N, 4.19.

2-p-Chlorophenyl-7,8-benzoquinolyl-4-α-piperidylcarbinol (IXa). In a 1 l. round-bottomed flask were placed 14.6 g. (0.022 mole) of crude (VIIa) and 400 cc. of absolute ethanol; air in the flask was swept out with nitrogen and, with swirling, 58 cc. of 14% aqueous sodium carbonate

was added and the mixture shaken with moist hydrogen at atmospheric pressure and room temperature; after about 11 hours, the rate of absorption had become negligible, and 1470 cc. of the gas had been taken up (theory 1145 cc.); the carbinol (IXa) crystallized out as a grey slurry after about 2 1/2 hours and 1100 cc. of the hydrogenation. The mixture was next treated with 160 cc. of benzene, heated to boiling on steam, and inorganic solids were filtered off and washed with 50 cc. of hot benzene. On evaporation to dryness on steam, a tan crystalline solid formed; 100 cc. of water was used to transfer it to a small Buchner, where it was washed with 50 cc. of boiling water. When dry, this solid weighed 8.8 g. and melted at 215-226°. It was redissolved in 25 cc. of boiling pyridine, centrifuged, diluted with 50 cc. of hot benzene, and placed in a refrigerator to crystallize; the resulting crop of fine, soft, white needle-clusters, filtered off, washed with benzene, and air-dried, weighed 6.0 g. A small sample recrystallized from benzene-pyridine melted at 224.9-225.5° to a red-brown liquid after some fusion from 223°.

Anal. Calc'd for $C_{25}H_{23}ClN_2O$: C, 74.52; H, 5.75; N, 6.95.

Found: C, 74.93; H, 6.01; N, 6.66.

Crop One (VIa). Bromination of 4.84 g. of this material gave 5.78 g. of crude (VIIa), 4.77 g. of which on ring-closure and reduction gave 2.73 g. of crude (IXa); 2.4 g. of this material on recrystallization gave 1.7 g. of pure (IXa). 37.2 g. of this crude (VIa) was recrystallized from aqueous acetic acid to give 30.2 g. of the pure hemihydrate; 21.1 g. of this recrystallized material yielded 31.9 g. of crude (VIIa), 29.1 g.

of which gave 14.2 g. of crude (IXa), recrystallizing to give 4.7 g. of pure (IXa).

Crop Two (VIa). Again 4.84 g. was brominated, giving 5.07 g. of crude (VIIa), 4.44 g. of which gave 2.40 g. of crude (IXa); similarly, 29.1 g. yielded 25.4 g. of crude (VIIa), which was converted to 13.9 g. of crude (IXa), recrystallized to 7.2 g. of pure carbinol.

Crop Three (VIa) appeared heterogeneous and did not recrystallize well from aqueous acetic acid, but a small sample gave a crystalline free base, so the bulk of it (22.0 g.) was dispersed in 300 cc. of boiling water, basified with 30% potassium hydroxide, and the free base extracted with about 500 cc. of benzene, centrifugation being required to remove some solid insoluble in both phases. After drying over sodium sulfate, the extracts were stripped of solvents on the steam bath, yielding a high-melting solid and a brown sirup; the solid was filtered off and discarded; the sirup, after complete removal of solvent, weighed 11.8 g., and yielded 15.0 g. of crude (VIIa). 14.6 g. of this material gave 8.8 g. of crude (IXa) and therefrom 6.0 g. of the pure carbinol.

A compilation of this data reveals that the yield in the step VIa (crude, as anhydrous monohydrobromide) ⟶ VIIa (crude as dihydrobromide monohydrate) was 72.3%; in the step VIIa ⟶ IXa (pure, recrystallized) the yield was 43.7%.

(IXa) Monohydrochloride was obtainable only by dissolving the carbinol in hot glacial acetic acid–12 N hydrochloric acid, diluting with methanol, then adding a trace of water; thus 17.8 g. of recrystallized (IXa) was dissolved in a boiling mixture of 100 cc. of glacial acetic

acid and 80 cc. of 12 N hydrochloric acid, diluted with 700 cc. of methanol and, with vigorous swirling, 27 cc. of water. A copious, white, finely-divided solid separated at once; filtered off an a sintered-glass funnel, washed with aqueous methanol and ether, and air-dried, it weighed 17.2 g. and, on slow heating from 242°, the salt fused and colored from 256 to 258°, where it melted to a clear, brown liquid. For analysis, a sample was reprecipitated twice in this manner.

Anal. Calc'd for $C_{25}H_{24}Cl_2N_2O \cdot 1/2H_2O$: C, 66.96; H, 5.62; N, 6.25.

Found: C, 66.57; H, 5.69; N, 6.13.

Series b

ϵ-(2-Phenyl-7,8-benzocinchoninyl)-n-amylamine Hydrobromide (VIb)

Sodamide was prepared by adding a trace of ferric chloride to a solution of 17.7 g. (0.17 mole) of clean metallic sodium in about 900 cc. of liquid ammonia in a 3-l. 3-necked flask. After evaporation of the excess ammonia, the cake of grey sodamide was quickly broken up with a spatula. 201 g. (0.613 mole) of recrystallized 2-phenyl-4-carbethoxy-7,8-benzoquinoline (IIIb)+ and 161 g. (0.613 mole) of (IV) were dissolved in 370 cc. of thiophene-free benzene in a 1-l. wide-mouthed conical flask, the level of the solution marked on the flask, an additional 100 cc. of benzene added, and solvent boiled off down to the mark. When cool, this solution was added to the sodamide, the 3-necked flask was equipped with a powerful, sleave-sealed Hershberg stirrer and a small Allihn reflux condenser protected by a potassium-hydroxide tube and the mixture was heated on a glycerin bath at about 96° with stirring for 28 hours. During the heating,

+Prepared in These Laboratories by J. A. Seneker.

the mixture first turned to a white paste; then, slowly, to a dark brown sirup.

After cooling, a cold solution of 319 cc. of CP concentrated sulfuric acid in 457 cc. of water was added to the reaction mixture; swirling to mix thoroughly, the mixture heated spontaneously to about 60° and separated into three phases. The benzene was distilled off and the residue refluxed over a free flame for 37 hours, when the mixture had turned to a clear, red-brown solution containing a little yellow crystalline solid. When cool, the mixture was poured onto about 6 l. of crushed ice in a 12-l. round-bottomed flask; with swirling and addition of more ice from time to time, a cool solution of 550 g. of sodium hydroxide pellets in 1840 cc. of water was added. A liter of chloroform was then added to dissolve the precipitated yellow curd, and some solid insoluble in both phases filtered off on a large Buchner; the filter cake was washed with 500 cc. of chloroform and the aqueous phase extracted further with two 250-cc. and one 150-cc. portions of the same solvent. The combined chloroform extracts were dried over sodium sulfate and freed of solvent on the steam bath, finally by applying an aspirator, leaving 160.5 g. of a dark-brown, viscous oil, which was transferred to a 500-cc. wide-mouthed conical flask with 71 g. (one equivalent) of reagent 48% hydrobromic acid and about 250 cc. of isopropanol. After standing over the week-end, the product (VIb) was filtered off on a sintered-glass funnel, washed with isopropanol and ethyl ether, and air-dried, 119.2 g. (43.2%) of dark-tan, flakey powder, crude m.p. 218-221°. On acidification, the aqueous phase separated (above) from the chloroform extracts gave 78.4 g. of 2-phenyl-7,8-benzocinchoninic acid

(corresponding to (IIIb)). (VIb), when recrystallized from ethanol–48% hydrobromic acid formed clusters of tiny, bright yellow needles melting at 225–226° when heated slowly; it crystallized from ethanol–water in clusters of tan, micaceous needles, m.p. 206–207°; from glacial acetic acid, the compound separated in clusters of yellow-brown needles of the same melting point, which were analyzed.

Anal. Calc'd for $C_{25}H_{25}BrN_2O$: C, 66.81; H, 5.61; N, 6.24.
Found: C, 66.64; H, 5.77; N, 6.19.

ϵ-Bromo-ϵ-(2-phenyl-7,8-benzocinchoninyl)-n-amylamine Hydrobromide (VIIb). Ninety-four and three-tenths grams (0.21 mole) of (VIb) was dissolved in 105 cc. of warm (60°) 48% hydrobromic acid and treated rapidly with a solution of 33.6 g. (0.21 mole) of bromine in 27 cc. of the same solvent; a small amount of oil precipitated, but soon dissolved with swirling and heating over a free flame. On cooling, the mixture set to a mass of tiny clusters of bright yellow needles; the entire mixture was redissolved by adding 275 cc. of 48% hydrobromic acid, 500 cc. of isopropanol, 800 cc. of ethanol, and 300 cc. of water and bringing to a boil. After cooling overnight, the mass of orange-yellow needles was filtered off, washed with ethanol and ether, and air-dried; the crystals of (VIIb) weighed 99.6 g. (83.9%), melted at 196° with decomposition, and analyzed directly for the monohydrobromide dihydrate.

Anal. Calc'd for $C_{25}H_{24}Br_2N_2O \cdot 2H_2O$: C, 53.21; H, 5.00; N, 4.97.
Found: C, 53.50; H, 4.84; N, 4.93.

No reproducible results were obtainable by recrystallizing (VIIb) from ethanol–48% hydrobromic acid, isopropanol–48% hydrobromic acid, or ethanol–water.

2-Phenyl-7,8-benzoquinolyl-4-α-piperidylcarbinol (IXb) Hydrochloride. A mixture of 60.9 g. (0.108 mole) of recrystallized (VIIb) and 1500 cc. of absolute ethanol was placed in a 5-l. round-bottomed flask, the air in the flask swept out with nitrogen, 232 cc. of 14% aqueous sodium carbonate added with swirling, the air again swept out, and the flask stoppered and shaken for 80 minutes. 0.75 g. of Adams' platinum oxide was then added to the light-tan, pastey suspension and the mixture shaken with hydrogen. After 25 hours, when 3052 cc. had been taken up (theory about 2900 cc.), the absorption of hydrogen stopped. The mixture was then heated to boiling on the steam bath and 300 cc. of butanone and 450 cc. of benzene were added to dissolve the organic solids; insoluble inorganic solids were filtered off and the clear brown filtrate evaporated to dryness on the steam bath. 500 cc. of chloroform and 250 cc. of water were added to the residual light-brown solid, about 25 g. of solid (A) insoluble in both solvents was filtered off, and the aqueous phase of the filtrate further extracted with two 100-cc. portions of chloroform. After drying over sodium sulfate, the chloroform extracts were freed of solvent on the steam bath, finally by boiling off small portions of alcohol; the solid (A) and 100 cc. of 95% ethanol were added to the residue, which was then saturated with anhydrous hydrogen chloride. The resulting light-brown, crystalline mush was filtered off on a sintered-glass funnel, washed with isopropanol and ether, and air-dried, crude yield 50.7 g., crude m.p. 266°. This crude product, which left some ash on combustion of a small portion, was redissolved in 100 cc. of water and 190 cc. of 12 N hydrochloric acid, norited, and allowed to crystallize; the large clusters of well-formed, yellow-brown needles were filtered off on a glass funnel, washed with

6 N hydrochloric acid and acetone, and air-dried, yield 49.6 g. (97.7%), m.p. 258° with decomposition.

Anal. Calc'd for $C_{25}H_{26}Cl_2N_2O \cdot 1\ 1/2\ H_2O$: C, 64.10; H, 6.24; N, 5.98.
Found: C, 64.16; H, 6.26; N, 5.81.

Boiling a suspension of the above dihydrochloride in pyridine-benzene and 4 N sodium hydroxide was necessary to liberate the free base; after centrifuging, the organic phase was removed and the aqueous phase extracted once more with benzene-pyridine. Evaporation of the extracts left a white crystalline solid (IXb) which formed minute white needles in compact clusters, m.p. 226.8-227.5°, from pyridine.

Anal. Calc'd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60.
Found: C, 81.23; H, 6.38; N, 7.88.

Series c

ϵ-Bromo-ϵ-(2-phenyl-8-chlorocinchoninyl)-n-amylamine Hydrobromide (VIIc).

In a 1-l. three-necked flask, sodamide was prepared from 8.50 g. (0.37 mole) of clean sodium by dissolving the metal in about 300 cc. of liquid ammonia and adding a pinch of anhydrous ferric chloride. When the deep blue color of the dissolved metallic sodium had disappeared, the excess ammonia was boiled off and the residual cake of grey sodamide quickly broken up with a stirring rod. Three-tenths of a mole each of (IV) and (IIIc)+ were rapidly added along with 180 cc. of thiophene-free benzene dried over sodium. A mercury-sealed Hershberg stirrer turned slowly by a powerful electric motor and a Friedrichs reflux condenser protected against moisture by a tube containing potassium hydroxide pellets were attached, and the third

+Prepared in These Laboratories by J. A. Seneker.

neck firmly stoppered. The temperature of the stirred mixture was slowly raised by means of a glycerin bath; after one-half hour, the bath was at 46° and the mixture had become a thick white paste, evolving ammonia; after two hours, the bath was at 72°; after 21 hours of stirring, the mixture had turned to a dark brown sirup, with the bath at 86°. The bath was removed and when the sirup had cooled to room temperature, the stirrer and drying tube were removed, a cooled solution of 156 cc. of concentrated sulfuric acid in 224 cc. of water added, the benzene distilled off, and the remaining clear, deep-red-yellow solution refluxed for 50 hours. After cooling, the mixture was poured into a 3-l. flask and treated with a solution of 269 g. of sodium hydroxide pellets in 900 cc. of water, cooling by swirling the flask in crushed ice. The resulting yellow-brown gum was taken up in 600, 250, and 200 cc. of chloroform, dried over sodium sulfate, and freed of solvent on the steam-cone and aspirator, leaving 73.4 g. of viscous, dark-brown oil. The basic aqueous phase on acidification gave 39.2 g. of 2-phenyl-8-chlorocinchoninic acid. The basic oil on treatment with 70 g. of 48% hydrobromic acid yielded some insoluble oil which crystallized, giving 9.8 g. of a solid which proved to be the starting ester (IIIc)! Cautious dilution of the aqueous portion until an oil began to separate, scratching, and allowing to stand gave 47.9 g. of a solid whose refusal to recrystallize cleanly was laid to the presence of more unhydrolyzed ester (IIIc); hence the solid was shaken vigorously with 70 cc. of 48% hydrobromic acid and 50 cc. of chloroform and 2.78 g. of bright yellow solid insoluble in both phases filtered off. This solid formed bright-yellow, hexagonal plates from ethanol-48% hydrobromic acid melting to a red froth at 160-163° (Anal. Found: C, 40.81, 40.78; H, 4.41,

4.60; N, 4.66, 4.21.); treatment with water or alcohols transformed this compound into a white solid, m.p. 263° from ethanol-water; dissolved in a little warm 48% hydrobromic acid and treated with bromine vapors, this bright yellow solid gave a salt whose melting point, mixed melting point, and recrystallization behavior were indistinguishable from those of (VIIc) (see below). The aqueous portion of the filtrate from the yellow solid was further washed with three 25-cc. portions of chloroform, freed of excess solvent in vacuo on the steam bath, and allowed to stand over the week-end, giving a sirupy, bright-yellow crystal-mush.

Tests on small portions of this material indicated the brominated compound to be more tractable, so the whole was dissolved in 50 cc. of hot 48% hydrobromic acid and treated with a 50% solution of bromine in the same solvent until the red-orange oil formed on addition of each portion of the bromine solution dissolved only with difficulty; at this point, 15.0 g. of bromine had been added. 50 cc. of solvent were removed in vacuo, heating on the steam bath, and the residual sirup rapidly dissolved in 50 cc. of absolute ethanol; on cooling, 30.2 g. of tiny, bright-yellow needles were deposited. Concentration and cooling gave 20.2 g. more of the solid (VIIc), representing a total yield of 28.3% from (IIIc); taking into account the amount of the cinchoninic acid recovered, the yield was 52.4%. Redissolved in boiling ethanol by addition of 48% hydrobromic acid, (VIIc) was recrystallized without appreciably raising the crude melting point, 171°, somewhat dependent upon the rate and period of heating.

Anal. Calc'd for $C_{21}H_{21}Br_2ClN_2O \cdot 3\ 1/2\ H_2O$: C, 43.81; H, 4.90; N, 4.87.

Found: C, 43.67; H, 4.52; N, 5.09.

2-Phenyl-8-chloroquinolyl-4-α-piperidylcarbinol (IXc) Hydrochloride. Thirty-nine and six tenths grams (0.0667 mole) of (VIIc) was placed in a 2-l. round-bottomed flask with 1 l. of absolute ethanol, the air swept out of the flask with nitrogen, 155 cc. of 14% aqueous sodium carbonate solution quickly added with swirling, and the flask tightly stoppered and shaken for one hour. Seventy-five hundredths of a gram of Adams' catalyst was then added to the orange-yellow solution and the mixture hydrogenated at room temperature and atmospheric pressure for 71 minutes, when the rate of hydrogen uptake was negligible and the theoretical amount (2080 cc.) had been absorbed; at this point the mixture had become colorless and a fine white solid had separated out; the mixture was heated to boiling on the steam bath, 300 cc. of butanone was added to dissolve the white organic solid, inorganic solids were filtered off on a Buchner funnel, and the filtrate evaporated to dryness on the steam bath. 200 cc. of chloroform and 100 cc, of water were added to the solid residue and 11.6 g. of the carbinol (IXc), insoluble in both phases, filtered off; recrystallized from a small amount of pyridine, the carbinol formed compact, colorless clusters, m.p. 217.7-218.6° when heated very slowly.

Anal. Calc'd for $C_{21}H_{21}ClN_2O$: C, 71.48; H, 6.00; N, 7.94.

Found: C, 71.15; H, 6.08; N, 8.10.

The brown chloroform phase of the above filtrate was drawn off, and the aqueous portion and various vessels further extracted and washed with 50 and 25 cc. of chloroform. The combined chloroform extracts were freed of solvent on the steam bath and 50 cc. of denatured alcohol was added to

the resulting slurry, which was then saturated with anhydrous hydrogen chloride; the original solid dissolved, then another separated out. After the solution had cooled to room temperature, the solid was filtered off on a sintered-glass funnel and the color washed from it with isopropanol and ether, leaving 7.38 g. of a light grey solid whose melting point was not appreciably raised by recrystallization from ethanol-water—pale pink, transparent bars, some in sparce clusters, m.p. 231.5-232.4° with gas evolution and coloring.

Anal. Calc'd for $C_{21}H_{22}Cl_2N_2O$: C, 64.78; H, 5.70; N, 7.20.

Found: C, 64.72; H, 5.79; N, 6.94.

The free base liberated from this hydrochloride was identical with the above carbinol, as was the salt itself identical with that prepared from the carbinol; together, the carbinol and its hydrochloride represent a yield of 87.4% from (VIIc), or 24.7% from (IIIc).

Series d

Ethyl 2-Phenyl-6-methylcinchoninate (IIId)(9). A mixture of 72 cc. (0.41 mole) of 50% aqueous pyruvic acid, 42.4 g. (0.40 mole) of freshly redistilled benzaldehyde, 42.8 g. (0.40 mole) of p-toluidine, and 1 l. of ethanol was refluxed on the steam bath for six hours. A solution of 16.8 g. of sodium hydroxide flakes in 500 cc. of water was added and the ethanol distilled off in vacuo; after cooling, the dark oil which separated was removed with isopropyl ether, a small quantity of a yellow crystalline solid (m.p. 209-210°; compare (9)) insoluble in both phases being filtered off to facilitate separation. Upon adding 59 cc. of 6 N hydrochloric acid to the aqueous phase, the crude acid separated as an oil

which soon crystallized to an orange solid; this was thrown onto a Buchner funnel, pressed as dry as possible, and spread to dry; the crude acid was too soluble in ethanol, methanol, and acetone to hasten the drying by washing out the water with any of these solvents. To the crude dry acid (68.9 g.) were added 700 cc. of absolute ethanol and 45 cc. of concentrated sulfuric acid, and the solution refluxed for 17 hours. After removal of the excess ethanol at water-aspirator pressure by heating on a steam bath, the residual dark brown sirup was cooled in crushed ice and treated with ice and 15 N ammonium hydroxide until basic (about 80 cc. required). The resulting oil was taken up in 300, 100, and 50 cc. of ethyl ether, dried over potassium carbonate, stripped of ether, and redissolved in 100 cc. of absolute ethanol; cooling in the icebox yielded 41.4 g. of light yellow-tan needles, m.p. 74.8-75.5° in agreement with literature values (9). The yield of (IIId) was 54.2% from the crude acid, or 35.7% from p-toluidine. Using glacial acetic acid in place of ethanol gave a higher yield (76%) of the crude acid, but the yield of the pure crystalline ester was less (17.6%) and the products were more difficult to work up.

ϵ-(2-Phenyl-6-methylcinchoninyl)-n-amylamine Dihydrobromide (VId). The sodamide condensation was carried out using 11.4 g. (0.496 mole) of sodium, 105.8 g. (0.402 mole) of (IV), 116.8 g. (0.402 mole) of (IIId)*, and 240 cc. of benzene and heating for 24 hours. The hydrolysis was accomplished by refluxing 54 hours with 300 cc. of water and 210 cc. of concentrated sulfuric acid. The crude, clear hydrolysate on cooling

*Part of this ester was supplied by R. C. Elderfield, Columbia University.

overnight deposited a large quantity of benzoic acid. The mixture was washed into a 3-l. conical flask with a little water, cooled by the addition of 834 g. of ice, and basified by adding a cool solution of 360 g. of sodium hydroxide pellets in 1200 cc. of water. The resulting yellow gum was extracted from the colorless aqueous phase with 800, 150, and two 50-cc. portions of chloroform. Fifty-five grams of 2-phenyl-6-methylcinchoninic acid was recovered by acidification of the aqueous phase with acetic acid. Freed of chloroform in vacuo on the steam bath, the basic extract was cautiously added to 150.0 g. of 48% hydrobromic acid; cooling and scratching gave a copious amount of a yellow solid which was filtered off on a sintered-glass funnel, washed with isopropanol and ether, and dried to give 77.3 g. of (VId); 19.0 g. more was obtained from the filtrate by concentration and cooling—total yield 48.3%. In a smaller run, starting with 0.134 mole of each of the reactants, a 41.8% yield of (VId) was obtained. Recrystallized from ethanol-water, the salt formed yellow bars, m.p. 244-245° with gas evolution and coloring.

Anal. Calc'd for $C_{22}H_{26}Br_2N_2O$: C, 53.45; H, 5.30; N, 5.67.
Found: C, 53.21; H, 5.62; N, 5.42.

ϵ-Bromo-ϵ-(2-phenyl-6-methylcinchoninyl)-n-amylamine Dihydrobromide (VIId). Seventy-seven and three-tenths grams (0.156 mole) of (VId) was dissolved in hot dilute hydrobromic acid and treated with a solution of 24.9 g. (0.156 mole) of bromine in 48% hydrobromic acid. Rapid addition of the bromine is advisable since the more insoluble bromoketone dihydrobromide (VIId) is difficult to redissolve once its separa-

tion from the solution begins. After filtering the product on a sintered-glass funnel, it showed orange patches due to local excesses of bromine, so it was dispersed in 400 cc. of boiling absolute ethanol and water added until a clear solution resulted, 56.5 cc. of water being required; on cooling, 54.5 g. of light yellow needle-clusters was obtained; an additional 9.8 g. was obtained by concentration and refrigeration of the mother liquors, representing in all a yield of 67.8% of recrystallized material. In a smaller (0.0542 mole) run, there was obtained an 89.8% yield of material with a melting point not appreciably lower than that of the recrystallized salt, 187.7-188.1°.

Anal. Calc'd for $C_{22}H_{25}Br_3N_2O \cdot 2H_2O$: C, 43.37; H, 4.80; N, 4.60.
Found: C, 43.32; H, 4.90; N, 4.63.

2-Phenyl-6-methylquinolyl-4-α-piperidylcarbinol (IXd) Dihydrochloride. Sixty and eight-tenths grams (0.106 mole) of recrystallized (VIId), 1600 cc. of absolute ethanol, and 246 cc. of 14% sodium carbonate were shaken in a 5-l. round-bottomed flask for one hour, the solution turning bright yellow. Three-quarters of a gram of $PtO_2 \cdot 2H_2O$ was added and the mixture hydrogenated at room temperature and atmospheric pressure; after two hours, the rate of hydrogen absorption had become negligible, and 2790 cc. of a theory of 3105 cc. had been taken up. The white solid components were filtered from the reaction mixture and the filter cake washed with ethanol and 300- and 200-cc. portions of boiling chloroform. Evaporation of solvents from the clear, light yellow filtrate left a crystal slurry which was treated with 100 cc. of water and 200 cc. of warm chloroform, 1.5 g. of a white fibrous solid insoluble in both

phases being filtered off. This solid melted at 246° to a red liquid after some previous fusion, and left a residue on ignition; when dispersed in water and treated with 6 N hydrochloric acid, the solid dissolved and, on scratching, the (IXd) hydrochloride melting at 208° (see below) separated; after basifying a solution of this hydrochloride with 4 N sodium hydroxide, the free carbinol (m.p. 182.5°) could be extracted with chloroform; the original solid may possibly have been the sodium carbamate of the carbinol.

After removing the brown chloroform phase from the filtrate, the aqueous was further extracted with two 50-cc. portions of chloroform and the combined extracts freed of solvent on the steam bath, finally by boiling small quantities of ethanol from it. The resulting brown crystal-slurry was taken up in 200 cc. of warm ethanol and saturated with anhydrous hydrogen chloride. After allowing to cool to room temperature, the crystalline salt was filtered off, washed with isopropanol and ether, and air-dried—27.0 g. of a light tan powder, crude m.p. 233-235° with decomposition. Concentration and cooling of the filtrate gave an additional 2.28 g. of the same material, representing a total yield of 69.6% of (IXd) hydrochloride from recrystallized (VIId). In another experiment starting from the crude (VIId) mentioned above as being obtained in 89.8% yield, the amount of the carbinol salt obtained was 49.1% of the theory. Over the three steps (IIId $\longrightarrow$ IXd·2HCl·H_2O), the best yield was 22.8%.

Recrystallized from ethanol-water, the salt formed a monohydrate, sparse clusters of small, colorless needles melting sharply at 233.6°

to a red-brown liquid.

Anal. Calc'd for $C_{22}H_{26}Cl_2N_2O \cdot H_2O$: C, 62.41; H, 6.67; N, 6.62.

Found: C, 62.24; H, 6.58; N, 6.22.

Under various conditions, salts of two other melting points were obtained, probably different hydrates of the dihydrochloride; details of the preparation of a salt melting at 208° are mentioned above; recrystallizing the 233.6° salt from 6 N hydrochloric acid-ethanol gave tiny colorless needles melting with gas evolution at about 244°.

The free base (IXd) formed clusters of colorless, hexagonal plates from acetonitrile, m.p. 182.5-182.9°.

Anal. Calc'd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43.

Found: C, 79.33; H, 7.15; N, 8.31.

As has been noted with other related carbinols (10) this one tends to form stable, well-crystallized solvates; when recrystallized from acetonitrile containing ethanol, large, colorless, latticed crystals were obtained, effervescing at about 109-114°, resolidifying, and clarifying again at 170-183°.

Series e

2,8-Diphenylcinchoninic Acid. A mixture of 169 g. (one mole) of Monsanto technical-grade o-aminobiphenyl, 100 cc. (one mole) of freshly redistilled benzaldehyde, 183 cc. (about one mole) of 50% aqueous pyruvic acid, and 2500 cc. of denatured alcohol was refluxed in a five-liter round-bottomed flask for twenty hours. To the resulting clear, deep yellow liquid was added a solution of 45 g. of sodium hydroxide chips in 1 l. of water and solvent distilled off under aspirator vacuum,

heating on a steam bath until the distillate was no longer inflammable. After extracting non-acidic oils with three 250-cc. portions of benzene, the aqueous phase was warmed to dissolved any solid which had separated, and acidified by the addition of about 200 cc. of 6 N acetic acid, precipitating a brown, gummy solid. After standing overnight, this crude product was thrown onto a Buchner funnel and the oils washed out with ethanol and methanol, these washings being kept separate from the aqueous filtrate. When dry, the brown-yellow needles left on the filter paper wieghed 37.2 g.; this free acid formed sparse clusters of fine yellow needles from absolute ethanol, m.p. 243.0-243.6°.

Anal. Calc'd for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.31.

Found: C, 81.16; H, 4.73; N, 4.68.

Ethyl 2,8-Diphenylcinchoninate (IIIe). Thirty-five grams (0.108 mole) of the above acid was heated with 400 cc. of absolute ethanol and 20 cc. of concentrated sulfuric acid, a clear solution resulting from about 10 minutes' heating; after refluxing overnight, the excess ethanol was stripped off on a steam cone, leaving a clear, viscous, yellow-brown sirup which was cooled in ice, treated with ice-water and 50 cc. of 15 N ammonium hydroxide, and the resulting pale yellow gum taken up in one 200 cc.- and two 50 cc.-portions of benzene. After drying over potassium carbonate, the extracts were freed of benzene in vacuo on the steam bath, leaving 44.9 g. of a viscous sirup which soon turned to a tan solid, crude m.p. 101-104°. The ethanol-methanol washings from the crude acid (see above) were freed of solvents and similarly esterified with 1 l. of ethanol containing 80 cc. of concentrated sulfuric acid; inorganic solids were filtered off and the filtrate cooled to about 4° C.,

giving 48.7 g. of white needles. These two crops of crude ester (IIIe) were combined and recrystallized from 700 cc. of absolute ethanol, giving 79.7 g. of pure (IIIe) (22.6% yield from o-aminobiphenyl), compact clusters of fine white needles from ethanol-benzene, m.p. 104.6-105.2°.

Anal. Calc'd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96.

Found: C, 81.77; H, 5.40; N, 3.97.

In another experiment of the same size, the crude gummy acid (see above) was transferred to a 3-l. flask with 1 l. of absolute ethanol and 500 cc. of isopropyl ether. Solvents were then slowly distilled off through a 60 cm. bead-packed column until the distillation temperature reached that of ethanol, 880 cc. of distillate having been collected; 400 cc. more of ethanol and 80 cc. of concentrated sulfuric acid were added to the boiler residue and the mixture was refluxed overnight. Inorganic solids were then filtered off and the filtrate cooled, yielding 82 g. of crude ester; recrystallization from 600 cc. of ethanol gave a first crop of 66 g. of pure (IIIe); small additional amounts of the ester were obtained by working up mother liquors by methods suggested in the above text.

<u>ε-(2,8-Diphenylcinchoninyl)-n-amylamine Hydrobromide (VIe)</u>. After condensing about 700 cc. of liquid ammonia in a 2-l. three-necked flask, 11.9 g. (0.517 mole) of metallic sodium and three pinches of anhydrous ferric chloride were added and the deep blue solution allowed to stand at room temperature; in three hours, the blue color was discharged. While the excess ammonia was boiling off the grey sodamide, 145.7 g. (0.413 mole) of recrystallized (IIIe) and 108.7 g. (0.413 mole) of ethyl

ϵ-benzamidocaproate were dissolved in 250 cc. of thiophene-free benzene in a 1-l. wide-mouthed conical flask; the solution was brought to a boil on a hot plate, the level of the solution marked on the flask, 60 cc. more of benzene added, then boiled off to the mark, and the solution cooled in running tap-water. It was then added to the dry sodamide and the reaction flask was equipped with a sleave-sealed Hershberg stirrer turned slowly by a powerful electric motor and a water-cooled Friedrichs condenser protected from moisture by a potassium-hydroxide tube. During the first half-hour, the mixture, heated to about 90° in a glycerine bath, turned to a white paste and evolved ammonia; overnight, it changed to a dark-brown sirup; the heating and stirring were continued for 40 hours. After cooling, a cool solution of 214 cc. of concentrated sulfuric acid in 308 cc. of water was added to the reaction mixture, which spontaneously heated to about 60° and separated into three liquid phases. Heating with a free flame, the benzene was distilled off, leaving two phases, which were resolved into a clear, red-yellow solution after two hours' refluxing; fifteen hours later, the heating was discontinued and the solution allowed to cool overnight. The resulting slurry was poured onto 1 kilogram of ice, 500 cc. of chloroform was added, and the mixture basified by adding a chilled solution of 367 g. of sodium hydroxide chips in 1500 cc. of water (all but about 100 cc. of the solution was required). An emulsion of tan solid in the chloroform phase necessitated centrifugation; a rather rigid layer of solid at the chloroform-water interface enabled the latter to be poured off with ease; it was replaced by benzene, the bottle shaken, and recentrifuged; the solid thus removed

was extracted further with 300 cc. of boiling chloroform and filtered off with the aid of "Cellite 535".

After concentrating these extracts in vacuo on the steam bath, a small amount of solid was filtered off on a fine Pyrex funnel and the filtrate freed of solvent as far as possible with aspirator and steam heating, finally under an oil-pump vacuum, leaving 143.4 g. of viscous brown oil. This was transferred to a 500-cc. wide-mouthed conical flask with 62 g. (one mole-equivalent) of 48% hydrobromic acid and 100 cc. of hot isopropyl alcohol; the alcohol was then removed by boiling off two 100-cc. portions of acetone and the residual oil dissolved in 250 cc. of acetone and allowed to crystallize in an icebox; the first crop, washed with acetone and ether and air-dried, weighed 38.5 g.; concentration and dilution of the mother liquors with acetone yielded two additional crops of 43.5 g. and 16.7 g., making a total of 98.7 g. or 43.0%; this crude material (VIe) melted at 223-226° and was sufficiently pure for the next step.

A small sample of the first crop of crude (VIe) was redissolved in a little boiling glacial acetic acid; on cooling, a small quantity of tiny tan needle-clusters emerged. One recrystallization of this material from the same solvent gave sparse clusters of glistening, colorless needles melting at 270.6-271.1°; since this substance was small in amount, it was not further investigated, beyond an analysis (C, 69.92; H, 5.68; N, 6.04) whose relatively high carbon value indicated it may have been the monohydrobromide (VIe, x = 1). Acetone-dilution of the mother liquors from this higher-melting compound gave a relatively large

quantity of golden-yellow, jagged clusters which were recrystallized by solution in a small amount of warm glacial acetic acid followed by dilution with acetone; this product melted at 224-226° after some sintering and discoloration from about 220°.

Anal. Calc'd for $C_{27}H_{28}Br_2N_2O$: C, 58.29; H, 5.07; N, 5.04.
Found: C, 58.08; H, 5.30; N, 4.62.

€-Bromo-€-(2,8-diphenylcinchoninyl)-n-amylamine Hydrobromide (VIIe). Eighty-one and four-tenths grams of crude (VIe) were dissolved in 172 cc. of hot 48% hydrobromic acid and treated with a solution of 27.4 g. (one equivalent) of bromine in 27 cc. of the same solvent, causing precipitation of a yellow oil which redissolved readily on warming. A small amount of tar was removed by filtering the hot solution. The filtrate was diluted with about 250 cc. of hot ethanol and cooled, giving clusters of fine, bright yellow needles which were filtered off an a sintered-glass funnel, washed with acetone and ether, and air-dried; concentration of the filtrates followed by dilution with ethanol gave a total of four crops weighing 84.7 g. and melting variously in the range 147-168°. Norited and recrystallized several times from glacial acetic acid, the compound (VIIe) melted fairly reproduceably at 177.1-177.4° to a black tar. Analysis of the salt indicated it to be hydrated.

Anal. Calc'd for $C_{27}H_{26}Br_2N_2O \cdot 1\ 1/2\ H_2O$; C, 55.78; H, 5.03; N, 4.82.
Found: C, 55.67; H, 5.11; N, 4.96.

2,8-Diphenylquinolyl-4-α-piperidylcarbinol (IXe). A 5-l. round-bottomed flask was charged with 63.7 g. (0.108 mole) of crude (VIIe) and 1500 cc. of absolute ethanol, the air in the flask swept out with

nitrogen, and 214 cc. of 14% aqueous sodium carbonate added with swirling. 0.75 g. of Adams' platinum oxide catalyst was added after shaking this mixture for 90 minutes, and it was then shaken with moist hydrogen at room temperature and atmospheric temperature. Thirty hours later (0.5 and 0.2 g. of platinum were added after three and twenty-two hours, respectively) the rate of hydrogen absorption had become negligible, and 3105 cc. of a theory of 3590 cc. had been taken up. The mixture was then heated to the boiling point on a steam bath and insoluble inorganic solids were filtered off and washed with a little hot ethanol; the yellow filtrate was evaporated on the steam bath, leaving a varicolored solid which was taken up in 300 cc. of hot benzene and washed with 100 cc. of water. After drying the brown benzene solution over sodium sulfate, it was freed of solvent on the steam bath, finally by boiling off two 25-cc. portions of ethanol. Attempts to prepare the hydrochloride of (IXe) from the residual solid being unpromising, it was dissolved in about 160 cc. of 6 N hydrochloric acid, washed with 300 cc. of benzene, basified with a solution of 54 g. of potassium hydroxide in 100 cc. of water, and the free base taken up in one 400-cc. and two 100-cc. portions of benzene. Most of the benzene was boiled off, 100 cc. of ethanol added, the slurry brought to a boil, and more benzene added until a clear solution resulted; on cooling overnight in a refrigerator, a crop of light tan needles emerged; these were filtered off, washed with cold ethanol, and air-dried, weight 16.9 g., crude melting point 195-197°; the mother liquors yielded an additional 3.3 g. of this material and a residual solid weighing 17.6 g. which did not behave like (IXe) in the conversion to the hydrochloride (see below). The first two crops, totaling 20.2 g.,

represented a yield of 47.5% of (IXe) from (VIIe). One recrystallization of (IXe) from ethanol-benzene gave clusters of fine white needles, m.p. 195.8-196.2°.

Anal. Calc'd for $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64; N, 7.10.
Found: C, 81.95; H, 6.62; N, 7.10.

When (IXe) was dissolved in about five volumes of hot 6 N hydrochloric acid and diluted quickly with 15 volumes of boiling water, beautiful, compact clusters of bright orange-yellow needles emerged, but on filtering and washing with acetone, this salt lost its color and became gummy; consequently the following procedure was found to be more serviceable: a solution of 20.1 g. of (IXe) in 100 cc. of hot 6 N hydrochloric acid was diluted with 650 cc. of acetone, followed by 100 cc. of water; on cooling in the icebox, 12.7 g. of colorless bars slowly emerged, m.p. 242°. Concentration and similar dilutions of the mother liquors gave 8.1 g. more of the salt in three crops. Recrystallized for analysis from ethanol-6 N hydrochloric acid, it melted at 242-243° to a dark brown liquid.

Anal. Calc'd for $C_{27}H_{27}ClN_2O$: C, 75.24; H, 6.32; N, 6.50.
Found: C, 75.32; H, 6.40; N, 6.38.

Series f

2-Phenyl-8-methylcinchoninic Acid. A solution of 212 cc. (2.0 moles) of Eastman practical-grade o-toluidine, 200 cc. (2.0 moles) of benzaldehyde, and 366 cc. (about two moles) of 50% aqueous pyruvic acid in 5 l. of denatured alcohol was refluxed 19 hours, then treated with a solution of 90 g. of sodium hydroxide chips in 2 l. of water, and solvent

distilled off on the steam bath until the distillate was no longer inflammable. Non-acidic substances were extracted with two 500-cc. portions of benzene and these extracts in turn washed with 300 cc. of warm water. The combined aqueous phases were warmed on a steam bath to dissolve any sodium salts which had separated, then acidified with 6 N acetic acid, precipitating a tan solid which, after cooling to about 4° C., was filtered off an a Buchner funnel, washed with water, and air-dried, yield 339.4 g. This crude product was recrystallized from a mixture of 2200 cc. of ethanol and 200 cc. of benzene, giving 104.6 g. of pale yellow needles (19.9% yield), m.p. 240° (Doebner and Gieseke (9) give m.p. 245°). A 1.0 mole run gave almost the same yield of the pure acid (19.5%).

Evaporation of the mother liquors from recrystallization of the acid to a small volume left, on cooling, a red-brown solid, rather readily soluble in ethanol, which was not further investigated.

Ethyl 2-Phenyl-8-methylcinchoninate (IIIf). One-hundred and four and six-tenths grams (0.398 mole) of the above recrystallized acid was suspended in 1500 cc. of absolute ethanol and 70 cc. of concentrated sulfuric acid added, causing the separation of a voluminous, bright-yellow solid, apparently the sulfate of the acid, which dissolved after a few minutes' refluxing. After continuing the refluxing for about 24 hours, the ethanol was stripped off in vacuo on the steam bath and the residual dark brown sirup covered with 500 cc. of benzene, ice added, then 176 cc. of 15 N ammonium hydroxide, and the near-colorless aqueous phase further extracted with two 100-cc. portions of benzene. The combined benzene extracts were dried over potassium carbonate, freed of

solvent on the steam bath under aspirator vacuum, the remaining oil transferred to a 500-cc. wide-mouthed conical flask with 200 cc. of isopropyl ether, and placed in the refrigerator overnight. The compact, light-tan, flakey clusters, filtered off, washed with ligroin, and air-dried, weighed 80.5 g.; a further 18.6 g. of (IIIf) was obtained by concentration of the mother liquors to about 50 cc. and cooling—yield 85.6% from the acid or 17.1% from o-toluidine. In a smaller run, starting from 51.2 g. (0.195 mole) of recrystallized acid, the residual oil from evaporation of the benzene extracts was seeded with the ester, giving 53.2 g. (94% from the acid) of m.p. 69-71°; recrystallization from 100 cc. of 60-70° petroleum ether gave a first crop of 49.2 g. A small sample recrystallized once from ligroin and once from a small amount of ethanol formed transparent, tan, irregular clusters, m.p. 71.3-71.8°.

Anal. Calc'd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81.

Found: C, 78.47; H, 6.01; N, 4.66.

The same product (IIIf) was obtained by treating a small portion of recrystallized acid successively with thionyl chloride and absolute ethanol. An esterification of the bulk of the crude acid obtained as noted above, without recrystallization, gave a dark brown oil which partially solidified only on seeding with (IIIf), and was very difficult to purify.

<u>ε-(2-Phenyl-8-methylcinchoninyl)-n-amylamine Hydrobromide (VIf)</u>. About 700 cc. of liquid ammonia was condensed in a 2-l. 3-necked flask, then 11.4 g. (0.496 mole) of metallic sodium and a pinch of anhydrous ferric chloride were added; after standing at room temperature for about one hour, the deep blue color of the solution had been discharged; and the

excess ammonia was then rapidly boiled off by setting the flask in a pan of ethanol stirred by a stream of air-bubbles. Meanwhile, 116.8 g. (0.402 mole) of (IIIf) and 105.8 g. (0.402 mole) of (IV) were dissolved in 300 cc. of thiophene-free benzene and 60 cc. of the solvent boiled off. Protected from moisture by a calcium-chloride tube, the solution was cooled and then added to the above-prepared sodamide; the reaction vessel was equipped with a sleeve-sealed Hershberg stirrer turned by a slow, powerful, electric motor, and a water-cooled Allihn condenser protected by a potassium-hydroxide tube. With stirring, the mixture was slowly heated to about 100° in a glycerin bath, turning to a white paste with evolution of ammonia, then to a dark brown sirup; after twenty hours' heating at this temperature, the mixture was cooled in a pan of tap-water and a cool solution of 210 cc. of concentrated sulfuric acid in 400 cc. of water was rapidly added causing the contents of the flask to heat spontaneously to about 60° and separate into two liquid phases. By application of a free flame, benzene was distilled off until vapors from the flask were no longer inflammable and the residual, clear, dark-brown solution was refluxed for about 43 hours; it was then poured onto about a liter of crushed ice and 800 cc. of chloroform and treated with a solution of 360 g. of sodium hydroxide flakes in 1200 cc. of water. The resulting mixture was run through a Buchner funnel to remove a large amount of solid suspended in the chloroform phase, and the filter cake and aqueous phases were further extracted with four 200-cc. portions of chloroform. On heating, the filter cake dissolved in the aqueous phase and yielded 46.5 g. of the starting acid on acidification with 6 N acetic

acid. The combined chloroform extracts were filtered once more to remove a small amount of flakey solid, then evaporated in vacuo on the steam bath, leaving 98 g. of dark-brown, viscous oil, which was transferred to a 250-cc. wide-mouthed conical flask with a little acetone, treated cautiously with 40.0 g. (one equivalent) of 48% hydrobromic acid, then diluted with about 100 cc. more of acetone. On standing overnight, 14.7 g. of light yellow flakes emerged which were filtered off, washed with acetone and ether, and air-dried, crude m.p. 132-137°; recrystallized twice from glacial acetic acid, the compound formed dense clusters of light yellow, thin, rectangular blades with bluntly-pointed terminations, m.p. 136-137° after some fusion from 132°, and analyzed as a hydrated dihydrobromide of the desired ketone (corresponding to (VIf).

Anal. Calc'd for $C_{22}H_{26}Br_2N_2O \cdot 2H_2O$: C, 49.82; H, 5.70; N, 5.28.
Found: C, 50.17; H, 5.73; N, 5.82.

Dilution of the mother liquors from this first crop with ether to incipient oil formation and cooling overnight in a refrigerator gave 42.7 g. of a tan powder melting at about 157°; further cooling of the mother liquors and washings (acetone and ether) from this crop gave an additional 7.2 g. of the same material, which crystallized from glacial acetic acid in clusters of light tan needles, m.p. 178-179°.

Anal. Calc'd for $C_{22}H_{25}BrN_2O$: C, 63.92; H, 6.10; N, 6.78.
Found: C, 64.07; H, 5.94; N, 6.88.

These three crops, the latter two calculated as monohydrobromide dihydrate, represent a yield of 34.6% from (IIIf), or 61.8% taking into account the recovered cinchoninic acid corresponding to (IIIf).

ε-Bromo-ε-(2-phenyl-8-methylcinchoninyl)-n-amylamine Hydrobromide (VIIf). In 93 cc. of hot 48% hydrobromic acid, 38.4 g. of (VIf) were dissolved and treated with a solution of 14.9 g. (one equivalent) of bromine in about 15 cc. of the same solvent; an orange oil was formed, but quickly redissolved. After filtering off a little tar, the warm solution was diluted with 200 cc. of isopropanol and cooled in a refrigerator; the clusters of tiny, pale-yellow needles thus formed were filtered off on a sintered-glass funnel, washed with isopropanol and ether, and dried to constant weight at the oil pump, yield 51.5 g. of (VIIf), m.p. 156-162°. A small sample (4.13 g.) of the dihydrobromide described above behaved in an identical manner, giving 3.44 g. of product. A portion of the product of the large run recrystallized twice from isopropanol-water gave sparse clusters of long, shiney, yellow needles, m.p. 175.8-176.0° to a dark red-brown liquid.

Anal. Calc'd for $C_{22}H_{24}Br_2N_2O \cdot H_2O$: C, 51.78; H, 5.14; N, 5.49.
Found: C, 52.23; H, 5.18; N, 5.88.

2-Phenyl-8-methylquinolyl-4-α-piperidylcarbinol (IXf). In a three-liter round-bottomed flask, 56.1 g. of (VIIf) derived from 42.5 g. of (VIf) was suspended in 1480 cc. of absolute ethanol, air swept from the flask with nitrogen, and 227 cc. of 14% aqueous sodium carbonate added with swirling; the initially white suspension turned bright yellow during 80 minutes of vigorous shaking. 0.75 g. of Adams' platinum oxide catalyst was added and the mixture shaken with moist hydrogen at room temperature and atmospheric pressure; after almost three hours, approximately the theoretical amount of hydrogen had been absorbed and the rate of uptake had become negligible. The resulting grey slurry in a greenish solution

was heated to boiling of the steam bath and insoluble inorganic solids were removed by filtration and washed several times with benzene. On evaporation, the clear yellow filtrate left a light tan, crystalline residue which was filtered off, washed well with water, and air-dried, yield 26.6 g. of (IXf) (84.2% based on 42.5 g. of (VIf) as the monohydrobromide dihydrate), crude m.p. about 178°. Three recrystallizations of a small sample from acetonitrile-pyridine gave clusters of brilliant, colorless needles, m.p. 187.8-188.3° after some previous fusion from 184°.

Anal.[+] Calc'd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43.
Found: C, 79.40; H, 7.15; N, 8.45.

For conversion to the hydrochloride, 26.2 g. of crude (IXf) was dissolved in 400 cc. of boiling absolute ethanol and treated with 13.9 cc. (one equivalent) of 6 N hydrochloric acid, giving a pink solution which soon set to a rigid mass of tiny white needles; these were filtered off on a sintered-glass funnel, washed with ethanol and ether, and air-dried, weight 25.7 g. Recrystallized from ethanol-water, the salt formed sparse clusters of colorless bars melting at 247° with decomposition.

Anal. Calc'd for $C_{22}H_{25}ClN_2O$: C, 71.63; H, 6.83; N, 7.60.
Found: C, 71.28; H, 6.72; N, 7.63.

Summary

The synthesis of five Ainley-King-type 2-phenylquinolyl-4-α-piperidylcarbinols has been described.

[+]Microanalysis by Huffman Microanalytical Laboratories, Denver, Colorado.

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(8) Hershberg, Ind. and Eng. Chem., Anal. Ed., 8, 313 (1936).

(9) Doebner and Gieseke, Ann., 242, 296 (1887); Beilstein, "Handbuch der organischen Chemie", 4th Ed., 1935, supplementary vol. XX/XXII, page 520.

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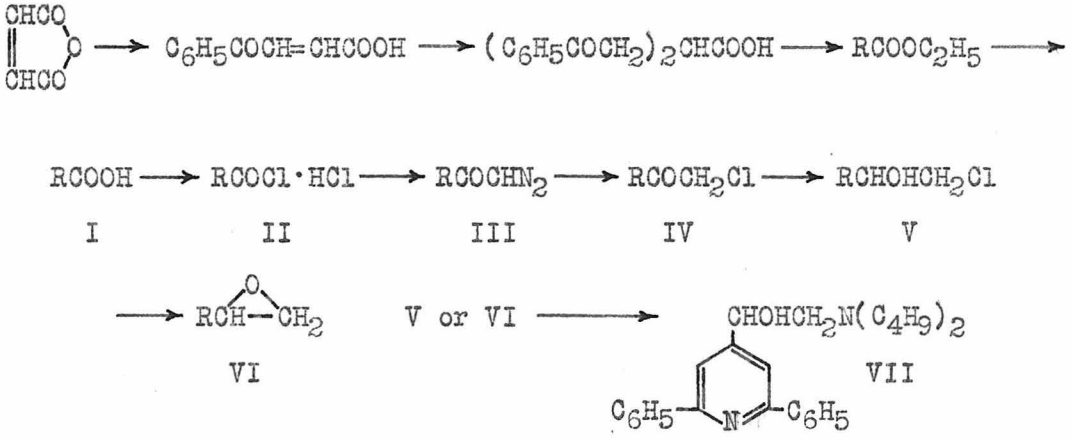
V. 2,6-DIPHENYLPYRIDYL-4-DI-n-BUTYLAMINOMETHYLCARBINOL.

2,6-DIPHENYLPYRIDYL-4-DI-n-BUTYLAMINOMETHYLCARBINOL[+]

Jacobs, Winstein, and collaborators (1) have developed a method of synthesizing various substituted naphthyl-aminomethylcarbinols starting with the corresponding naphthoic acids; we have extended the method to 2,6-diphenylisonicotinic acid (I).

The ethyl ester of the acid was prepared in good yield by an extension of the sym-triphenylpyridine synthesis of Wislicenus (2); refluxing diphenacylacetic acid with hydroxylamine hydrochloride in absolute ethanol gave the ester directly. With maleic anhydride as the starting material, the hydrochloride of the desired carbinolamine (VII) was obtained in a 25% overall yield following the steps outlined below, where R represents the 2,6-diphenylpyridyl-4 group:



The crude dry acid chloride hydrochloride (II) obtained from the acid (I) by the action of thionyl chloride was added to an ethereal solution of diazomethane and the crude crystalline diazoketone (III) obtained on

[+]The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

evaporation was treated at once with concentrated aqueous hydrochloric acid to give the α-chloroketone (IV). (IV) was then reduced by a short-period treatment with aluminum isopropylate to the chlorohydrin (V). (V) or the oxide (VI) derived from it by means of alcoholic sodium hydroxide gave the desired carbinolamine (VII) on reacting with di-n-butylamine.

When the chlorohydrin was heated with di-n-butylamine, a small amount of carbonylic byproduct was obtained which analyses showed was isomeric with the oxide (VI); in view of the similar conversion of phenylethylene oxide to phenylacetaldehyde (3), the compound is probably 2,6-diphenylpyridyl-4-acetaldehyde.

It was considered noteworthy that ethyl 2,6-diphenylisonicotinate and the supposed 2,6-diphenylpyridyl-4-acetaldehyde were both observed to crystallize from solutions in two distinct forms having the same melting point and giving no melting-point depression when mixed.

Experimental[+]

Diphenacylacetic Acid (4). In a five-liter flask were placed 111.9 g. (0.636 mole) of β-benzoylacrylic acid (prepared in 64% yield by the method of Gabriel and Colman (5)), 490 cc. (4.2 moles) of acetophenone, 168 cc. of 6 N sodium hydroxide, 2500 cc. of water, and enough ethanol (about 1400 cc.) to obtain a clear solution. The flask was stoppered and allowed to stand at room temperature for about three days; solvent was then distilled off in vacuo on the steam bath until the residue separated into two phases, the excess acetophenone extracted with isopropyl ether,

[+]All melting points are corrected. Microanalyses are by Dr. G. Oppenheimer and her staff.

and the aqueous phase acidified with acetic acid. The oily, colorless acid, which solidified on cooling with ice, was filtered off on a Buchner funnel, washed with water, and air-dried to constant weight; the yield (186.4 g.) was almost quantitative. This crude product melted at 128.5-130.5° and was sufficiently pure for the next step.

Ethyl 2,6-Diphenylisonicotinate. A solution of 186.4 g. (0.63 mole) of the above diphenacylacetic acid and 87.3 g. (1.26 moles) of hydroxylamine hydrochloride in 4 l. of absolute ethanol was refluxed for 22 hours. When the volume of the solution had been reduced to about one and one-half liters on the steam bath, the ester crystallized out as tiny white needles; after cooling, the product was filtered off, washed with cold ethanol and ether and air-dried, 127.7 g., m.p. 97.4-97.8°, not appreciably raised by recrystallization from ethanol. Working up the filtrate and washings raised the yield to 163.4 g. (85.5%). On standing, the slurry of white needles recrystallizing from ethanol deposited a second crystalline modification of the ester, large, well-formed rhombic plates. Hot alcoholic solutions of the ester deposited either form, depending on which form they were seeded with; both had the same melting point, which was not depressed by mixing the two.

Anal. Calc'd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62.

Found: C, 79.32; H, 5.66; N, 4.37.

2,6-Diphenylisonicotinic Acid (I) was obtained by hydrolyzing the ethyl ester. It was also obtained in 44% yield by heating diphenacylacetic acid in a sealed tube with alcoholic ammonia according to the method of Paal and Strasser (6), sparse clusters of colorless bars

from ethanol, m.p. 283.9-284.7° (Paal and Strasser (6) give m.p. 275°).

2,6-Diphenyl-4-chloroacetylpyridine (IV). Diazomethane (about 2.8 g. or 0.067 mole) was liberated into 100 cc. of ethyl ether by slowly adding 10.0 g. of N-nitrosomethylurea to 30 cc. of cold 40% potassium hydroxide (7); the bright yellow ethereal solution was separated from the aqueous phase and dried over potassium hydroxide pellets during the preparation of the acid chloride hydrochloride (II). A mixture of 4.58 g. (0.0167 mole) of recrystallized acid (I) and 8 cc. of purified thionyl chloride (8) was refluxed in an all-glass apparatus over a free flame; a clear solution was obtained after about five minutes; after refluxing twenty minutes more, the evolution of hydrogen chloride had become negligible, and the excess thionyl chloride was removed by aspirator, leaving a dry, apparently non-hygroscopic, buff powder (II); this was added with stirring and ice-cooling to the above diazomethane solution. The resulting clear yellow solution was allowed to stand at room temperature overnight, then freed of ether by applying an aspirator, leaving a yellow, somewhat oily solid weighing 5.36 g. This crude diazoketone (III) was taken up in 50 cc. of benzene, cooled in ice, and treated with 5 cc. of 12 N hydrochloric acid; after the vigorous gas evolution had ceased, the dark red aqueous sirup was cautiously basified by the addition of a solution of 5 g. of potassium carbonate in 100 cc. of water. Evaporation of the benzene extracts left a viscous orange oil which soon turned to a non-oily solid weighing 5.30 g. and melting at 114-117°. Two recrystallizations from isopropyl ether-benzene gave clusters of irregular, pale yellow-orange, micaceous plates, m.p. 122.7-123.0°.

Anal. Calc'd for $C_{19}H_{14}ClNO$: C, 74.15; H, 4.58; N, 4.55.

Found: C, 74.30; H, 4.64; N, 4.77.

α-(2,6-Diphenylpyridyl-4)-β-chloroethanol (V). In a 50-cc. reflux apparatus protected by a calcium chloride tube were placed 1.54 g. (0.005 mole) of recrystallized (IV), 5.0 g. (0.025 mole) of redistilled aluminum isopropylate, and 20 cc. of isopropanol distilled off sodium. After refluxing thirty minutes over a free flame, the hot solution was poured onto a mixture of about 50 cc. of crushed ice and 13 cc. of 6 N hydrochloric acid; the resulting gummy solid was extracted with 100 cc. of hot benzene, dried over potassium carbonate, and freed of solvent on the steam cone and aspirator, leaving a viscous golden-brown oil which deposited compact needle clusters on standing, crude m.p. 103-108°; recrystallization from isopropyl ether-benzene gave 1.24 g. (80%) of pale tan, diamond clusters, m.p. 135.0-135.6°. A small sample recrystallized once more gave compact colorless clusters of the same melting point.

Anal. Calc'd for $C_{19}H_{16}ClNO$: C, 73.66; H, 5.21; N, 4.52.

Found: C, 73.88; H, 5.09; N, 4.52.

In another experiment the acid chloride hydrochloride (II) from 11.00 g. (0.04 mole) of the acid (I) was reacted with the diazomethane from 24.0 g. of N-nitrosomethylurea; following the same procedure, 11.1 g. of crude (IV) was obtained and reduced directly without recrystallization; two recrystallizations of the crude product from benzene gave 6.39 g. (51.6%) of pure (V), m.p. 134.6-135.1°. A larger run on 0.10 mole of (I) gave 50.4% of pure (V).

2,6-Diphenylpyridyl-4-ethylene oxide (VI). Fifteen and three-tenths

grams (0.0493 mole) of recrystallized (V) was dissolved in 250 cc. of hot absolute ethanol, the solution rapidly cooled and treated with a cold solution of 2.12 g. (theory 2.0 g.) of sodium hydroxide pellets in 25 cc. of absolute ethanol, After standing at room temperature for thirteen minutes, the ethanol was removed by aspirator over a period of about two and one-half hours at 25-45°. The residual light brown solid was treated with 50 cc. of benzene and 25 cc. of water; the benzene extracts were washed with 15 and 10 cc. of water, the combined aqueous washings extracted with 15 and 10 cc. of benzene, and the benzene extracts dried over sodium sulfate. Removal of the benzene on the steam cone and aspirator and oil-pump left 13.41 g. (97.2%) of crystalline material, m.p. 89-91°. Two recrystallizations from ethanol gave clusters of light tan flakes, m.p. 92.9-93.4°.

Anal. Calc'd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.13.

Found: C, 83.67; H, 5.40; N, 5.36.

2,6-Diphenylpyridyl-4-di-n-butylaminomethylcarbinol (VII) Hydrochloride from (V). Five and seventy-three hundredths grams (0.0185 mole) of recrystallized (V) and 4.77 g. (0.0365 mole) of redistilled Sharples' di-n-butylamine were sealed in a Pyrex tube and heated at 100° for 17 hours. The resulting brown slurry was removed with 25 cc. of water and 15 cc. of benzene and treated with 3.1 cc. (one equivalent) of 6 N hydrochloric acid, whereupon the benzene phase solidified with clusters of small white needles; these were filtered off, washed with water and benzene and air-dried, leaving 6.03 g. (74.2%) of (VII) hydrochloride as a white solid, m.p. 202-203°, insoluble in water and

quite soluble in ethanol; recrystallizing from 80 cc. of 50% ethanol gave 5.26 g. of light cream needles. For analysis, a sample was recrystallized from aqueous ethanol, colorless, brilliant needles, m.p. 200.3–201.3° when heated slowly.

Anal. Calc'd for $C_{27}H_{35}ClN_2O$: C, 73.86; H, 8.04; N, 6.38.
Found: C, 73.97; H, 7.88; N, 6.49.

The free base obtained from the above hydrochloride was a viscous, colorless oil which could not be induced to crystallize.

Evaporation of the benzene portion of the filtrate and washings from the initial crop of (VII) hydrochloride above left 1.33 g. of a viscous light-brown oil which crystallized; a portion of it was recrystallized from isopropyl ether containing a few drops of ethanol, yielding peculiarly-shaped tan crystals like concoidal chips of glass, m.p. 111.1–111.3°. In a recrystallization from isopropanol, the compound was obtained as a mixture of two distinct forms—colorless flakes and clear, light yellow granules—which were easily separated mechanically; they had identical melting points, undepressed by admixture. Analysis indicated this compound to be isomeric with the oxide (VI).

Anal. Calc'd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.13.
Found: C, 83.59; H, 5.50; N, 5.25.

The oxime of this compound was prepared by the pyridine method of Shriner and Fuson (9), crude m.p. 165–167°, raised to 169.9–170.5° by one recrystallization from water–ethanol, sparse clusters of colorless, irregularly curved needles.

(VII) Hydrochloride from (VI). In a 200-cc. flask equipped with a

reflux condenser were placed 13.41 g. (0.0479 mole) of (VI), 6.21 g. (0.0482 mole) of di-n-butylamine, and 25 cc. of C.P. benzene. The resulting clear solution was refluxed over a small free flame until the temperature registered by a thermometer dipping into the boiling solution no longer dropped (11 hours). Solvent was then removed on the steam bath and aspirator, the residual clear orange-brown oil transferred to a 300-cc. conical with 100 cc. of warm ethanol, and 8.0 cc. (one equivalent) of 6 N hydrochloric acid added. Water was then added until cloudiness persisted (65 cc. required) and the compound crystallized out; it was filtered off, washed with 50% ethanol, benzene, and ether, then air-dried, giving 13.63 g. of (VII) hydrochloride; working up the mother liquors gave an additional 2.91 g. of the material, representing a combined crude yield of 78.3%.

Summary

The synthesis of 2,6-diphenylpyridyl-4-di-n-butylaminomethylcarbinol has been described.

References

(1) Jacobs, Winstein, and collaborators, unpublished.

(2) Wislicenus, Ann., 302, 191 (1898).

(3) Fourneau and Tiffeneau, Compt. rend., 140, 1596 (1905). See Beilstein, "Handbuch der organischen Chemie", fourth edition, 1925, Vol. VII, page 292.

(4) Bougault, Ann. chim., (8) 15, 502 (1908).

(5) Gabriel and Colman, Ber., 32, 397 (1899).

(6) Paal and Strasser, Ber., 20, 2756 (1887); Paal, Ber., 29, 798 (1896).

(7) See Fieser, "Experiments in Organic Chemistry", second edition, Part II, D. C. Heath and Company, New York City, 1941, page 378.

(8) See (7), page 381.

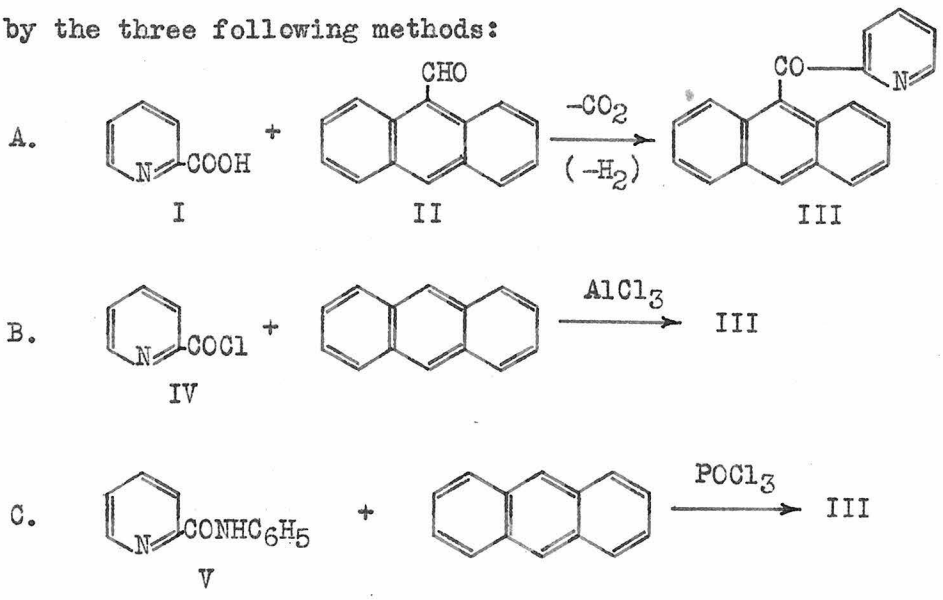
(9) Shriner and Fuson, "Systematic Identification of Organic Compounds", second edition, John Wiley and Sons, Inc., New York City, 1940, page 167.

VI. PREPARATION AND REDUCTION OF 9-PICOLINYLANTHRACENE.

Preliminary work on this problem was done by Dr. Bernard Nelson; some of his experiments are included.

PREPARATION AND REDUCTION OF 9-PICOLINYLANTHRACENE[+]

Interest in the basic carbinols which might be derived from it by reduction led us to investigate the synthesis of 9-picolinylanthracene (III) by the three following methods:



The Hammick reaction (1) (Method A), involving the thermal decarboxylation of picolinic acid (I) in the presence of aromatic aldehydes or ketones to yield α-pyridylcarbinols (sometimes oxidized in situ to the corresponding ketones), has been applied in these laboratories (2, 3) to a variety of aldehydes. Heating (I) with a 5:1 excess of the readily-available 9-anthraldehyde (II) (4) gave the desired ketone (III) in 38% yield (based on (I)). Although (III) gave no functional derivatives, its bright yellow color, weak basicity[++], and elementary analyses indi-

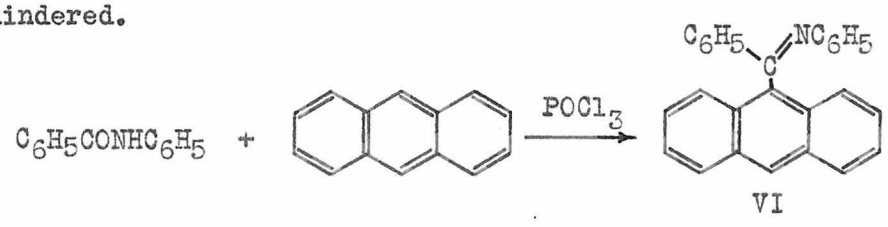
[+]The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

[++]In certain Hammick reactions giving mixtures of carbinols and ketones, Golding and Sargent (2) noted that the former were much more basic.

cated its correct formulation as ketonic.

The Friedel-Craft reaction (Method B) (in a single experiment) failed to give detectable amounts of (III) although Wolffenstein and Hartwich (5) have shown that picolinyl chloride (IV) reacts normally with other aromatic compounds, and anthracene is known to be attacked at a meso position, at least initially and under very mild conditions (6).

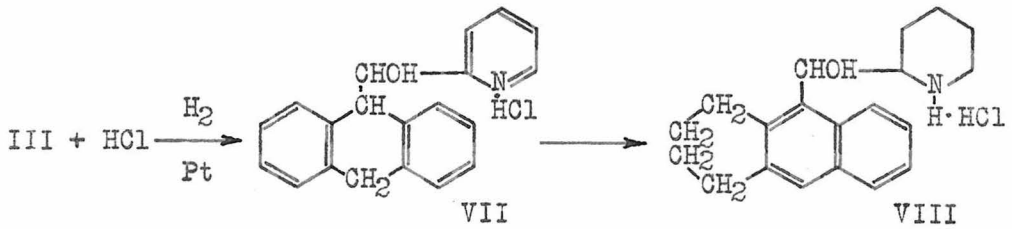
The reaction of various substituted formamides with aromatic compounds under the influence of certain inorganic chlorides to give aromatic aldehydes or ketones is a general one, examples ranging from formylation with formamide itself (7) to benzoylation with N-methylbenzanilide (8). By treating N-methylacetanilide with phosphorus oxychloride, Friedel (9) was apparently the first to carry out a reaction of this type, although the structure of his product was not formulated correctly until the work of Fischer, Müller, and Vilsmeier (10) showed it to be 2-methyl-4-chloroquinoline methochloride, derived from the initially-formed o-acetyl-N-methylacetanilide. Dimroth and Zoeppritz (11) first used the reaction for formylation; the preparation of (II) (4, 12) extended this modification of the reaction to the anthracene series. Benzoylation with benzanilide and phosphorus oxychloride was first described in an early patent (13); applying this method to anthracene, we were able to isolate what is apparently 9-benzoylanthraceneanil (VI), a type of intermediate often postulated (see (8)) and probably obtained here because hydrolysis is sterically hindered.



VI

The anomalous behavior of the anilide of o-nitrobenzoic acid in reactions of this type studied by Shah, Deshpande, and Chaubal (8) and the often-noticed similarity in the reactions of corresponding pyridine and o-nitrobenzene derivatives perhaps explain our failure to obtain (III) or its anil by Method C.

Shroeter (14) and Fries and Schilling (15) have shown that the catalytic hydrogenation of anthracene gives first 9,10-dihydroanthracene, then 1,2,3,4-tetrahydroanthracene and 1,2,3,4,5,6,7,8-octahydroanthracene; the hydrogenation of (III) in the presence of Adams' catalyst and hydrochloric acid apparently follows a similar course: interruption of the hydrogenation after between three and five moles had been taken up gave mixtures of 9,10-dihydroanthracyl-9-α-pyridylcarbinol hydrochloride (VII) and 1,2,3,4-tetrahydroanthracyl-9-α-piperidylcarbinol hydrochloride (VIII), which was also obtained by hydrogenation of pure (VII), about four mole-equivalents of hydrogen being absorbed in the reduction.



The assigned structure of (VII) is supported by elementary analyses of the hydrochloride, the free base, the benzoate, and the acetate; and the fact that heating it with an excess of acetic anhydride gives a monoacetate which is readily soluble in cold 6 N hydrochloric acid; yet its ultraviolet absorption spectrum has a series of maxima in the near-visible which is present in compounds containing the intact anthracene ring-

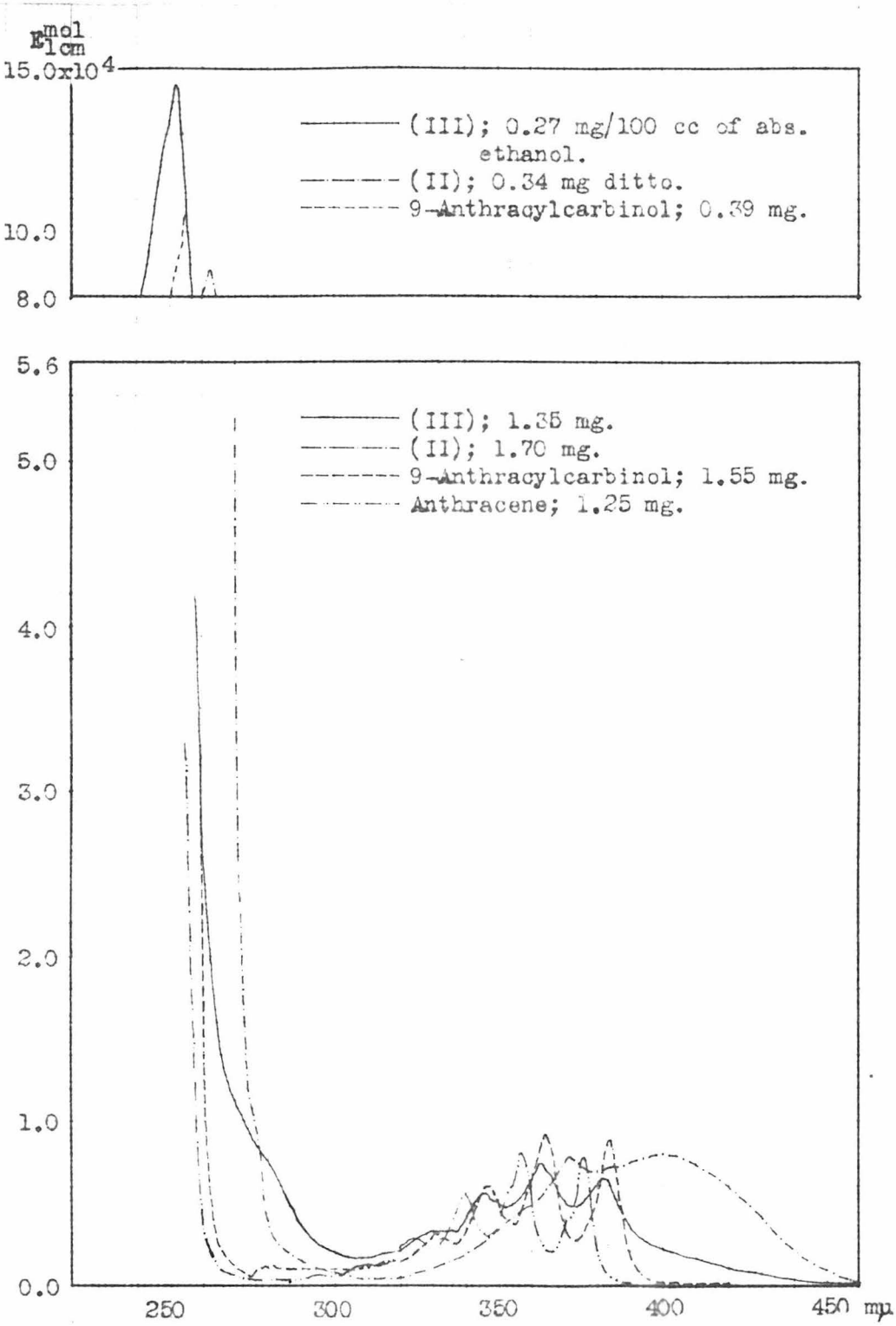


Fig. 1

Comparisons of the spectra of 9-anthraldehyde (II), 9-anthracylcarbinol, 9-picolinylanthracene (III), and anthracene.

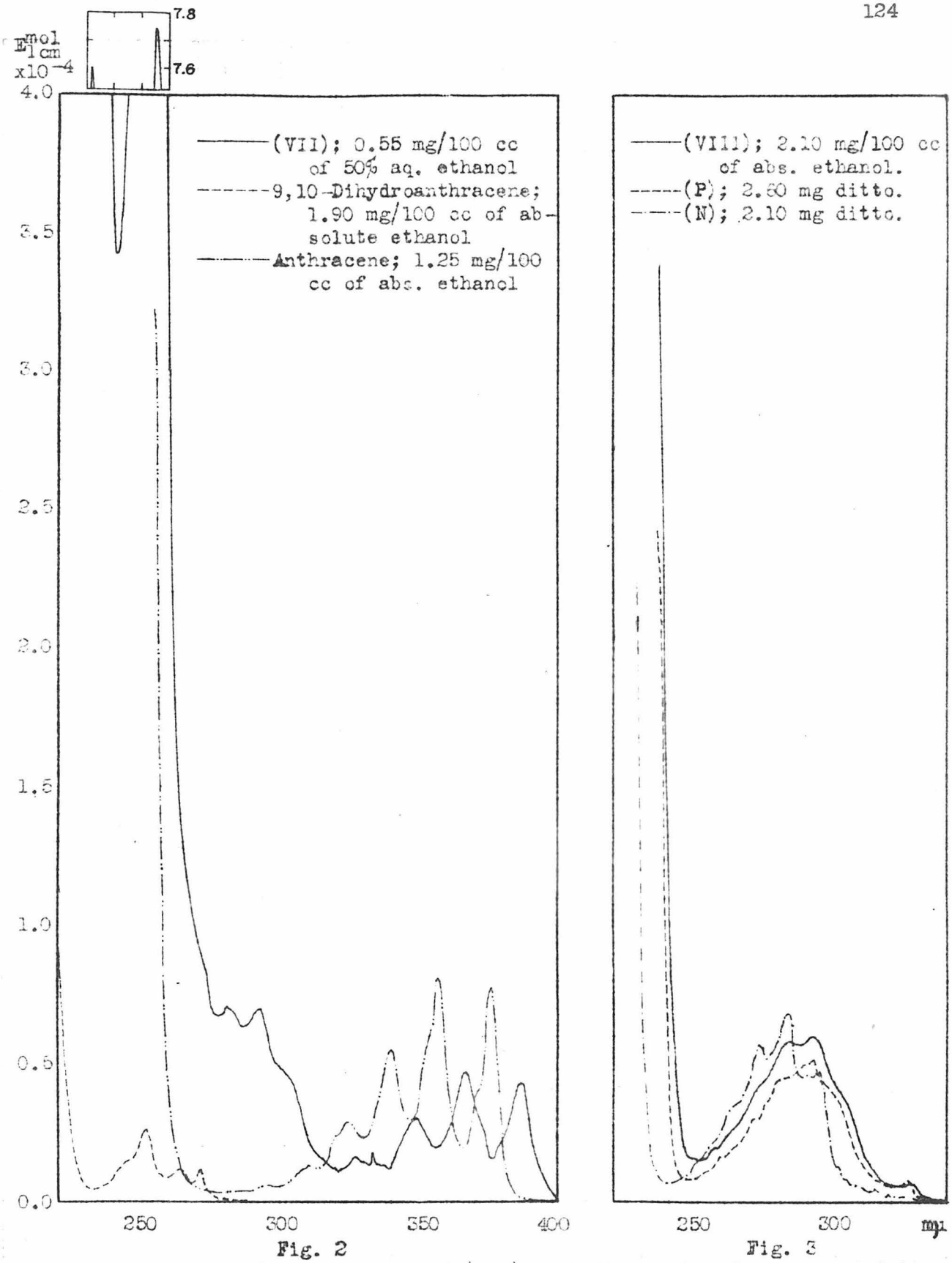


Fig. 2

Fig. 3

Comparison of the spectrum of (VII) with those of anthracene and 9,10-dihydroanthracene.

Comparison of the spectrum of (VIII) with those of the α-diastereoisomer of 1-naphthyl-α-piperidylcarbinol hydrobromide (N) and 1,2,3,4-tetrahydrophenanthryl-9-α-piperidylcarbinol hydrobromide (P).

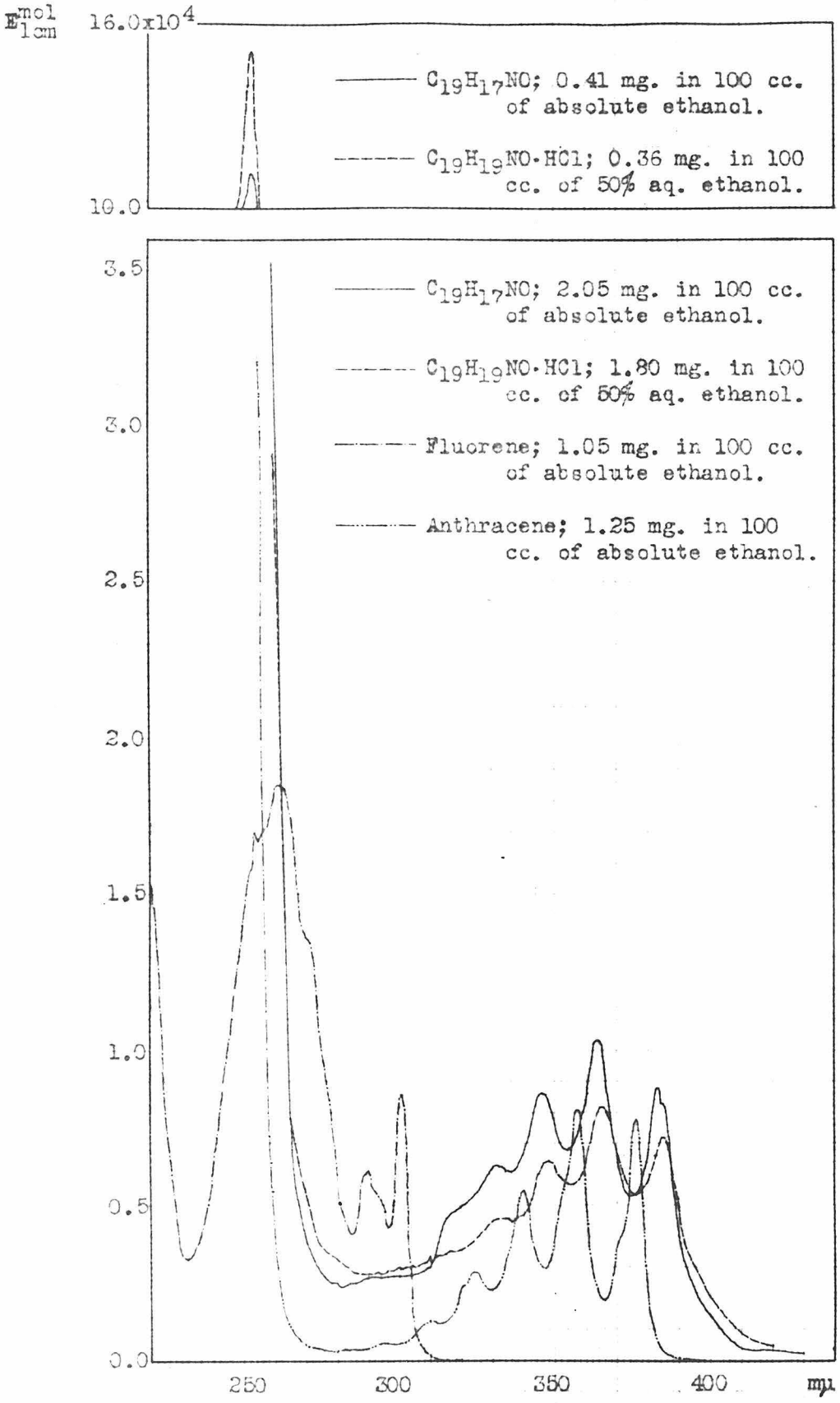


Figure 4

Comparison of the spectra of two of the anomalous C_{19} compounds with those of anthracene and fluorene.

system and absent in 9,10-dihydroanthracene (see Figure 2); the fact that both the free base and the acetate turned brown on standing, particularly at surfaces exposed to light, suggests that the anomalous spectrum of (VII) may be due to an oxidative removal of the 9,10 hydrogens in the ethanolic solution from which the spectrum was obtained.

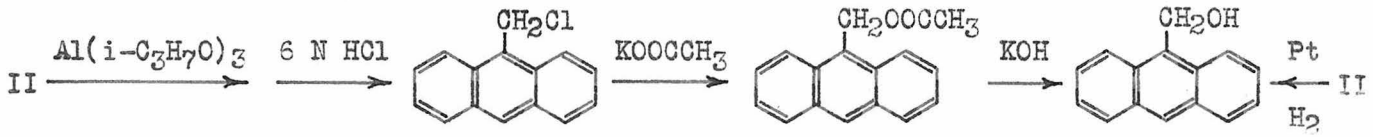
Elementary analyses of (VIII) and the free base and derivatives obtained from it are in accordance with the 1,2,3,4-tetrahydroanthracyl-9-α-piperidylcarbinol formulation, as are too the formation of a diacetate and the nature of the ultraviolet absorption spectrum, which lacks the anthracene near-visible peaks mentioned above and closely resembles those of the 1,2,3,4-tetrahydrophenanthryl-9- and 1-naphthyl-α-piperidylcarbinol hydrobromides prepared by Sargent, Golding, and Myers (3) (see Figure 3).

During the course of this work, a number of compounds were isolated having one less carbon atom than those of the anthracyl-pyridyl series; the possibility of explaining these anomalous substances as being derived from fluorene present in the anthracene used as a starting material for (II) was negated by the observation that fluorene gives no aldehydic product when treated under conditions used to prepare (II). Also, the ultraviolet absorption spectra of some of these anomalous compounds showed a series of peaks in the near-visible characteristic of anthracene and absent in the spectrum of fluorene (see Figure 4; compare (16)).

Some uncertainty exists in the literature over the characterization of (II) oxime. Hinkel, Ayling, and Beynon (17) describe the oxime as pale yellow laminae from ethanol, m.p. 186-187°. Fieser and Hartwell (4)

obtained an oxime melting at 165–165.5°, long yellow needles from ethanol. Our product (II) gave two isomeric oximes, one forming clusters of colorless, flat needles from benzene–pyridine, m.p. 217° with decomposition; the other crystallized from ethanol in sparse clusters of irregular yellow bars melting at 161.0–161.5°.

The product of the Meerwein–Ponndorf reduction of (II) was converted by contact with 6 N hydrochloric acid into 9–chloromethylanthracene, which could be converted over the acetate into the carbinol, identical with that obtained by catalytic reduction of the aldehyde (II).



Experimental[+]

9–Anthraldehyde (II) was prepared by the method used by Fieser and Hartwell (4), fine, bright–yellow needles from isopropyl ether–ethanol, m.p. 105.4–105.7° in agreement with literature values (4, 17).

The ultraviolet absorption spectrum of (II) in ethanol showed maxima at 234, 262, 372, and 400 mμ (see Figure 1).

Preparation of the oximes by the pyridine method described by Shriner and Fuson (18) gave a crude product melting from 157° to 197°. Recrystallization of this material from benzene–pyridine gave the α–form, clusters of colorless, flat needles melting to a dark brown liquid at

[+]All melting points are corrected. We are indebted to Dr. G. Oppenheimer and her staff for microanalyses, and to Mrs. M. Howton, Miss P. Baskett, and Mrs. B. Dandliker for spectrophotometric data, which were obtained on the Beckman machine.

217° on slow heating; this melting point varied somewhat with the rate and range of heating. From the mother liquors, the β-form was isolated; it crystallized from ethanol in sparse clusters of yellow, light-refracting, irregular bars, m.p. 161.0-161.5° to a cloudy melt which became clear at 163.0°.

Anal.	Calc'd for $C_{15}H_{11}NO$:	C, 81.42;	H, 5.01;	N, 6.33.
	Found: (α-form)	C, 81.24;	H, 4.97;	N, 6.37.
	(β-form)	C, 81.58;	H, 5.26;	N, 6.43.

Attempted Formylation of Fluorene. One-tenth mole (16.6 g.) of fluorene was treated with N-methyl-formanilide and phosphorus oxychloride, following the directions used in the preparation of (II) closely; 19.7 g. of steam-involatile, water-insoluble material was obtained. Recrystallization of a portion of this product from ethanol showed it to be principally starting material; 5.0 g. dissolved in 50 cc. of benzene and shaken with 25 cc. of half-saturated aqueous sodium bisulfite gave an aqueous solution from which, after acidification and removal of sulfur dioxide with a stream of nitrogen, only a trace of yellow-brown oil was extractable with benzene.

The ultraviolet absorption spectrum of fluorene (Eastman Practical, twice recrystallized from 60-70° petroleum ether, m.p. 113.8-114.1°) in ethanol showed maxima at 261, 290, and 301 mμ and the solution was practically transparent above about 310 mμ, in good agreement with the results of Askew (16) (see Figure 4).

Reduction of (II). 9-Anthracylcarbinol. Five grams of (II) was dissolved in 150 cc. of ethanol, 2 cc. of 12 N hydrochloric acid

and 0.1 g. of Adams' platinum oxide were added, and the mixture was shaken with hydrogen; after about 18 hours, a little more than one mole of hydrogen had been taken up and the rate of absorption was negligible. After neutralizing the solution with sodium hydroxide, it was evaporated under reduced pressure and the residue extracted with about 75 cc. of isopropyl ether. These extracts were evaporated to about one-third of their volume and allowed to cool, whereupon fine orange needles of the carbinol separated out, m.p. 157-163°; recrystallized from absolute ethanol, it formed light-yellow clusters of irregular, jagged, micaceous sheets, m.p. 164.1-164.5°.

Anal. Calc'd for $C_{15}H_{12}O$: C, 86.50; H, 5.81.

Found: C, 86.20; H, 6.00.

In alcohol, the carbinol showed spectrum maxima at 255, 281, 316-318, 331, 346, 364, and 384 mμ (see Figure 1).

Another reduction of 2.06 g. (0.01 mole) of (II) in 50 cc. of ethanol with 0.25 g. of platinum oxide and no acid absorbed 1.45 moles of hydrogen before the uptake-rate became negligibly slow (5 1/2 hours). The crude product was a mixture which was fractionally recrystallized to give 0.40 g. of the carbinol and smaller amounts of a high-melting solid, sparse clusters of long, yellow needles from pyridine, m.p. 284-285°. Analysis indicated this product to be isomeric with the known anthracene-9-carboxylic acid (19), but its melting point was much higher and it was quite insoluble in hot 4 N sodium hydroxide.

Anal. Calc'd for $C_{15}H_{10}O_2$: C, 81.06; H, 4.54.

Found: C, 81.17; H, 4.33.

Five grams (0.0242 mole) of (II), 17.5 g. (0.084 mole) of aluminum isopropoxide, and 275 cc. of isopropanol (freshly distilled from sodium) were refluxed until no test for acetone was discernable in the distillate collected off an efficient fractionating column, then thirty minutes longer. After removing the alcohol under reduced pressure, the residue was treated with 200 cc. of 6 N hydrochloric acid and the resulting yellow solid extracted with 150 cc. of benzene. The product left by evaporation of the benzene after two recrystallizations from isopropyl ether and one from ethanol-benzene formed clusters of pale yellow or tan flakey needles, m.p. 138.6-138.8°. This substance gave a qualitative test for halogen and analyzed for 9-chloromethylanthracene, formed by the action of the hydrochloric acid on the carbinol.

Anal. Calc'd for $C_{15}H_{11}Cl$: C, 79.47; H, 4.85.

Found: C, 79.94; H, 4.90.

The spectrum of this chloride is very similar to that of the parent carbinol (see Figure 1) with maxima at 255, 278, 317, 331, 347, 364, and 384 mμ.

Following a procedure used on 7-chloromethyltetraphene (20), the 9-chloromethylanthracene was converted to 9-acetoxymethylanthracene, clusters of irregular, micaceous swords from ethanol, m.p. 111.7-112.2°; this acetate was then hydrolyzed to the carbinol, identical with that obtained above in the catalytic reduction.

9-Picolinylanthracene (III) (Method A). A mixture of 131 g. (0.636 mole) of 9-anthraldehyde and 15.7 g. (0.127 mole) of picolinic acid was heated in a 1-l. round-bottomed flask immersed in a wax bath at

156-166° for 30 hours, when the carbon dioxide evolution had ceased. On cooling, the reaction mixture solidified. It was dissolved in 400 cc. of hot benzene and extracted with one 50- and two 25-cc. portions of 6 N hydrochloric acid. These combined dark red extracts were diluted with about 200 cc. of water, when the color changed to yellow and a yellow solid separated out; it was filtered off, washed with water, and air-dried, yield 11.7 g.; further extractions of the benzene solution gave an additional 2.1 g. of the substance, representing a combined yield of 38.2% based on picolinic acid, or 24.9% on unrecovered (II). Red needles—apparently the hydrochloride of the ketone (III)—occasionally separated from the hydrochloric acid extracts, but could be redissolved easily by warming. Excess (II) recovered from the benzene phase was recrystallized from isopropyl ether-ethanol and weighed 90.9 g.

An alternate method was used on a run of 360 g. of the aldehyde and 75 g. of picolinic acid (ratio 2.88 to 1). The reaction mixture was dissolved in about 800 cc. of chloroform, diluted with 7 l. of ethyl ether, and saturated with anhydrous hydrogen chloride; the precipitated red salt was filtered off and decomposed with water and the free base (III) recrystallized from chloroform-isopropyl ether, yield 35 g. (20.3%) of dark yellow needles, m.p. 210°. A smaller run using the same aldehyde-acid ratio and the first method of isolation gave 20.8% of the desired product. Heating for periods longer than 30 hours seemed to be detrimental to the yield.

For analysis, a sample of (III) was recrystallized from acetonitrile-pyridine, long, shiny, bright yellow needles, m.p. 210.3-210.7°.

Anal. Calc'd for $C_{20}H_{15}NO$: C, 84.21; H, 5.26; N, 4.91.

for $C_{20}H_{13}NO$: C, 84.80; H, 4.59; N, 4.94.

Found: C, 84.62; H, 4.34; N, 4.83.

The absorption spectrum of (III) in ethanol showed maxima at 252, 278, 314, 329-331, 346, 363, and 382 mμ (see Figure 1).

The red, supposed hydrochloride of (III) rapidly turned yellow on drying and so could not be analyzed; it was quite soluble in chloroform, but insoluble in benzene or ether. (III) gave no derivatives using standard procedures for preparing oximes, benzoates, or acetates; refluxing 0.001 mole of (III) with 0.002 mole of freshly sublimed maleic anhydride in 10 cc. of benzene for 30 hours (21) gave 0.23 g. of starting material (III) and 0.10 g. of a tan solid, m.p. 239-240°; recrystallization from benzene pyridine gave colorless granules, m.p. 241°. Analysis of the substance indicated that a molecule of oxygen had added to (III), probably across the meso positions (22).

Anal. Calc'd for $C_{20}H_{13}NO_3$: C, 76.18; H, 4.15; N, 4.44.

Found: C, 76.28; H, 4.22; N, 4.43.

C, 76.01; H, 4.24; N, 4.21.

In a preparation of (III) by the first method described above, besides 9.9 g. of the desired product, basification of the aqueous filtrate with sodium hydroxide yielded 0.34 g. of a product which, after two recrystallizations from acetonitrile-pyridine, formed long, thin, colorless rectangular bars, m.p. 219.2-219.8°. The analysis indicated this to be a C_{19} compound.

Anal. Calc'd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.13.

Found: C, 83.21; H, 6.01; N, 5.18.

Attempted Preparation of (III) by the Friedel-Craft Reaction (Method B). To 6.15 g. (0.05 mole) of picolinic acid (recrystallized from ethanol) in a 200 cc. three-necked flask equipped with a reflux condenser protected by a calcium-chloride tube was added 15 cc. of purified thionyl chloride (23); refluxed over a small free flame until gases ceased being evolved (one-half hour), the mixture turned from a blue-green mush to a clear, wine-colored solution. Removal of the excess thionyl chloride by aspirator left a mat of long, flat needles (crude IV hydrochloride). After attaching a sleeve-sealed Hershberg stirrer, 8.9 g. (0.05 mole) of anthracene and 50 cc. of nitrobenzene were added to the crude acid chloride hydrochloride and the stirred mixture was cooled in an ice-alcohol bath during the slow addition of 6.7 g. (0.05 mole) of Braun "resublimed" aluminum chloride. The resulting brown paste gave off no hydrogen chloride while stirring for three hours at room temperature; a little was evolved on heating at about 60° overnight. 50 cc. of 6 N hydrochloric acid was then added to the mixture, insoluble solids filtered off, and the filtrate separated into a dark-brown nitrobenzene phase and a pea-green aqueous phase. The latter precipitated nothing on dilution with water; basification with 4 N sodium hydroxide gave a flocculent precipitate which redissolved on further addition of the base.

Reaction of Anthracene with Benzanilide. A mixture of 19.7 g. (0.1 mole) of benzanilide, 11.5 g. (0.136 mole) of phosphorus oxychloride, and 50 cc. of Eastman Practical (95%) o-dichlorobenzene was made up in a 1-l. three-necked flask without any noticeable heat-effect; the flask was e-

quipped with a sleeve-sealed Hershberg stirrer, a reflux condenser protected with a glass-wool plug, and a thermometer dipping into the reaction mixture. After adding 17.8 g. (0.1 mole) of anthracene, a wax bath was used to heat the stirred mixture to 168° during 15 minutes; the mixture turned dark red, frothed, and evolved hydrogen chloride. The stirring was continued as the bath was allowed to cool to about 100° during two hours; the bath was then dropped and when the reaction mixture had cooled to 40°, it was treated with 13 cc. of 12 N hydrochloric acid diluted to 100 cc., causing the temperature to rise to about 75° and a solid to separate out. Over a period of two hours, the dichlorobenzene was steam-distilled out, leaving 33.3 g. of light-brown, varicolored, water-insoluble solid, m.p. 135-190°. Exactly one gram of this solid was extracted with 12 cc. of boiling ethyl acetate, the extract concentrated to about 5 cc. and allowed to crystallize, yielding a mixture, separated mechanically into 0.0364 g. of anthracene, and 0.2672 g. (representing 24.9% yield) of massive yellow rhombs, m.p. 180-183° raised to 184.2-184.5° by one recrystallization from ethyl acetate. This solid analyzed as the anil of 9-benzoylanthracene (VI).

Anal. Calc'd for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92.

Found: C, 90.79; H, 5.36; N, 4.19.

Picolinanilide (V). In a 200-cc. ground-glass-necked flask with a small side-arm, 8.0 g. (0.05 mole) of picolinic acid hydrochloride was refluxed with 50 cc. of thionyl chloride (Eastman White Label) until a clear amber solution was obtained (2.25 hours were required). Excess thionyl chloride was then removed by aspirator (line and capillary through the small side arm of the flask protected by calcium-

chloride tubes) heating toward the end with a small sooty flame; 50 cc. of benzene (dried over sodium) was added and distilled off in the same way. Fifteen milliliters (slightly more than 0.15 mole) of redistilled aniline was cautiously added with an additional 50 cc. of benzene to the residual amber sirupy (IV) hydrochloride; a copious precipitate of tan solid separated and, after refluxing a few minutes, this was filtered off and washed with 50 cc. of warm benzene. Removal of benzene from the filtrate left a red-brown crystal-mush from which the oil was washed with 60-70° petroleum ether containing a little absolute ethanol; the residual cream-colored solid (V) weighed 2.38 g. and melted at 75.5-76.2°. The filtrate and washings freed of solvent, dissolved in 10 cc. of absolute ethanol, seeded, and let stand overnight at 0° gave a second crop of (V) as light orange-brown needle-clusters, m.p. 74.7-75.6° (Engler (24) gives m.p. 76°). These two crops represent a yield of 60% from (I) hydrochloride. In Engler's method (heating equivalent amounts of (I) and aniline together—yield 50%) and a slight modification using toluene to remove the water formed, some difficulty was experienced separating the product (V) from unreacted picolinic acid (I).

Reaction of (V) with Anthracene (Method C). In an experiment starting with 9.9 g. (0.05 mole) of (V) and following the procedure used above to obtain (VI), a black-brown tarry solid and a deep red aqueous solution were left after the steam distillation. Dilution of the aqueous phase resulted in no change of color or precipitation of solid (see behavior of acid solutions of (III) described above); basification with 4 N sodium hydroxide gave a small amount of violet,

amorphous solid, very soluble in methanol; benzene extracts of the aqueous filtrate from this solid were purple and changed to orange-yellow on standing. The black-brown, tarry solid (see above) was extracted with 50 cc. of boiling 6 N hydrochloric acid; dilution of a portion of the resulting red extract gave a small amount of light brown amorphous solid, a solution of which in acetonitrile gave no growth on seeding with (III). Another experiment consisted of refluxing a mixture of 2.38 g. (0.012 mole) of (V), 2.8 g. (0.018 mole) of phosphorus oxychloride, and 1.07 g. (0.006 mole) of anthracene in 6 cc. of o-dichlorobenzene (95%) for two hours; on cooling, the resulting red liquid solidified; this solid was treated with a solution of 7.8 g. of sodium acetate in 16 cc. of water and allowed to stand overnight. After decanting the aqueous phase, the residual tarry solid was extracted with 50 cc. of boiling o-dichlorobenzene; evaporation of the resulting deep red-brown extract left an oily solid consisting principally of anthracene. Extraction of the o-dichlorobenzene-insoluble tar with 25 cc. of boiling 12 N hydrochloric acid gave a red solution which behaved like that of the other experiment.

9,10-Dihydroanthracyl-9-α-pyridylcarbinol Hydrochloride (VII). Thirty-five grams (0.122 mole) of (III), 2.5 l. of absolute ethanol, 12 cc. of 12 N hydrochloric acid, and 0.5 g. of Adams' platinum oxide were placed in a 5 l. round-bottomed flask and hydrogenated with shaking at one atmosphere pressure for 66 hours, when the absorption had become very slow, and 3 moles of hydrogen per mole of (III) had been taken up. After filtering off the platinum, the alcohol was removed under reduced

pressure and the residue diluted with about 100 cc. of butanone, whereupon 17 g. of a white solid (A) melting at 225-227° separated out. Working up the filtrate gave 3 g. of a second solid (B) melting at 265-268° with decomposition. Fractional recrystallization of (A) from ethanol-water gave 8.71 g. of (VII), 2.35 g. of material corresponding to (B), and 1.40 g. of material melting at 236° with decomposition, which was probably (VIII) (see below).

A similar reduction of 5.85 g. (0.0205 mole) of (III) took up 2555 cc. of moist hydrogen (theory 2595 for five mole-equivalents) before being stopped; working up in the same way gave 1.5 g. of crude (VII), m.p. 227-228° decomp. and 1.3 g. of crude (VIII), m.p. 168-172° decomp., raised to 240-241° by dissolving in ethanol and diluting with ether (mixed m.p. with (VIII) showed no depression).

(VII) crystallized from ethanol-water in irregular clusters of colorless, rhombic plates, m.p. 224-225° with decomposition.

Anal. Calc'd for $C_{20}H_{18}ClNO$: C, 74.18; H, 5.60; N, 4.33.
Found: C, 73.97; H, 5.87; N, 4.49.

An alcoholic solution of this hydrochloride showed ultraviolet absorption maxima at 232, 255, 281, 292, 327, 349, 366, and 386 mμ (see Figure 2).

Liberation of the free base from (VII) into chloroform by treating an aqueous-ethanol solution of the hydrochloride with 4 N sodium hydroxide, followed by two recrystallizations from isopropyl ether-ethanol, gave compact puffs of fine white needles, m.p. 104-105°, which turned rusty-brown on standing for about one year, particularly at surfaces exposed to light.

Anal. Calc'd for $C_{20}H_{17}NO$: C, 83.56; H, 5.96; N, 4.87.

Found: C, 83.28; H, 5.97; N, 4.65.

Formed from (VII) by heating with pyridine and an excess of acetic anhydride, the acetate of the free base was obtained, crude m.p. 176–178°, raised to 180.1–180.7° by two recrystallizations from acetonitrile-pyridine, dense rosettes of colorless, rectangular plates. This derivative was readily soluble in cold 6 N hydrochloric acid; on long standing, it turned brown on surfaces exposed to light.

Anal. Calc'd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25.

Found: C, 80.00; H, 6.08; N, 4.17.

Two moles of benzoyl chloride heated with one of (VII) in pyridine gave the benzoate of the free base, well-formed, colorless, stubby prisms in sparse clusters from ethanol-pyridine, m.p. 226–247° with decomposition.

Anal. Calc'd for $C_{27}H_{21}NO_2$: C, 82.84; H, 5.41; N, 3.58.

Found: C, 83.06; H, 5.67; N, 3.63.

Fraction (B) (see above) recrystallized from ethanol-water in a mass of interlocking, colorless needles, m.p. 266–267° with decomposition, varying with the rate and period of heating; on standing exposed to light, this salt slowly turned to a red-brown color on the surface.

Anal. Calc'd for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.42; N, 4.46.

Found: C, 72.01; H, 6.69; N, 4.34.

The ultraviolet absorption spectrum of an aqueous-ethanol solution of this hydrochloride showed maxima at 253, 333–334, 348, 365, and 385 mμ. (see Figure 4).

The free base was liberated from an aqueous-ethanol solution of recrystallized (B) by treatment with 4 N sodium hydroxide; recrystallized from acetonitrile, it formed massive clusters of yellow bars, which slowly developed a red-brown coating on exposure to light and air, m.p. 144.7-145.6° with some previous fusion.

Anal. Calc'd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05.
Found: C, 82.18; H, 6.42; N, 5.12.

An acetate was prepared by boiling a pyridine solution of this free base with an excess of acetic anhydride; the derivative formed massive clusters of large colorless parallelepipeds from acetonitrile-pyridine, m.p. 228.6-229.4°; its analysis showed it to be a monoacetate.

Anal. Calc'd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39.
Found: C, 79.49; H, 6.41; N, 4.32.

Small amounts of a higher-melting substance were isolated along with this free base from (B), melting from 174 to 190°, depending upon the rate and period of heating. A sample recrystallized from acetonitrile, forming large, well-formed, highly-refracting, yellow prisms and melting at 174-175° was analyzed.

Anal. Calc'd for $C_{19}H_{17}NO$: C, 82.88; H, 6.23; N, 5.09.
Found: C, 82.58; H, 6.14; N, 5.08.

This material gave no new product when heated with pyridine and acetic anhydride; its ultraviolet spectrum in ethanol showed maxima at 253, 331, 346, 363-364, and 383-384 mμ (see Figure 4).

9,10-Dihydroanthracene, prepared according to Miller and Bachmann (25), m.p. 106.7-108.2° after two recrystallizations from 60-70° petro-

leum ether, formed clusters of very thin, colorless slats with bluntly pointed ends. Its absorption spectrum (in ethanol) showed maxima at 252, 264, and 271 mμ with essentially no absorption above 280 mμ (see Figure 2).

1,2,3,4-Tetrahydroanthracyl-9-α-piperidylcarbinol Hydrochloride (VIII). A mixture of 3.24 g. (0.01 mole) of recrystallized (VII), 50 cc. of redistilled methanol, and 0.15 g. of platinum oxide was shaken with hydrogen for 53 hours, when the hydrogen uptake had become negligible, and between 0.035 and 0.04 moles of hydrogen had been absorbed. After standing overnight, the clear, colorless solution was pipetted and centrifuged from the catalyst and freed of solvent on the steam bath. The residual glass was dissolved in 10 cc. of absolute ethanol, whereupon the product crystallized out in a solid mass of white needles; it crystallized slowly from absolute ethanol in clusters of colorless, light-refracting bars, m.p. 243-244° with decomposition.

Anal. Calc'd for $C_{20}H_{26}ClNO$: C, 72.38; H, 7.90; N, 4.22.
Found: C, 72.29; H, 7.95; N, 4.28.

A solution of (VIII) in ethanol showed ultraviolet absorption maxima at 232-233, 283, 292, and 327 mμ and was practically transparent above 330 mμ (see Figure 3).

The free base, obtained from (VIII) in the usual way, formed sparse clusters of brilliant, colorless bars from acetonitrile-pyridine, m.p. 163.0-163.3°.

Anal. Calc'd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74.
Found: C, 81.10; H, 8.54; N, 4.76.

Heating (VIII) in pyridine with an excess of acetic anhydride gave

a diacetate, colorless octagonal plates or massive granules from isopropyl ether–ethanol, showing a marked purple fluorescence in diffuse sunlight, m.p. 146.2–146.9°.

Anal. Calc'd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69.
Found: C, 76.18; H, 7.52; N, 3.73.

A mixture of 0.215 g. of the recrystallized free base from (VIII) and 0.069 g. of benzaldehyde in 0.5 cc. of pyridine was heated overnight in a steam jet; the pyridine was then partially removed in an air stream. The residual, viscous, light-brown syrup was dissolved in a little benzene–ligroin and allowed to stand and evaporate spontaneously overnight, whereupon two bursts of fine colorless needles separated. Recrystallization of this material from benzene gave tiny white needle clusters, m.p. 189° with decomposition, analyzing as N-phenylhydroxymethyl-1,2,3,4-tetrahydroanthracyl-9-α-piperidylcarbinol.

Anal. Calc'd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78.
Found: C, 80.31; H, 7.94.

Summary

9-Picolinylanthracene has been prepared by the Hammick reaction; its catalytic hydrogenation has been shown to follow a course reported in similar reductions of anthracene itself.

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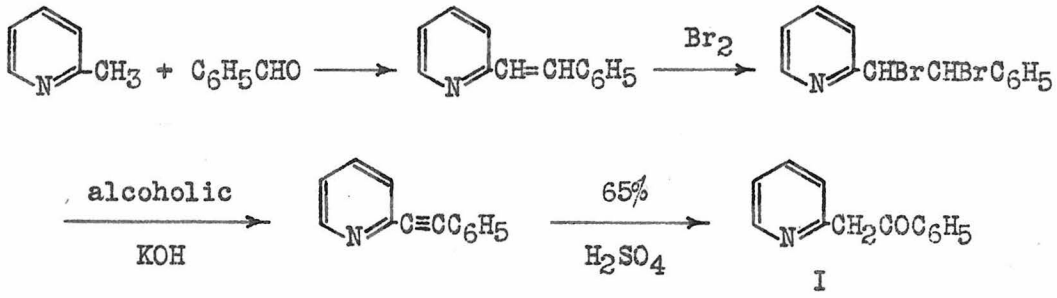
VII. PREPARATION AND REDUCTION OF α-PHENACYLPYRIDINE.

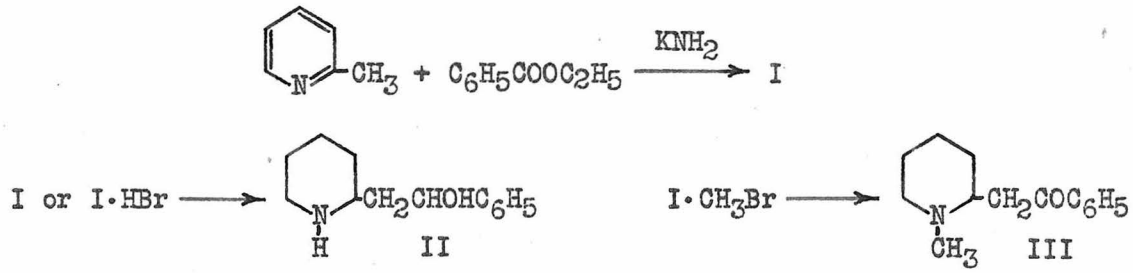
Experimental work on the preparation of α-phenacylpyridine and its hydrogenation over Raney-nickel was done by Dr. D. R. V. Golding.

PREPARATION AND REDUCTION OF α-PHENACYLPYRIDINE[+]

α-Phenacylpyridine (I) was apparently first prepared by Ladenburg and Kroener (1) by a method verified and developed by Scheuing and Winterhalder (2):



Recent exploitation of the reactions of picolyl-metal derivatives resulted in the synthesis of (I) by Bergmann and Rosenthal (3) from α-picolyl-lithium and benzoyl chloride, and by Tchitchibabin (4) through the action of sodamide on mixtures of α-picoline with benzoic esters or benzonitrile. The simplicity of the last procedure led us to investigate it and to evolve the method described in this paper (compare (5)): α-picoline and ethyl benzoate added in that order to a solution of potassium amide in liquid ammonia gave a 38% yield of (I), separated as the hydrobromide from the benzamide simultaneously formed.



[+]The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

Hydrogenation of the hydrobromide of (I) over Adams' catalyst at atmospheric pressure or of the free base over Raney-nickel at 140 atmospheres gave in each case mixtures of two diastereoisomeric β-(2-piperidyl)-α-phenylethanols (II) melting at 112.5° and 98.5°; the carbinol described by Scheuing and Winterhalder (2) (m.p. 85°) was apparently a mixture of the two isomers.

During the reduction of the methbromide of (I) over Adams' catalyst at atmospheric pressure, three mole-equivalents of hydrogen were rapidly absorbed; the rate then fell off and more than four moles were taken up before it became negligible. Conversion of the crude reduction product to its picrate showed it to be a mixture of 1-methyl-2-phenacylpiperidine (III) and a second basic substance the analyses of whose derivatives indicated that the phenyl group had been reduced. Termination of the hydrogenation at three mole-equivalents gave excellent yields of (III)[+].

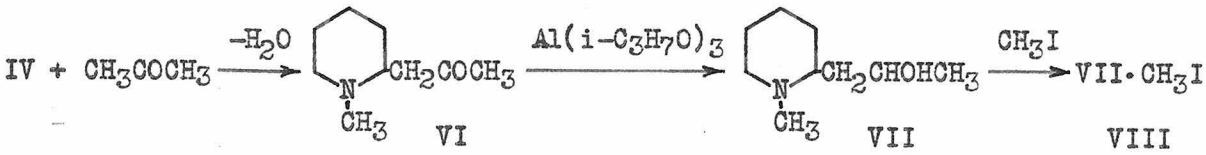
An attempted Meerwein-Ponndorf reduction of (III) gave a mixture of products. One of these was non-basic and was identified as methylphenylcarbinol (V), apparently derived from acetophenone, which could arise as a result of a reverse-Mannich reaction upon the β-aminoketone (III):

$$\text{III} \longrightarrow \underset{\text{IV}}{CH_3NH(CH_2)_4CHO} + CH_3COC_6H_5 \xrightarrow{Al(i\text{-}C_3H_7O)_3} \underset{\text{V}}{CH_3CHOHC_6H_5} + CH_3COCH_3$$

From the basic products of this reduction, a methiodide was prepared (m.p.

[+]Wieland and Ishimasa (6) isolated a minor Lobelia alkaloid for which they suggested the structure N-methyl-(II), or dihydro-(III); they oxidized this carbinol to the corresponding ketone, whose hydrochloride monohydrate melted at 109°; whether either of these compounds is optically active was not revealed by them. Our racemic ketone (III) gave an anhydrous hydrochloride, m.p. 172-173°, dec.

175° after some previous fusion) which gave analytical figures compatible with those calculated for the compound (VIII)[+], which could have been derived from the postulated intermediate (IV) in the following way:



Experimental[++]

α-Phenacylpyridine (I) Hydrobromide. Sixty-three grams (1.6 gram-atoms) of potassium was converted to potassium amide in about one liter of liquid ammonia, using a ferric chloride catalyst. 80 g. (0.86 mole) of α-picoline was added with stirring during the course of six minutes, giving a deep-red solution. 220 g. (1.46 moles) of ethyl benzoate was then added over a period of eight minutes, yielding a yellowish-brick-colored suspension which, during 20 minutes' stirring, lightened in color to lemon-yellow. 500 cc. of ether was then added and the mixture stirred for six hours, additional ether being added when it became too thick to stir; the mixture warmed to room temperature within one hour after the addition of the ether. Upon addition of a solution of 85 g.

[+]Hess (7) reduced a sample of natural N-methylisopelletierine (VI) with sodium-amalgam and water to obtain an oily product which he divided into approximately equal amounts on a basis of slightly different boiling ranges. From these oils, he prepared two methiodides to which he assigned the structure (VIII); one melted at 176°, the other at 176-177°, mixed m.p. 170-175°. Wieland and Dane (6) suggested the formula (VII) for a minor Lobelia alkaloid, m.p. 85-87°, but did not describe any derivatives of it.

[++]All melting points are corrected. For the included microanalyses, we are indebted to Dr. G. Oppenheimer and her staff.

(1.6 moles) of ammonium chloride in 500 cc. of water, the mixture foamed badly, then subsided. The dark-green organic layer was separated, the aqueous phase extracted with ether, and the combined ether extracts extracted in turn with 1200 cc. of 1 N hydrochloric acid. The acid extract was then neutralized with excess potassium carbonate and extracted with ether; this procedure did not separate the bases completely from the benzamide. After drying and removing the solvent, these ether extracts gave a distillate, b.p. 138-150° at 0.5 mm., which crystallized, weighed 112 g., and contained a large amount of benzamide (Scheuing and Winterhalder (E.P. 311387) (2) give the b.p. of (I) as about 159° at 1 mm.). Dissolved in a liter of acetone, the distillate was treated with 65 cc. of 48% hydrobromic acid, giving a colorless, crystalline precipitate of (I) hydrobromide weighing 105 g. (37.8%) and melting at 142-147° with some previous sintering. This salt crystallized from isopropyl ether-ethanol in beautiful, colorless, rhombic plates melting at 157.2-157.9° (Kröhnke (8) gives m.p. 156-157°). The oxime of the free base (m.p. 47-53°) melted at 116° (the melting point of the free base is given by Ladenburg and Kroener (1) as 50-51°, by Scheuing and Winterhalder (2) and Bergmann and Rosenthal(3) as 59°, and by Tchitchibabin (4) as 56°; the melting point of the oxime is given as 118°(9) and 120° (2); it should be noted that Ladenburg and Kroener (1) claimed that their ketobase did not react with hydroxylamine). (I) picrate crystallized from ethanol-acetonitrile or acetonitrile alone in sparse clusters of yellow, rectangular bars, some of which were tubular; others were in the form of tubes with a longitudinal opening down one face; the salt

melted at 181.8-182.3° (Ladenburg and Kroener (1) describe a picrate melting at 176-177°).

Anal. Calc'd for $C_{19}H_{14}N_4O_8$: C, 53.52; H, 3.31; N, 13.14.

Found: C, 53.56; H, 3.50; N, 12.96.

(I) Methbromide was prepared by heating a solution of 1.74 g. of (I) in about 5 cc. of methyl bromide in a sealed tube at about 60° for 16 hours; during the heating the initially clear, deep-yellow solution lightened, became cloudy, and then deposited clusters of pale brown flakes. After removing the excess methyl bromide, the crude product weighed 2.42 g. One recrystallization from ethanol-water gave large, well-formed, colorless prisms weighing 1.93 g. (74.8%). In another experiment, the free base (I) liberated from 27.7 g. (0.1 mole) of the hydrobromide was dissolved in 50 cc. of absolute ethanol containing 10 cc. of methyl bromide and allowed to stand, tightly stoppered, at room temperature. The next day, crystals of the methbromide began to form, slowly growing into very large, light yellow rhomboids; three days later, an additional 10 cc. of methyl bromide was added and the mixture was set in an icebox for 24 days, when the salt was washed with ethanol and ether and air-dried, yield 21.6 g. (73.8%); small additional amounts crystallized from the mother liquors on slow, spontaneous evaporation. A sample recrystallized from ethanol for analysis formed clusters of colorless plates, m.p. 214.0-214.2° with gas evolution.

Anal. Calc'd for $C_{14}H_{14}BrNO$: C, 57.55; H, 4.83; N, 4.79.

Found: C, 57.66; H, 4.89; N, 4.95.

β-(2-Piperidyl)-α-phenylethanols (II). a) By Hydrogenation of (I)

Hydrobromide over Adams' Catalyst. In a typical experiment, 27.7 g. (0.1 mole) of (I) hydrobromide, 75 cc. of absolute ethanol, and 1.0 g. of American Platinum Works' $PtO_2 \cdot 2H_2O$ were shaken with moist hydrogen at room temperature and atmospheric pressure. After 31 hours, the uptake was negligible and about 13.5 l. of the gas had been absorbed (theory 10.4 l.); plugging of the hydrogen-inlet tube was troublesome at first, but decreased during the course of the reduction. After filtering off the catalyst, evaporating the clear, colorless filtrate and washings to about 100 cc., and setting in the icebox for two days, 1.18 g. of crude α-(II) hydrobromide, m.p. 149-153°, was deposited. Removal of the ethanol from the filtrate, replacing with 50 cc. of acetone, seeding, and cooling gave 6.2 g. of colorless, irregular needles, m.p. 142°. Mother liquors from this second crop were freed of solvent, dissolved in 25 cc. of butanone, and treated with isopropyl ether until a permanent cloudiness developed (18 cc. required); on standing, a third crop weighing 4.0 g. and melting at about 134° was obtained. Similar treatment of these mother liquors with 15 cc. each of butanone and isopropyl ether gave 4.2 g. of hygroscopic material (A) melting up to 111° after drying in a vacuum dessicator over concentrated sulfuric acid. A number of similar reductions of (I) hydrobromide gave yields of crude α-(II) hydrobromide ranging from 39.7% to (in the experiment described here) 54.8%.

A crude α-(II) hydrobromide, m.p. 142-146°, required three recrystallizations from acetone-ethanol to bring it to a constant melting point, 156.4-157.0°, clusters of very thin colorless blades with bluntly-

pointed ends.

Anal. Calc'd for $C_{13}H_{20}BrNO$: C, 54.55; H, 7.04; N, 4.89.
Found: C, 54.83; H, 7.14; N, 4.76.

The free base α-(II) was liberated from a recrystallized sample of the hydrobromide and, after three recrystallizations from ligroin-isopropyl ether, formed sparsely-clustered colorless bars, m.p. 112.0-112.5°. Three recrystallizations of (A) (see above), the first by dissolving in acetone and diluting with ether, the others from acetone-ethanol, raised the melting point to 152-153° (α-(II) hydrobromide—mixed m.p.); basification of the mother liquors from the second recrystallization of this material (A), followed by five recrystallizations from 60-70° petroleum ether, gave pure β-(II), m.p. 97.8-98.5°.

Anal. Calc'd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82.
Found (α-II): C, 76.16; H, 9.70; N, 6.63.
(β-II): C, 76.20; H, 9.80; N, 6.84.

The picrates of both forms of (II) were oils.

Treatment of β-(II) with 48% hydrobromic acid and removal of water by evaporating off several small portions of acetone at oil-pump vacuum gave a crystalline solid, colorless rectilinear plates from ethanol-water melting at 186-187° (somewhat dependent upon the rate of heating), with very gentle gas evolution; analysis of this salt indicated a replacement of the hydroxyl group of (II) by bromine. Liberation of the free base from this salt into ether, followed by drying and evaporation, gave an ether-insoluble, oily solid containing halogen (Beilstein).

Anal. Calc'd for $C_{13}H_{19}Br_2N$: C, 44.72; H, 5.49; N, 4.01; Br, 45.78.

Found: (Br by diff.) C, {47.27; 47.98;} H, {5.53; 5.90;} N, 3.90; Br, {43.30. 42.22.}

Basification of the mother liquors from (A) (see above) and working up gave 0.10 g. of α-(II) and 4.54 g. of white crystalline material melting over a range(80-110°); repeated recrystallization from 60-70° petroleum ether gave clusters of white, irregular crystals which appeared homogeneous, but did not melt sharply. Treatment of 0.19 g. of such recrystallized material with 0.32 g. (two equivalents) of 48% hydrobromic acid gave 0.04 g. of a salt which proved identical to that obtained under the same conditions from β-(II) (see above).

b) By Hydrogenation of (I) over Raney Nickel. Subsequent experiments showed that the starting material used in this reduction was only about 60% (I), the remainder being benzamide, so the 20 g. used contained about 0.06 mole of each of these compounds; dissolved in 150 cc. of dioxane, it was shaken with 11 cc. of Raney-nickel paste and hydrogen at a pressure of 2100 lbs./ $in.^2$ (measured at 25°). In five hours at 85-145°, the pressure dropped 195 lbs./ $in.^2$ (25°); assuming 0.12 moles of material to be present, the pressure drop per equivalent would be 51 lbs./ $in.^2$ (25°). Distillation of the crude reduction product gave a mixture of oil and crystals, b.p. 100-145° at 1 mm. (Scheuing and Winterhalder's (2) (II) mixture boiled at 165° at 4 mm.).

The crystalline portion of this distillate gave, after repeated recrystallization from benzene, a non-basic substance, m.p. 186-187°, presumably hexahydrobenzamide (Markownikow (10) gives m.p. 185-186°).

Anal. Calc'd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01.

Found: C, 65.99; H, 10.08; N, 11.62.

From the oily portion of the distillate, which crystallized on standing, the two piperidylcarbinols (II) were isolated; five grams of this material was dissolved in five milliliters of warm benzene and, on cooling, the α-isomer separated, identified by m.p. and mixed m.p. of the free base and its hydrobromide as the α-(II) described above. On further standing, the benzene mother liquors from the α-form deposited crystals of the more soluble β-form, identical with the minor product of the platinum reduction by m.p. and mixed m.p.

With due acknowledgement of the heterogeneous nature of the material, a few reduction experiments on the above-described (I)-benzamide mixture should be mentioned. An ethanolic solution of it containing Adams' catalyst absorbed no hydrogen. A methanolic solution (1.07 g. in 50 cc. with 0.1 g. of $PtO_2 \cdot 2H_2O$) absorbed one mole-equivalent of hydrogen in 11 hours and yielded a small amount of colorless flake-clusters from isopropyl ether-ethanol, m.p. 92.4-93.0° (Anal. Found: C, 75.69; H, 6.61; N, 7.66); this material gave no isopropyl-ether-insoluble picrate. (Scheuing and Winterhalder (2) report the successful reduction of (I) in methanol over platinum on barium sulfate to α-picolyl-phenylcarbinol). An attempt to reduce the mixture with aluminum isopropylate in isopropanol was apparently unsuccessful, but this failure is not surprising in view of the similarity of (I) to a β-diketone.

1-Methyl-2-Phenacylpiperidine (III). After cooling to room temperature, 2.0 g. of platinum oxide (American Platinum works' $PtO_2 \cdot 2H_2O$) was added to 21.6 g. (0.0737 mole) of (I) methbromide dissolved in 250 cc.

of warm methanol; upon shaking the mixture with moist hydrogen at atmospheric pressure, 6300 cc. (three mole-equivalents) was taken up in 21 minutes, when the reduction was stopped, although the absorption rate was still rapid at this point. The catalyst was filtered off, the methanol removed on the steam bath, and the sirupy residue dissolved in 32 cc. of ethanol and diluted with 75 cc. of acetone. Cooling the resulting solution gave 6.07 g. of crystalline material, m.p. 145-146°; replacing the solvent of the mother liquors with 50 cc. of acetone and cooling gave a second crop weighing 12.04 g. and melting at 147-150° (rapid heating); treatment of the non-volatile residues from the second crop with 15 cc. of acetone gave 1.29 g. more of the product, m.p. 141-144°, the total yield of (III) hydrobromide being 19.40 g. or 88.3%. A solution of 18.1 g. (0.0608 mole) of this salt in 25 cc. of water was basified with 25 cc. of 4 N sodium hydroxide and the free base (III) extracted with 50 cc. of isopropyl ether. Distillation at 1 mm. gave 12.29 g. (93% recovery) of somewhat-viscous, pale-yellow oil, b.p. 124°.

Anal. Calc'd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45.

Found: C, 77.25; H, 8.90; N, 6.42.

The hydrobromide of (III), dissolved in a little ethanol and diluted (1:1) with acetone, emerged slowly in compact clusters of colorless granules which initially appeared cubic, m.p. 148.8-149.4°.

Anal. Calc'd for $C_{14}H_{20}BrNO$: C, 56.38; H, 6.76; N, 4.70.

Found: C, 56.51; H, 6.88; N, 4.83.

(III) hydrochloride in a little warm ethanol diluted with about 10 volumes of ether slowly crystallized in compact micro-needle clusters,

m.p. 172-173° with decomposition, the melting point being somewhat lower (166°) on very slow heating.

Anal. Calc'd for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94; N, 5.52.
Found: C, 66.89; H, 8.16; N, 5.42.

The picrate of (III) formed tiny, bright-yellow or orange granular clusters from ethanol-acetonitrile, m.p. 159.2-159.4°.

Anal. Calc'd for $C_{20}H_{22}N_4O_8$: C, 53.81; H, 4.97; N, 12.84.
Found: C, 54.10; H, 5.16; N, 12.55.

(III) acid-oxalate formed puffballs of tiny, white, needle-clusters from isopropyl ether-ethanol, m.p. 131-133°.

Anal. Calc'd for $C_{14}H_{19}NO \cdot C_2H_2O_4$: C, 62.52; H, 6.89; N, 4.56.
Found: C, 63.06; H, 6.95; N, 4.65.

Addition of several drops of 48% hydrobromic acid to a mixture of (III) hydrobromide and 2,4-dinitrophenylhydrazine in boiling 95% ethanol caused the reactants to dissolve and the hydrobromide of (III) 2,4-dinitrophenylhydrazone to separate as an orange, crystalline solid, m.p. 237-240° with decomposition, difficultly soluble in the ordinary solvents. Obtained by basifying a warm aqueous suspension of the salt, the free derivative formed tiny clusters of orange leaves from isopropyl ether-acetonitrile, m.p. 138.1-138.6°.

Further Platinum Hydrogenation of (III) Methbromide. A mixture of 21.24 g. (0.0728 mole) of (III) methbromide and 0.3 g. of platinum oxide in 60 cc. of methanol was shaken with hydrogen as before, but allowed to continue until the rate of absorption was negligibly slow, seven hours being required, during which time 8500 cc. of hydrogen was taken up

(theory for four mole-equivalents, about 7600 cc.). Treatment of the crude reduction product with 12.2 g. of anhydrous oxalic acid in 50 cc. of methanol gave 6.32 g. (28.1%) of (III) oxalate (further identified by conversion to the picrate and the hydrochloride) in three crops. Residual bases were liberated from the oxalate mother liquors with potassium hydroxide and treated with 10.8 g. of picric acid in 25 cc. of boiling ethanol, acetonitrile being added as the hot solution cooled to maintain clarity; seeded with (III) picrate, the solution slowly deposited a small amount of this salt and, after ten days' standing, a large quantity of bright-yellow needle-tufts. After removing a seed crystal of this new picrate (P), the mixture was brought to a boil, allowed to cool in contact with the small amount of (III) picrate, and decanted when (P) began to crystallize out. In this way, 6.82 g. (about 21%) of (P) was obtained; it could be easily separated from traces of (III) picrate since the latter emerges very slowly, even when seeded, while (P) forms relatively stable supersaturated solutions, but emerges rapidly when seeded. Recrystallized from methanol-acetonitrile, (P) melted at 131.4-131.8°.

Anal. Found: C, 53.45; H, 6.47; N, 12.17.

Calc'd for $C_{14}H_{25}NO \cdot C_6H_3N_3O_7$: C, 53.09; H, 6.24; N, 12.38.

The oily, colorless free base was liberated from (P) in 82% yield, b.p. 127-132° at 1.5 mm.

Anal. Found: C, 76.09; H, 11.02; N, 6.60.

Calc'd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27.

The methiodide of the free base from (P) crystallized from ethyl acetate-ethanol in clusters of thin, colorless slats, m.p. 163.1-163.5°

after some sintering from 159°.

Anal. Found: C, 49.53; H, 7.75; N, 3.71.

Calc'd for $C_{14}H_{25}NO \cdot CH_3I$: C, 49.32; H, 7.73; N, 3.83.

Attempts to prepare the oxime, 2,4-dinitrophenylhydrazone, phenylurethane, and p-nitrobenzoate gave inconclusive results.

Meerwein-Ponndorf Reduction of (III). To 10.85 g. (0.05 mole) of freshly-distilled (III) were added 10 g. (0.05 mole) of distilled aluminum isopropylate and 50 cc. of dry isopropanol (distilled from aluminum isopropylate); adding small additional amounts of the alcohol when necessary, solvent was slowly distilled off through a short Vigreau column until the distillate gave negative tests for acetone with a 2,4-dinitrophenylhydrazine reagent (11); seven hours were required. After removing the excess isopropanol in vacuo, the residual wine-red sirup was treated with ice-water and 12.5 g. of sodium hydroxide and extracted with benzene. Dried over potassium carbonate, these extracts were freed of solvent, leaving 10.05 g. of dark-brown, viscous oil. Noting that a drop of this material was only partly soluble in 48% hydrobromic acid, the bulk of it was treated with 20 cc. of 6 N hydrochloric acid, the non-basic portion extracted with ether, dried, and distilled, yielding 2.61 g. (representing 43.4% of the starting material) of brilliant, colorless oil, b.p. 94° at 13 mm., solidifying at 0°, melting at the temperature of the hand, and giving an α-naphthylurethane, colorless needle-clusters from ligroin-isopropyl ether, m.p. 105.6-106.0° (methylphenylcarbinol boils at 94° at 12 mm. (12), freezes at 20.1° (13), and forms an α-naphthylurethane of m.p. 106° (14)). The basic reduction products were

liberated from the acidic aqueous phase by adding 25 cc. of 30% potassium hydroxide solution and were extracted with ether, giving 6.55 g. of dark-brown, viscous oil. 2.43 g. of this material was distilled at 1 mm., yielding 0.46 g. of pale-yellow oil (B), b.p. 74-105°, 0.90 g. of viscous, yellow oil (C), b.p. 127-147°, and a dark-brown, very viscous residue of about 1 cc.

A sample of (B) dissolved in a little ethyl acetate and treated with a slight excess of methyl iodide plus enough ethanol to keep the solution clear gave a methiodide in good yield; this salt crystallized very slowly from ethyl acetate-ethanol in hard, pale-yellow clumps of unsharp but characteristic melting-point; it fused slowly at 150-165° to a cloudy melt which clarified rather sharply at 175°.

Anal. Calc'd for $C_{10}H_{22}INO$: C, 40.14; H, 7.91; N, 4.68.

Found: C, 39.79; H, 7.46; N, 4.69.

Both (B) and (C) formed oily picrates which could not be induced to crystallize. Two analyses of (C) gave C, 76.00, 76.79; H, 10.08, 9.91; N, 8.11, 8.71; its methiodide was an orange-brown oil.

Summary

Reductions of α-phenacylpyridine, its hydrobromide, and its methbromide have been studied.

An improved synthesis of α-phenacylpyridine has been described.

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A NEW GUINEA PIG TEST FOR RELAXIN ACTIVITY

For suggesting this problem and for constant interest and assistance in its execution, the author wishes to thank Prof. C. A. G. Wiersma; and to him and to the other members of the teaching staff of the Animal Physiology Department of the Kerckhoff Laboratories of the Biological Sciences at the Institute, the author expresses his indebtedness.

A NEW GUINEA PIG TEST FOR RELAXIN ACTIVITY

Although it has long been known that a softening of the ligaments joining the bones of the pelvic girdle occurs during the pregnancy period of vertebrate animals, Hisaw (1) first indicated that this birth-facilitating process might be caused by a hormone, to which he gave the name "Relaxin".

In reviewing the rather thorough investigation of Hisaw and his co-workers on the properties of relaxin, it is well to bear in mind the methods they used as a basis for their observations; Fevold, Hisaw, and Meyer (2) give the following description of their assay method: "The potency of different preparations of relaxin is standardized in terms of their ability to produce relaxation of the pelvic ligaments of virgin female guinea pigs which are in full oestrum. These animals are injected subcutaneously with a definite amount of the preparation to be tested and after ten to twleve hours the pelvic ligaments are palpated gently to see if they have become loose. Loosening can best be determined by alternately moving each half of the pelvis up and down vertically while at the same time keeping a finger over the symphysis pubis. The minimum amount of hormone which causes a definite loosening of the ligaments within ten to twleve hours after a single injection is taken as a guinea pig unit." In practice, artificial oestrum is induced in castrate female guinea pigs by injections of estradiol over a period of days prior to the test (compare (3)).

Relaxin was found by these workers to be present in the corpora lutea and placentae of sows, the blood sera of pregnant sows, dogs, cats,

mares, rabbits, guinea pigs, and women, and the urine of pregnant guinea pigs. Marder and Money (4) showed that in the pregnancy period of rabbits (about 30 days) relaxin is detectable in the blood serum as early as the third day after mating, the amount increasing rapidly between the twelfth and twenty-fourth days, then remaining relatively constant (on the twenty-seventh day of pregnancy, 0.1 cc. of blood serum contains 1 GPU of relaxin) until parturition, which brings a sharp decline until the hormone disappears completely about three days later; relaxin is detectable in the urine of these rabbits on the fifth day of pregnancy, the amounts excreted increasing steadily during the gestation period. It is important to remember that relaxin is physiologically effective only when the animal is in oestrum; castrate male guinea pigs can be relaxed if feminized by ovarian grafts or given prolonged oestri injections.

Soon after crystalline progesterone became available, Haterius and Fugo (5), who were aware of Hisaw's work, injected oöphorectomized virgin female guinea pigs in artificial oestrum with the pure hormone and obtained pelvic relaxations (observed by palpation) which they intimated might throw some doubt on Hisaw's work. Later, Hisaw's group (6) published data showing that progesterone caused relaxations in two to six days comparable to those induced by their relaxin concentrates in about six hours.

In experiments aimed at concentrating and determining the chemical properties of relaxin, Fevold, Hisaw, and Meyer (2) extracted dried sow corpora lutea with acidulated alcohol, freed these extracts of proteins, phospholipins, and other fatty substances, and evaporated the residual

solution to dryness; recrystallization of the residue from glacial acetic acid gave a solid, partly sodium chloride, which had a potency of 1 GPU per milligram. An alternate procedure involving precipitating the hormone with picric acid gave a solid 0.035 mg. of which was equivalent to 1 GPU. Relaxin is amphoteric (soluble in acids or bases, but only slightly so in water), has a definite isoelectric point (pH 5.4-5.5 for a 0.1% solution), is thermolabile, and is destroyed by oxidizing agents, strong bases, and proteolytic enzymes (trypsin and pepsin); it is negative toward the Millon, ninhydrin, and Molisch tests and gives a faint violet in the Poser ring biuret test; relaxin contains about 15.5% nitrogen (6).

Due credit must be given Hisaw and his coworkers for their painstaking researches on the nature of this interesting hormone, yet in view of their method of testing for activity, these studies were at best qualitative and could hardly have been subject to more personal error. In the interest of placing further relaxin-investigations upon a more quantitative basis, we have devised the simple mechanical testing procedure described and illustrated in this paper.

In vertebrate anatomy, the ligaments form a very important group which has been collectively termed by Annovazzi (7) the "organ of resistance". Although their principal function is a static one, namely to maintain the positions of the bones, muscles, and organs of the body, their limited elasticity also assumes important aspects, as in the enlargement of the pelvic girdle during parturition. It is therefore surprising to find how very little work has been done on the dynamic

properties of this type of tissue. Annovazzi (8) has made a histological study of the ligaments from the joints of the elbow, knee, hip, wrist, and ankle, and distinguished four types of such tissue, which is composed of mixtures of elastic and collagenous fibers, based upon the relative amounts and orientations of these two constituents, but concluded there was no relation between these types and their functions as far as stresses were concerned.

A search of the biological literature of the past 15 years revealed only two papers dealing with the stretching properties of ligaments. Redenz (9) stretched unfixed transverse sections of the human aorta and reported that this ligamentous tissue showed little elasticity but great extensibility. Annovazzi (7) studied ligaments removed from dogs immediately after death and made a number of interesting observations: ligaments lacking elastic fibers are more elastic than those composed exclusively of elastic fibers, although the later can be stretched farther without losing their elasticity; in ligaments containing both elastic and collagenous fibers, only the former are stretched with small weights, while the others require greater weights in order to be elongated and are so stretched only after the elastic limit of the elastic fibers is reached.

Methods

Half-grown virgin female guinea pigs (weighing between 300 and 600 grams and in artificial oestrum produced according to Hisaw and coworkers (3)) were anaesthetized with nembutal and laid on their backs on a wooden board firmly clamped to the laboratory table. A slit was

then cut along the ventral midline, extending upward from the vaginal opening about one inch and exposing the symphysis pubis, which was then cut free of attached muscles, care being taken to avoid severing any large blood vessels. The ends of a short piece of strong string were then tightly tied to the animal's right pubic and ischial bones as close to their juncture with the pubic symphysis as possible (see Figures 1 and 2); two longer loops were tied between the corresponding bones to the left of the symphysis. After the short single loop was placed around a peg in the board, the animal was arranged so that this loop was taunt, its hind legs were stapled to the board in such a way as not to interfer with the lateral freedom of the strings, and two nails were driven into the board on either side of the animal, just above the hind legs in such a way as to hold the pelvis in a fixed position on the board, essentially perpendicular to the laterally extended string-loops. Of the two loops on the animal's left side, the lower was hooked to a string to which, after running over suitable pulleys, various weights (100-500 g.) could be applied; the upper loop was hooked to a second string leading over a similar pulley-system, weighted just heavily enough to keep it taunt, and carrying a small celluloid-film scribe made by a few twists of the string to bear upon a smoked drum turning at a rate of about one revolution per hour (see Figure 2).

By this procedure, the recorded stretching of the string itself under application of the rather large weight is reduced to a minimum; of course, the anchoring loop (on the animal's right) should be as short as possible.

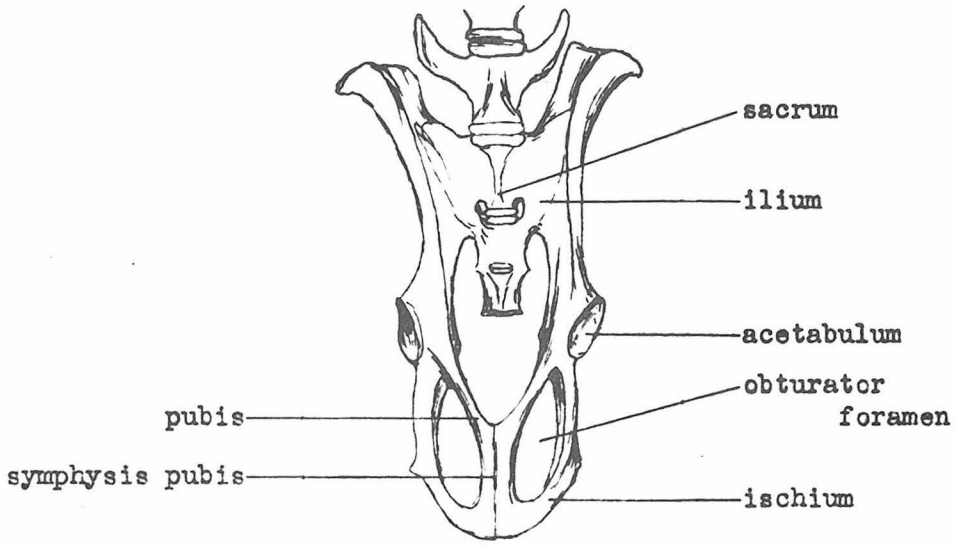


Fig. 1. Ventral plan of guinea pig pelvis (♀).

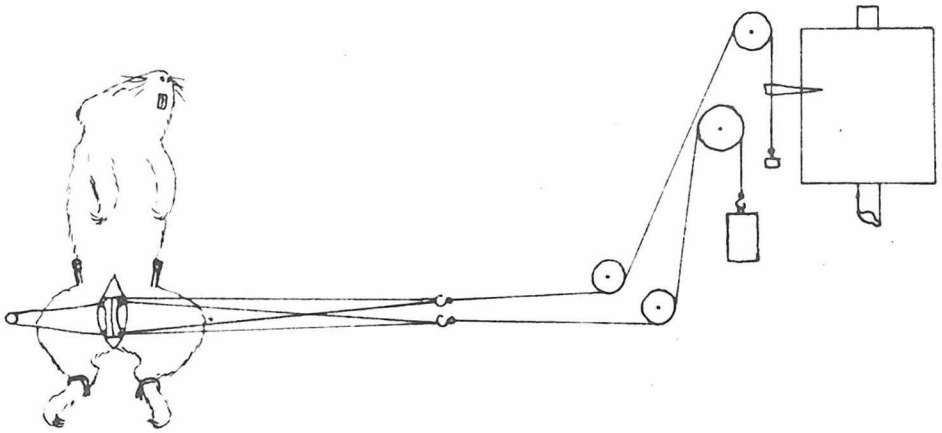


Fig. 2. Plan of stretch-recording apparatus.

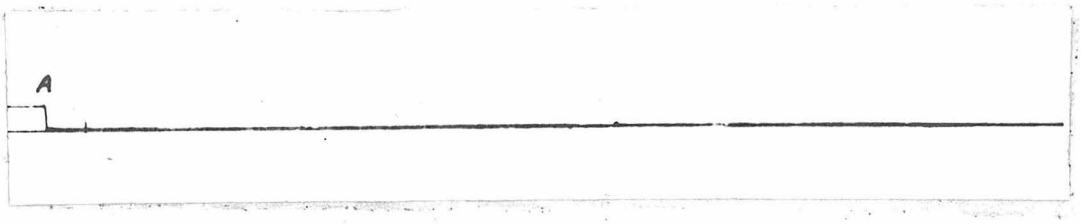


Fig. 3

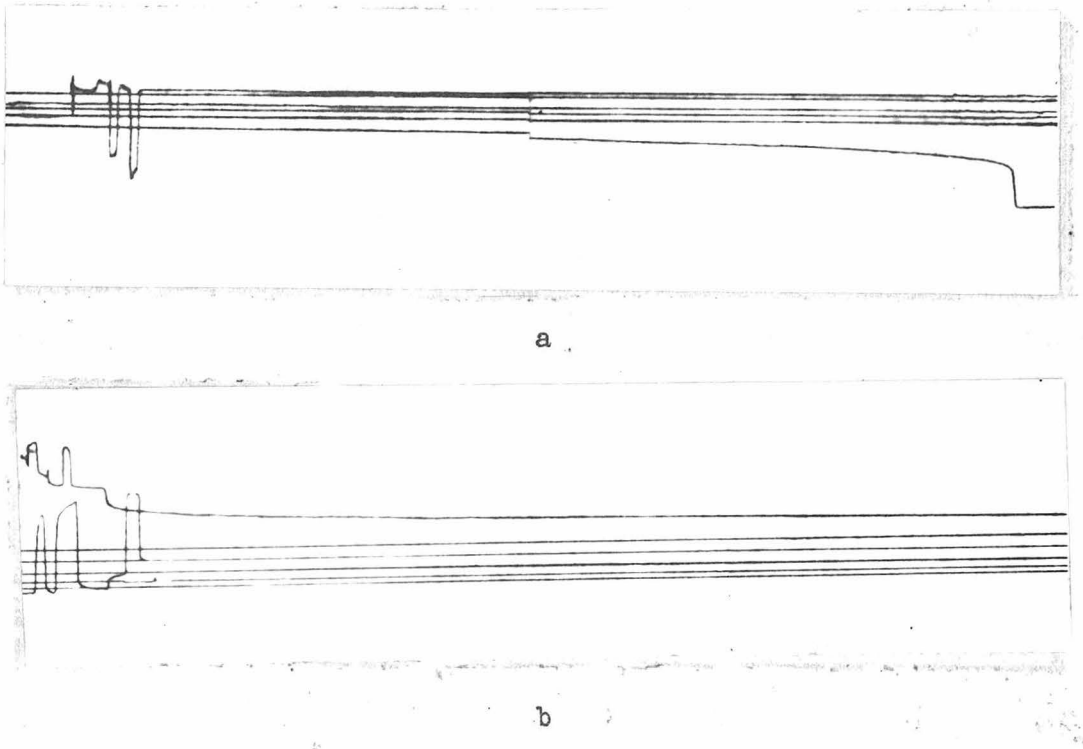
Figure 3 shows a segment of a kymogram made by applying a weight of 100 g. across the pubic symphysis of a stiff, dry, unstretchable guinea pig skeleton. After establishing a short base-line, the weight was applied at A; the quick drop of about 3.5 mm. is due to elastic stretching of the anchor loop of string; it can be seen that subsequent stretching is negligible (compare Figure 4). Also, after each actual run, a strong hemostat was used to pinch the stretched symphysis back to its original position, the scribe (see Figure 4) returning almost to the starting level on the drum, except for a small discrepancy of the same order of magnitude as the initial drop in the skeleton experiment.

The included hymographic figures are photographic contact-negatives of the actual kymograms.

Results

Before one of us (D.R.H.) was forced by urgent war-work to abandon further experiments, a number of runs were made, with and without previous injections of up to 2 cc. of pregnant-rabbit serum; the rate of stretch was rapid initially and tapered off until it was practically negligible after about a six-hour period. We were, however, unable to notice any marked, consistent effect of the pregnancy-serum upon the results obtained; this uncertainty in our experiments was shown

by the senior author to be due, at least in part, to the extreme sensitivity of the tension of the ligament concerned to small changes in temperature, so that the rate of stretch recorded on the kymogram was noticeably affected by altering the distance of a small desk lamp, placed more or less at random in the early experiments to keep the animal warm. Thus determination of the true worth of this method of testing for relaxin-activity awaits further experiments under thermostatic conditions.



a

b

Fig. 4

Figure 4a is a graph of the stretching of a castrate virgin female guinea pig in artificial oestrum, under a weight of 200 g.; a three-inch piece (representing about 10 minutes) has been removed from the center of this segment. The initial rapid stretch of the anchoring

loop is plainly discernable; the actual stretching of the symphysis pubis is fairly rapid at first and assumes a rather constant rate after about one-hour's application of the weight. To the right are seen the vertical marks produced by pinching the symphysis back together with a strong hemostat (see Methods); the scribe is seen to have returned to the starting level, except for the amount of stretch due to the anchoring loop.

The animal from which record 4b was made was, in addition to the preparation described for the other animal, injected with 0.3 cc. of pregnant-rabbit serum about 1 1/2 hours before stretching with 100 g.; it is noted that there is little significant change in the rate of stretching 7 1/2 hours after the serum injection (sixth line down represents about six hours of stretching). The pinch marks, made at the end of the experiment, are seen this time at the left, for better comparison with the starting level. Note that the anchor-loop drop is about half that in 4a, corresponding to the difference in stretching weights.

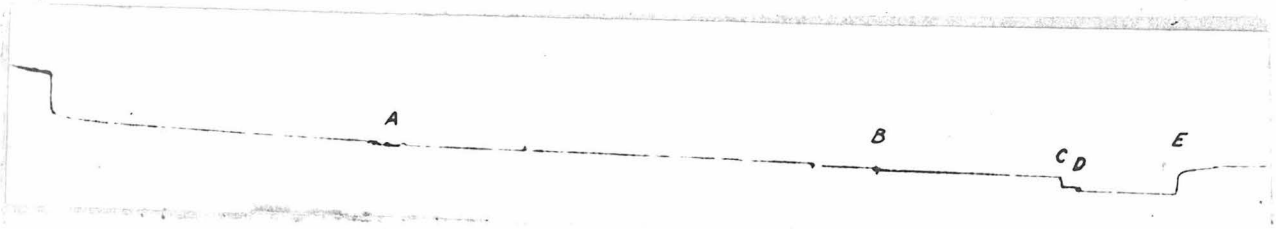


Fig. 5

To produce Figure 5, a 500 g. weight was used for the stretching; at A, the string supporting the stretching weight was clamped, and released at B, six minutes later; the string was clamped again at C, the kymograph drum stopped, then released again at D, an hour and

45 minutes later. At E, the stretching weight was removed. Although the significance of the small drops at B and D is questionable, because of the possible superposition of artifacts inherent in the clamping and releasing procedures (see points A and C), the nature of the recovery on removal of the stretching weight (following E), which was noted in numerous other cases, needs interpretation.

That there are plastic elements involved in the stretching of a ligament may be deduced from the observation that some elongation continues during the prolonged application of a constant weight; the presence of elastic elements is shown by the measure of restoration following the removal of the weight. A purely elastic body if clamped under tension would not show any release of this tension during the clamping (provided the elastic limit is not exceeded); tension on a plastic body would be relieved during the clamping so that a further extension would result on reapplication of the initial stretching force. A combination of plastic and elastic elements in a series-arrangement might give a stretching curve such as is observed here with the pubic symphysis ligament, but the restoration curve of such a body would exhibit only the quick recovery of the elastic units[+]. The observation that the restoration curve is an almost exact inversion of the stretching curve indicates that the restorative force of the elastic elements is being applied against the resistance of plastic elements. Such behavior could be explained by a parallel-arrangement of the two types of stretchable elements, with extensive friction of some sort between the two to

[+]It is difficult to correlate Annovazzi's reported relative properties of the collagenous and elastic fibers of canine ligaments with any other than a series-arrangement.

prevent buckling of the plastic elements under the compressional force. The imaginable characteristics of a coil-spring imbedded in a very viscous substance such as tar are brought to mind.

It is almost certain that in these experiments the stretching process is more or less destructional, that is, that the elastic limit of the elastic units involved is exceeded, and so we would not expect the ligament to return completely to its original length after removal of the stretching weight, even after an indefinite time. Even in the very natural process of childbirth, the pelvic ligaments often cannot accommodate the strains placed upon them without destructive stretching; thus in a series of autopses, Sutro (10) found clefts in the interpubic tissues and ligaments, particularly in multiparae.

Summary

A survey of recent literature concerning the hormone relaxin and the stretching of ligaments has been made and commented upon.

A semi-quantitative guinea-pig method for assaying potential relaxin-containing materials has been devised. Kymograms obtained by this method have been interpreted on a basis of a modified parallel-arrangement of the elastic and collagenous (plastic) tissues of the pubic symphysis ligaments.

References

(1) Hisaw, Anal. Record, 37, 126 (1927).

(2) Fevold, Hisaw, and Meyer, J. Am. Chem. Soc., 52, 3340 (1930).

(3) Abramowitz, Money, Zarrow, Talmadge, Kleinholz, and Hisaw, Endocrinol., 34, 103 (1944).

(4) Marder and Money, Endocrinol., 34, 115 (1944).

(5) Haterius and Fugo, Proc. Soc. Exp. Biol. and Med., 42, 155 (1939).

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(7) Annovazzi, Arch. Sci. Biol. (Napoli), 11, 467 (1928). See Biol. Absts., 5, abstract 2751 (1931).

(8) Annovazzi, Monitore Zoologico Ital., 36, 285 (1926). See Biol. Absts., 4, abstract 29317 (1930).

(9) Redenz, Zeitschr. Wiss. Biol. Abt. B. Zeitschr. Zellsforsch. und Mikrosk. Anat., 4, 611 (1927). See Biol. Absts., 3, abstract 3250 (1929).

(10) Sutro, Arch. Surg., 32, 823 (1936). See Biol. Absts., 11, abstract 19443 (1937).

COLLECTED SUMMARIES

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The Synthesis of Potential Antimalarials

I.

A representative 3-alkylsubstituted piperidone-4, the 1,3-dimethyl derivative, has been prepared by standard methods.

Acrylic esters combine much more readily than methacrylic esters with primary and secondary bases.

II.

The Darzens-Claisen reaction has been successfully applied to the conversion of a typical β-dialkylaminoketone into a mixture of two basic glycidic esters which have been separated as their dilituratesand degraded to the same basic aldehyde.

III.

The two racemic 6'-methoxyrubanols-9 (vinyl-free quinines) have been prepared by improvements on known methods and intermediates in the synthesis further characterized.

The (++)(--) racemate and the antipodes obtained from it by resolution with l-malic acid have been shown to have antimalarial activities comparable with that of quinine; the (+-)(-+) racemate was found to be inactive.

IV.

The synthesis of five Ainley-King-type 2-phenylquinolyl-4-α-piperidylcarbinols has been described.

V.

The synthesis of 2,6-diphenylpyridyl-4-di-n-butylaminomethylcarbinol has been described.

VI.

9-Picolinylanthracene has been prepared by the Hammick reaction; its catalytic hydrogenation has been shown to follow a course reported in similar reductions of anthracene itself.

VII.

Reductions of α-phenacylpyridine, its hydrobromide, and its methbromide have been studied.

An improved synthesis of α-phenacylpyridine has been described.

A New Guinea Pig Test for Relaxin Activity

A survey of recent literature concerning the hormone relaxin and the stretching of ligaments has been made and commented upon.

A semi-quantitative guinea-pig method for assaying potential relaxin-containing materials has been devised. Kymograms obtained by this method have been interpreted on a basis of a modified parallel-arrangement of the elastic and collagenous (plastic) tissues of the pubic symphysis ligaments.

PROPOSITIONS

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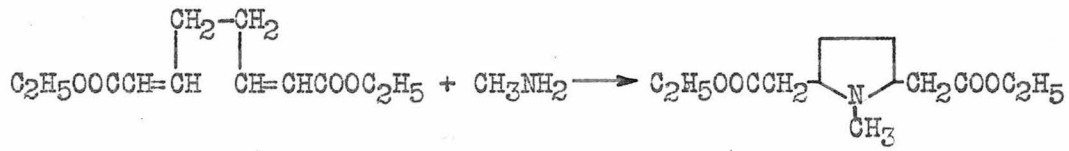
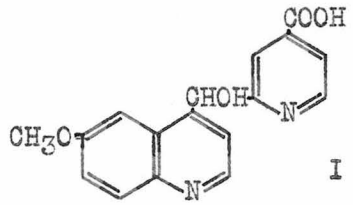
1. 2,5-Dicarbethoxymethyl-N-methylpyrrolidine, an intermediate in the tropinone synthesis of Willstätter and Bommer (Ann., 422, 15 (1921)), could be made simply and in good yield by the following method:



2. Details of the preparation of niquine from quinine (Solomon, J. Chem. Soc., 1941, 77) indicate the formaldehyde ultimately liberated is initially bound to the product as part of an oxazolidine ring which is broken on treatment with an acid.

3. Dihydroniquine could be synthesized and its structure thus firmly established by applying the Ainley-King series of reactions (Proc. Roy. Soc., 125 B, 60 (1938)) to ethyl γ-n-propyl-ε-benzamidocaproate.

4. Gibbs and Henry (J. Chem. Soc., 1939, 1294) give a tentative formulation (I) to an acid obtained by permanganate oxidation of niquidine; (I) could be synthesized in one step by a modification of the Hammick reaction (J. Chem. Soc., 1937, 1724; ibid., 1939, 809).



I

5. The synthesis of the pharmacologically-important alkaloid lobeline by Scheuing and Winterhalder (Ann., 473, 126 (1929)) involves a four-step process of obtaining 2,6-diphenacylpyridine from 2,6-lutidine; I propose preparing this intermediate in one step by a method investigated in These Laboratories (see Paper VII of this thesis).

6. The work of Johnson (J. Am. Chem. Soc., 65, 1317 (1943); ibid., 66, 215 (1944)) on the introduction of "angular" methyl groups suggests a simple cantharidine synthesis starting from the Diels-Alder addition product of furane and p-benzoquinone.

7. I propose that a convention be adopted in describing solvent-couples used for recrystallizing organic compounds: namely, that the solvent in which the compound is less readily soluble be named first. For example, "A is recrystallized from benzene-pyridine" indicating that A was suspended in boiling benzene and pyridine added dropwise until the solid dissolved.

8. The quininic ester synthesis of Thielepape and Fulde (Ber., 72, 1440 (1939)) suggests a new method of preparing certain substituted 2-phenylcinchoninic esters from acetophenone-anils where costly substituted anilines or benzaldehydes would make the low yields of the Doebner method (Ann., 242, 270 (1887)) undesirable.

9. The proposed structure of pilosine (Pyman, J. Chem. Soc., 101, 2260 (1912)) could be confirmed by its synthesis from pilosinine through a Claisen-type condensation with ethyl benzoate.

10. The translation of any of numerous recent German monographs would be a fruitful supplementary problem for graduate chemists.

11. The highly-specific action of lobeline upon the chemo-receptor of the carotid sinus, demonstrated by the method of Zotterman (see Skandinav. Arch. f. Physiol., 83, 132 (1939)) offers an unparalleled opportunity for the study of one phase of the relation between chemical structure and physiological activity.