Part I The Synthesis of Potential Antimalarials. Some 2-Substituted 8-(3-Diethylaminopropylamino)-quinolines.

Part II Isomorphism in Relation to Serological Specificity.

Part III A Study on the Hammick Reaction.

Thesis by

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Contents

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## PART I.[1]

The Synthesis of Potential Antimalarials.
Some 2-Substituted 8-(δ-Diethylaminopropylamino)-quinolines.

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[1] This work was done under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

# INTRODUCTION

From the time of the elucidation of the structure of the cinchona alkaloids (by Rabe in 1908) until the First World War, the major effort of chemists in their search for improved quinoline-type antimalarials was directed towards modifying some features of the quinine molecule while keeping the general structure intact. The inability of Germany during 1914-1918 to import the naturally-occurring alkaloids instigated intensive investigations with the object of finding a synthetic substitute. The culmination of these researches was the synthesis, in 1926, of pamaquine (or plasmochin) by chemists of the I.G. Farbenindustrie.

During the Second World War, this country found itself in a position similar to that of Germany in the First World War. The supply of naturally occurring cinchona alkaloids had been cut off, and the toxicity of pamaquine prevented its large-scale distribution as a drug. For that reason a program was begun under the Committee for Medical Research in the hope of finding a drug with the desirable antimalarial properties of pamaquine but without its high toxicity.

In a recent investigation (1), an <u>in vitro</u> degradation product of quinine (CDP) was isolated which was less toxic,

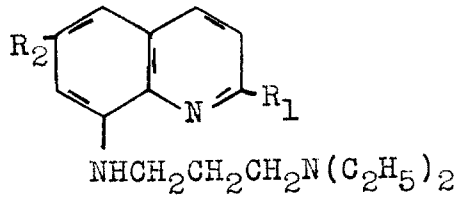
although also less active, than quinine itself. Later evidence (2) indicated that QDP was 2'-hydroxy-6'-methoxy-3-vinylruban-9-ol, a carbostyril derivative. It seemed of interest, therefore, to prepare some pamaquine analogues having the carbostyril or 2-alkoxyquinoline nucleus, and in this way obtain less toxic pamaquine-type antimalarials.

The preparation of certain 2-hydroxy-4-methyl-8-(dialkylaminoalkylamino)-quinolines as potential antimalarials had previously been reported (3). Since these compounds had a lepidine nucleus they differed radically from the pamaquine-type of structure. The compounds prepared in This Laboratory had, except in the case of 2-methoxy-8-(diethylaminopropylamino)-quinoline, a hydroxyl or methoxyl group in the 6-position, in view of the fact that quinine, as well as pamaquine, owes its activity in part to the presence of the methoxyl group in the 6-position.

It had originally been intended in this work to attach to the 8-aminoquinoline nucleus the side-chain of pamaquine, but recent evidence (4) indicates that the use of this side-chain may give rise to highly toxic isomers. Hence the 3-diethylaminopropyl side-chain was chosen for this purpose, since no isomerization is known to occur during its preparation.

The compounds which are described here are therefore of the plasmocide, rather than the pamaquine, type. Although this meant a departure from the original purpose of synthesising pamaquine derivatives, it permitted the comparison of the toxicity of various plasmocide derivatives without the danger of complications from an isomerized noval side-chain.

The compounds which were prepared in this series are the following.




I. 2-Methoxy-8-(3-diethylaminopropylamino)-quinoline

$R_1$ - $OCH_3$ $R_2$ - H

II. 2,6-Dimethoxy-8-(3-diethylaminopropylamino)-quinoline

$R_1$ - $OCH_3$ $R_2$ - $OCH_3$

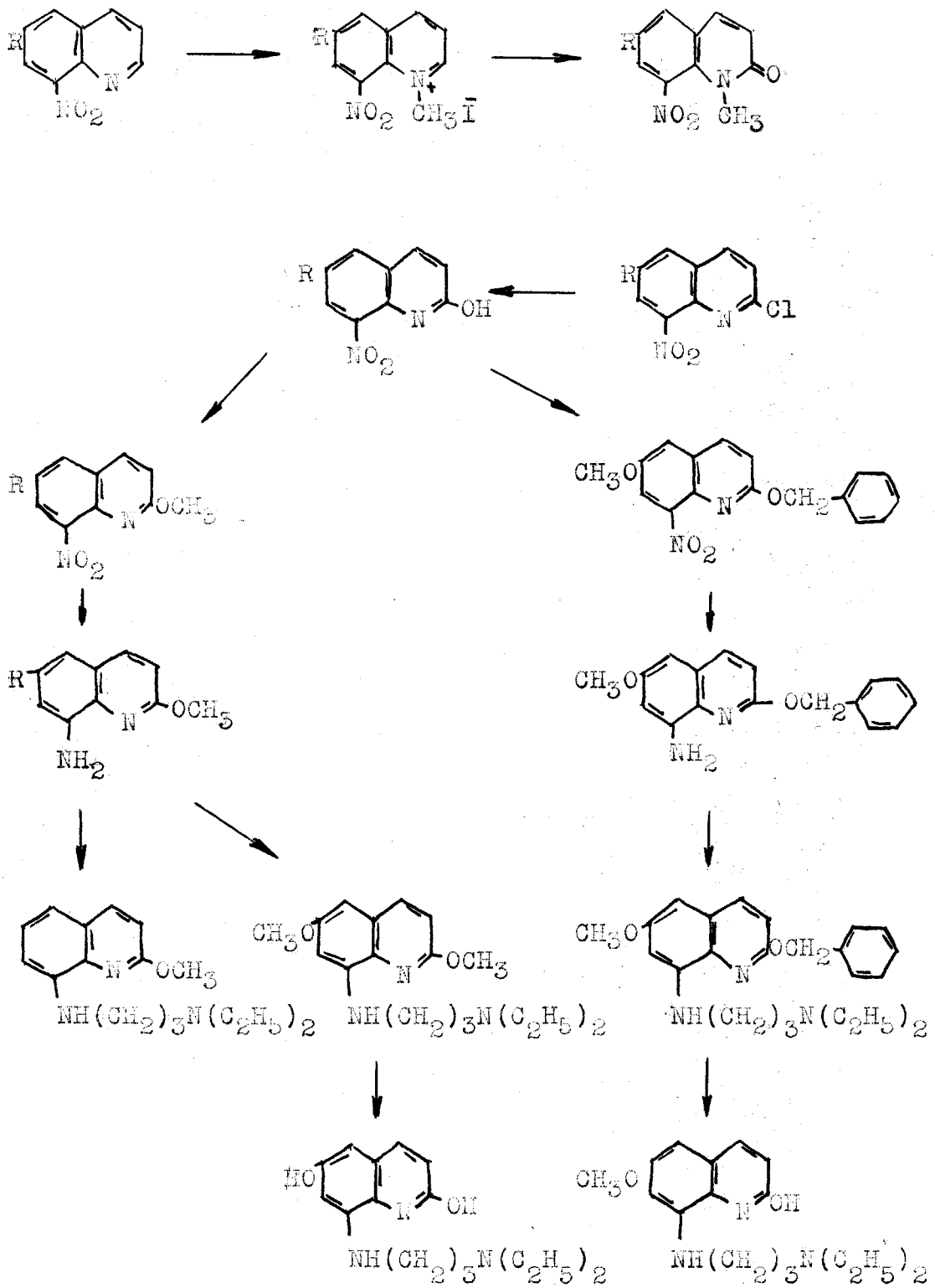
III. 8-(3-Diethylaminopropylamino)-2,6-quinolinediol

$R_1$ - OH $R_2$ - OH

IV. 6-Methoxy-8-(3-diethylaminopropylamino)-carbostyril

$R_1$ - OH $R_2$ - $OCH_3$

Their preparation is indicated in the accompanying general scheme, where R represents -H or -$OCH_3$.


R
N
NO2
CH3I
O
CH3
OH
Cl
OCH3
OCH2
NH2
CH3O
NH(CH2)3N(C2H5)2
HO

I. 2-Methoxy-8-(3-diethylaminopropylamino)-quinoline

8-Nitroquinoline was prepared in 62 per cent yield from o-nitroaniline by the Knüppel modification of the Skraup synthesis (6). Arsenic oxide was used instead of arsenic acid, but that procedure did not improve the yield. The N-methyl iodide derivative (7), prepared in 84 per cent yield, was then oxidized in 68 per cent yield to 1-methyl-8-nitro-2-quinoline (8). This oxidation proceeded more smoothly when 30% hydrogen peroxide, instead of potassium ferricyanide, was used. This method has been used by Ing(9) in the preparation of a different 2-quinolone.

1-Methyl-8-nitro-2-quinolone was converted into 2-chloro-8-nitroquinoline in 85 per cent yield by heating the quinolone with phosphorus pentachloride (8) according to the method of Fischer (10). Subsequent hydrolysis in 20% hydrochloric acid gave 8-nitrocarbostyril (8, 11) in 88 per cent yield. Methylation of the carbostyril with methyl sulfate (7, 12) gave a 79 per cent yield of 2-methoxy-8-nitroquinoline. This compound was first prepared by Decker (12), who believed it to be 1-methyl-8-nitro-2-quinolone, although in a later publication (7) he recognized its true nature. Since no details are mentioned on its preparation, it seems advisable to give them in this work. An attempt to prepare it by reacting 2-chloro-8-nitroquinoline with sodium methoxide was unsuccessful.

Reduction of 2-methoxy-8-nitroquinoline with hydrogen in the presence of platinum oxide gave a 90 per cent yield of 2-methoxy-8-aminoquinoline, and by condensing this compound with 1-diethylamino-3-chloropropane hydrochloride, 2-methoxy-8-(3-diethylaminopropylamino)-quinoline was obtained in 78 per cent yield. The base is very unstable to air and was submitted for testing as the dihydriodide, which, unlike the dihydrochloride, is not hygroscopic.

## Experimental Part[1]

8-Nitroquinoline (6). 880 g. of glycerol, 400 g. of o-nitroaniline (E.K. practical), 254 g. of arsenic oxide and 800 g. of sulfuric acid were refluxed for 3 hours and the desired product was isolated from the reaction mixture following the procedure described by Knüppel (6). The yield was 316 g. (62%). It was found necessary to purify the compound by extracting the crude product with boiling benzene (13).

8-Nitroquinoline Methiodide (7). The procedure used by Decker et al. (7) was found to give excellent yields. A mixture of 109 g. of 8-nitroquinoline and 119 ml. of methyl sulfate was heated on the steam bath for 3½ hours. The solution was diluted with 157 ml. of water and chilled to

[1] All melting points are corrected; microanalyses by Dr. G. Oppenheimer and G. A. Swinehart.

15°. 210 g. of potassium iodide was then added while the solution was stirred vigorously, and the orange-red methiodide precipitated. The yield was 166 g. (84%).

1-Methyl-8-nitro-2-quinolone (8). 195 g. of 8-nitroquinoline methiodide was suspended in 1 lt. of 96% ethanol and 450 ml. of 20 wt.% potassium hydroxide was added. When all of the base had been added, the methiodide dissolved to give a deep red solution which, on standing for a few minutes, set to a crystalline paste, probably due to precipitation of the N-methyl hydroxide. While the paste was stirred vigorously and kept below 45° in an ice bath, 740 ml. of 30% hydrogen peroxide (Dupont "Albone") was added in 50 ml. portions. The reaction was not very vigorous. When all of the peroxide had been added, the suspension was allowed to stand overnight, filtered and the residue washed with 2 lt. of water. 85 g. (68%) of lemon yellow crystals were obtained, which melted at 132-133° (reported (8) 133-134°).

2-Chloro-8-nitroquinoline (8). This compound was prepared by heating a mixture of 72 g. of 1-methyl-8-nitro-2-quinolone and 72 g. of phosphorus pentachloride for 15 min. at 150±5° until effervescence had ceased and refluxing the resulting liquid for 1 hour. From the reaction mixture, 63 g. (85%) of light tan product was isolated, which melted at 151-152° (reported variously at 152° (8) and 149° (11)).

8-Nitrocarbostyril (8, 11). 63 g. of 2-chloro-8-nitroquinoline was refluxed for 2 hours in 500 ml. of 20% hydrochloric acid. The solution was neutralized with 40 wt.% sodium hydroxide, made just acid with 10% hydrochloric acid and cooled. The resulting suspension was filtered and the residue dried to give 50.5 g. (88%) of light yellow crystals of 8-nitrocarbostyril.

2-Methoxy-8-nitroquinoline (7, 12). 40 g. of 8-nitrocarbostyril was dissolved in 900 ml. of hot 10% sodium hydroxide. While the solution was kept hot on the steam bath, 610 ml. of methyl sulfate was added in 100 ml. portions. Between each addition the suspension was stirred vigorously and made alkaline with solid sodium hydroxide. Finally the alkaline solution was cooled, filtered and the residue washed with water until the washings were colorless. The product was recrystallized from ethanol to give 33.8 g. (79%) of colorless crystals, m.p. 122-123° (reported (7, 12) 124-125°).

2-Methoxy-8-aminoquinoline. 24.9 g. of 2-methoxy-8-nitroquinoline was suspended in 500 ml. of absolute ethanol and shaken with hydrogen at 1 atm. and room temperature in the presence of 0.25 g. of platinum oxide. After ½ hour, 9.2 lt. of hydrogen had been taken up, and the rate of hydrogen uptake had decreased to 1 ml./min. Theory

required 9.2 lt. The solution was filtered from the catalyst, the solvent removed and the residual oil distilled in vacuo. The amine came over at 125-129°/0.2 mm. and crystallized readily to give 19.0 g. (90%) of colorless needles, which were recrystallized from ethanol and melted at 75-76°.

Anal. Calcd. for $C_{10}H_{10}ON_2$ (174.2): C, 68.95; H, 5.79; N, 16.08.

Found: C, 68.89; H, 5.79; N, 1606.

1-Diethylamino-3-chloropropane hydrochloride. The bulk of this material was supplied by Columbia University. Part of it was also prepared by reacting 271 g. (1 mole) of C.P. phosphorus tribromide with 189 g. (2 moles) of trimethylene chlorohydrin to give 178 g. (56%) of trimethylene chlorobromide (14). 100 g. (0.63 moles) of this compound was reacted with 129.6 ml. (1.77 moles) of diethylamine to give 34.5 g. (37%) of 1-diethylamino-3-chloropropane (15). The hydrochloride was obtained by passing dry hydrogen chloride through an ethereal solution of the base and removing the solvent (16). The hydrochloride is extremely hygroscopic and has to be kept over sulfuric acid.

2-Methoxy-8-(3-diethylaminopropylamino)-quinoline. The modified (17) procedure of Magidson et al. (18, 19) was followed in this condensation. A solution of 7.0 g.

(0.04 mole) of 2-methoxy-8-aminoquinoline, 16.4 g. (0.2 mole) of sodium acetate and 7.4 g. (0.04 mole) of 1-diethylamino-3-chloropropane hydrochloride in 150 ml. of 66% ethanol was refluxed on the steambath for 5 days, with an additional 7.4 g. of 1-diethylamino-3-chloropropane hydrochloride added each day. At the end of that time the light brown solution was diluted to 300 ml. with water, made alkaline with 150 ml. of 25% sodium hydroxide, saturated with potassium carbonate and extracted three times with 50 ml. portions of ether. The ether extracts were dried over potassium carbonate, the solvent removed and the residue distilled in vacuo under nitrogen. After the unreacted 1-diethylamino-3-chloropropane had distilled at 60-80°/0.5-1.5 mm., the desired base came over as a viscous, yellow oil, b.p. 190-192°/0.15 mm. The yield was 9.0 g. (78%) based on 2-methoxy-8-aminoquinoline.

The base, which is unstable in air, was dissolved in 38 ml. of ethanol and a solution of 8.5 ml. of hydriodic acid (sp. g. 1.7) in 38 ml. of ethanol was added. The solution was diluted with ether until slightly turbid and allowed to stand at 5° overnight. The colorless, crystalline dihydriodide which had come out of solution was filtered, recrystallized from ethanol and dried. It melted at 140-142° (dec.). The yield was 9.6 g. (56.5%)

from the base or an overall yield of 44% based on 2-methoxy-8-aminoquinoline.

Anal. Calcd. for $C_{17}H_{27}ON_3I_2$ (543.2): C, 37.58; H, 5.01; N, 7.74.

Found: C, 37.84; H, 5.15; N, 7.57.

## II. 2,6-Dimethoxy-8-(3-diethylaminopropylamino)-quinoline and 8-(3-Diethylaminopropylamino)-2,6-quinolinediol

The preparation of 2,6-dimethoxy-8-(3-diethylamino-propylamino)-quinoline was analogous to that of 2-methoxy-8-(3-diethylaminopropylamino)-quinoline. The overall yield of the 2,6-dimethoxy base was 17 per cent as compared to 23.6 per cent of the 2-methoxy analogue, based on 6-methoxy-8-nitroquinoline and 8-nitroquinoline respectively. As a whole, the 2-position of this series of compounds was found to be considerably stabilized by the substitution of methoxyl in the 6-position, and more strenuous conditions were required for the preparation of the intermediates.

2,6-Dimethoxy-8-(3-diethylaminopropylamino)-quinoline is even more unstable in air than the 2-methoxy analogue, and it was submitted for testing as the dihydriodide. This derivative was chosen because, unlike the dihydrochloride, it is a non-hygroscopic salt.

8-(3-Diethylaminopropylamino)-2,6-quinolinediol was obtained in 26 per cent yield by hydrolysis of the 2,6-dimethoxy analogue in 20% hydrochloric acid. The base was a high melting solid and was stable in air, in contrast to the 2-methoxy and 2,6-dimethoxy analogues.

## Experimental Part[1]

6-Methoxy-8-nitroquinoline Methiodide. A mixture of 408 g. (2 mole) of 6-methoxy-8-nitroquinoline (Winthrop Tech.) and 380 ml. (4 mole) of methyl sulfate was heated on the steam bath for 4 hours. The hot oil was diluted with 500 ml. of water and the solution cooled and extracted twice with 500 ml. portions of ether. The aqueous layer was heated on the steam bath to expel most of the dissolved ether and cooled to room temperature. 600 g. of sodium iodide was added to the solution while stirring vigorously and cooling in an ice bath, and after the addition was completed, the suspension was stirred for some time, filtered and the residue dried to give 662 g. (96%) of red needles. It was found unnecessary to recrystallize the bulk of the material for the next step. A sample was recrystallized from butanol, and melted at 149°(dec.).

Anal. Calcd. for $C_{11}H_{11}O_3N_2I$ (346.1): C, 38.17; H, 3.20; N, 8.10.

Found: C, 38.26; H, 3.06; N, 8.31.

6-Methoxy-1-methyl-8-nitro-2-quinolone. 242 g. of crude 6-methoxy-8-nitroquinoline methiodide was suspended in 1150 ml. of 96% ethanol in a 4 lt. beaker and 460 ml. of

[1] All melting points are corrected; microanalyses by Dr. G. Oppenheimer and G. A. Swinehart.

20 wt.% potassium hydroxide was added. When all of the base had been added, the methiodide dissolved momentarily to form a deep red solution, which almost immediately set to an orange, crystalline slurry. While the mixture was stirred vigorously and kept at 30-50° in an ice bath, 920 ml. of 30% hydrogen peroxide (Dupont "Albone") was added in 50 ml. portions. The reaction was violent and very exothermic, and it was necessary to wait about 5 minutes between each addition. When all of the peroxide had been added, the suspension was allowed to stand overnight, filtered and the residue washed with 1½ lt. of water. The residue was recrystallized from methanol to give 95 g. (58%) of long, lemon-yellow needles, m.p. 186-187°.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$ (234.2): C, 56.40; H, 4.30; N, 11.96.

Found: C, 56.76; H, 4.21; N, 12.21.

2-Chloro-6-methoxy-8-nitroquinoline. A mixture of 169 g. of 6-methoxy-1-methyl-8-nitro-2-quinolone, 169 g. of phosphorus pentachloride and 3 ml. of phosphorus oxychloride was heated under reflux on an oil bath at 180±5° for 5½ hours. A calcium chloride seal was found to be sufficient protection from moisture. During the heating process, the reaction mixture remained solid. The resulting cake was hydrolyzed by the addition of 1 lt. of water, the suspension

made alkaline with ammonium hydroxide and filtered. The residue was dried, pulverized (10 mesh) and suspended in 1 lt. of cellosolve. The suspension was boiled for 1 minute, chilled to 20° and filtered. The residue was washed with ethanol and dried to yield 133 g. (77%) of colorless crystals, m.p. 225-226°, recrystallized from methyl cellosolve.

Anal. Calcd. for $C_{10}H_7O_3N_2Cl$ (238.6): C, 50.32; H, 2.96; N, 11.74.

Found: C, 50.30; H, 3.00; N, 11.74.

6-Methoxy-8-nitrocarbostyril. A suspension of 125 g. of 2-chloro-6-methoxy-8-nitroquinoline in 1200 ml. of 20% hydrochloric acid was refluxed for 24 hours. Since considerable foaming took place, 3 ml. of capryl alconol was used as a depressant. The suspension was neutralized with 40 wt.% sodium hydroxide and made just acid with 10% hydrochloric acid. It was cooled, filtered and the residue suspended in 1 lt. of boiling water. 40 wt.% sodium hydroxide was added until the solid had dissolved. The hot solution was filtered through Celite, acidified with 10% hydrochloric acid and chilled. The yellow precipitate was filtered and recrystallized from methyl cellosolve to give 96 g. (83%) of golden platelets, m.p. 210-211°.

Anal. Calcd. for $C_{10}H_8O_4N_2$ (220.2): C, 54.54; H, 3.66; N, 12.73.

Found: C, 54.33; H, 3.50; N, 12.87.

2,6-Dimethoxy-8-nitroquinoline. This compound was prepared by the same method as 2-methoxy-8-nitroquinoline. 95.4 g. of 6-methoxy-8-nitrocarbostyril in 2 lt. of hot 10 wt.% sodium hydroxide and 800 ml. of methyl sulfate gave 76.8 g. (76%) of light yellow crystals. The product was recrystallized from ethanol and melted at 149-150°.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$ (234.2): C, 56.40; H, 4.30; N, 11.96.

Found: C, 56.29; H, 4.30; N, 12.03.

2,6-Dimethoxy-8-aminoquinoline. A suspension of 70 g. of 2,6-dimethoxy-8-nitroquinoline and 0.4 g. of platinum oxide in 1 lt. of absolute ethanol was shaken with hydrogen at 1 atm. and room temperature. After 1 hour 21.0 lt. of hydrogen had been taken up, and the rate of hydrogen uptake had decreased to 1 ml./min. Theory required 22.4 lt. The solution was filtered from the catalyst, concentrated to 100 ml., diluted to 1 lt. with water and filtered. The residue was recrystallized from ethanol to give 43.8 g. (72%) of silvery crystals, m.p. 135-136°.

Anal. Calcd. for $C_{11}H_{12}O_2N_2$ (204.2): C, 64.71; H, 5.93; N, 13.72.

Found: C, 64.62; H, 5.88; N, 13.95.

2,6-Dimethoxy-8-(3-diethylaminopropylamino)-quinoline. A solution of 8.2 g. (0.04 mole) of 2,6-dimethoxy-8-aminoquinoline, 16.4 g. (0.2 mole) of sodium acetate and 7.4 g.

(0.04 mole) of 1-diethylamino-3-chloropropane hydrochloride in 150 ml. of 66% ethanol was refluxed on the steam bath for 5 days with an additional 7.4 g. of 1-diethylamino-3-chloropropane hydrochloride added each day. At the end of that time the solution was diluted to 300 ml. with water, made alkaline with 150 ml. of 25 wt.% sodium hydroxide, saturated with potassium carbonate and extracted three times with 50 ml. portions of ether. The ether extracts were dried over potassium carbonate, the solvent removed and the residue distilled in vacuo under nitrogen. After the unreacted 1-diethylamino-3-chloropropane had distilled at 60-80°/0.5-1.5 mm., the desired base came over as a viscous, yellow oil, b.p. 216-218°/0.15 mm. The yield was 11.0 g., 86% of the theory based on 2,6-dimethoxy-8-aminoquinoline.

The base was immediately dissolved in 43 ml. of ethanol. To this solution was added a solution of 9.4 ml. of hydriodic acid (sp.g. 1.7) in 43 ml. of ethanol. The red solution was warmed at 60-70° for a few minutes and chilled at 5° overnight. The dihydriodide which had precipitated overnight was filtered and washed with ethanol to yield 15.2 g. (76%) of colorless needles, recrystallized from ethanol, m.p. 139-140° (dec.).

Anal. Calcd. for $C_{18}H_{29}O_2N_3I_2$ (573.3): C, 37.70; H, 5.10; N, 7.33.

Found: C, 37.91; H, 4.98; N, 7.28.

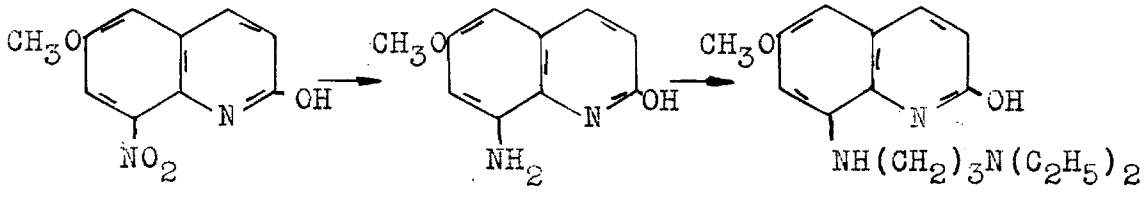
8-(3-Diethylaminopropylamino)-2,6-quinolinediol. 36.5 g. of 2,6-dimethoxy-8-(3-diethylaminopropylamino)-quinoline was dissolved in 182 ml. of 20% hydrochloric acid and the solution refluxed for 4½ hours. The red solution was cooled, neutralized with ammonium hydroxide, and the green gum which precipitated was collected by centrigugation. By stirring and scratching this gum with a few ml. of boiling ethanol, it was possible to convert it into a greenish yellow solid. The solid was recrystallized from methyl cellosolve to give 8.5 g. (26%) of lemon yellow prisms, m.p. 208-210° (dec.)

Anal. Calcd. for $C_{16}H_{23}O_2N_3$ (289.4): C, 66.40; H, 8.01; N, 14.52.

Found: C, 66.14; H, 8.24; N, 14.60.

III. 6-Methoxy-8-(3-diethylaminopropylamino)-carbostyril

Considerable difficulty was encountered in finding a workable synthesis of this compound. The first method of attack was based on the series of reactions:

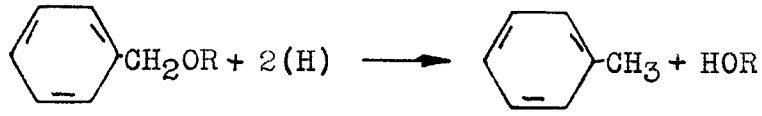



However it was found that 6-methoxy-8-aminocarbostyril, obtained in a 91 per cent yield by the catalytic reduction of 6-methoxy-8-nitrocarbostyril, was an extremely high melting compound which was only slightly soluble in most organic solvents. The condensation with 1-diethylamino-3-chloropropane hydrochloride therefore had to be attempted under heterogeneous conditions, and the starting materials were recovered quantitatively.

The second attempt was based on the assumption that the 2-methoxy group in 2,6-dimethoxy-8-(3-diethylamino-propylamino)-quinoline was more labile than the 6-methoxy group, and that the former could be hydrolyzed preferentially to the latter. However this assumption proved to be fallacious, since even during very short (1 hour) periods of refluxing in 20% hydrochloric acid the 6-methoxy group was hydrolyzed, resulting, in every attempt made, in the

formation of 8-(3-diethylaminopropylamino)-2,6-quinolinediol. It was also anticipated that, even if a procedure of hydrolysis could eventually be worked out resulting in at least partial formation of the 2-hydroxy-6-methoxy derivative, the separation of the 2,6-dihydroxy- and the 2-hydroxy-6-methoxy- derivatives would involve a rather complicated procedure, based on the relative solubilities of the compounds in sodium hydroxide, and probably resulting in a very low yield of the desired product. Therefore this line of attack was abandoned.

The problem was finally solved by making use of the well known hydrogenolysis of benzyloxy compounds to the corresponding alcohols, using palladium catalysts (20,21).




This method, though finding considerable application in sugar chemistry (22,23), had never been applied to pyridine or quinoline benzyloxy derivatives, but it proved to be excellent when it was applied to the present series of compounds.

6-Methoxy-8-nitrocarbostyril was benzylated in alkaline solution with benzyl chloride, giving a 68 per cent yield of the 2-benzyloxy derivative. The latter was reduced with iron and a 0.2% solution of hydrochloric

acid in ethanol to give a 64 per cent yield of 2-benzyloxy-6-methoxy-8-aminoquinoline. The primary amine was then condensed with 1-diethylamino-3-chloropropane hydrochloride in the usual fashion to give an 81 per cent yield of 2-benzyloxy-6-methoxy-8-(3-diethylaminopropylamino)-quinoline, a compound which was unstable in air, though to a much lesser extent than the corresponding 2-methoxy analogue.

Attempts were subsequently made to reduce the benzyloxy base as the dihydriodide derivative, but all proved unsuccessful. The catalysts used were palladium black (24), palladium on charcoal (25) and palladium oxide. In each case 1 g. of the dihydriodide in 100 ml. of absolute ethanol was shaken with an equivalent of 100 mg. of palladium (e.g. 115 mg. of palladium oxide) under hydrogen at 1 atm. and room temperature for 1 hour. In order to determine the amount of hydrogen required by the catalyst itself, the same amount of catalyst suspended in 100 ml. of absolute ethanol was then shaken under the same conditions. Finally 166 mg. of benzyl alcohol, an amount which theoretically would absorb the same volume of hydrogen as 1 g. of the dihydriodide, was shaken with the same amount of catalyst in 100 ml. of absolute ethanol under the same conditions.

It was found that each catalyst reduced benzyl alcohol

quantitatively: palladium on charcoal in 35 minutes, palladium black in 60 minutes and palladium oxide in 11 minutes after a 5 minute lag. When the dihydriodide was used, the hydrogen uptake decreased to 0.25 ml./min. after the amount of hydrogen had been absorbed which was required by the catalyst itself.

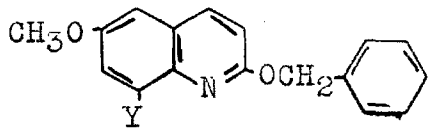
It may be noted that Raney nickel was also used, but no hydrogen was taken up at all. Platinum catalysts were not used since the possibility existed of reducing the benzene ring in the benzyloxy side-chain, thus preventing hydrogenolysis (20).

It was concluded that the iodide ion was responsible for these failures, and the free base was therefore employed in the following attempts at hydrogenolysis. Palladium oxide, since its rate of reducing benzyl alcohol was the highest, was used as a catalyst. It was found that, when absolute ethanol was the medium, the hydrogen uptake virtually stopped after the amount required by the free catalyst had been absorbed. However when a 4% solution of glacial acetic acid in absolute ethanol was used, complete reduction took place in 80 minutes.

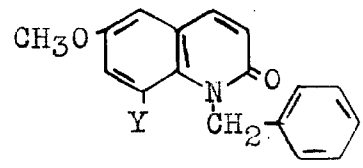
It did not seem feasible to isolate the free base as such from the reaction mixture, which contained an equivalent amount of toluene, and the compound was therefore isolated as the hydriodide. The dihydriodide could not

be prepared, probably because the quinoline nitrogen and the 2-hydroxyl group tautomerize as lactam-lactim, thus destroying the capacity of the nitrogen to accept protons.

It remained to be shown whether benzyl chloride had benzylated the oxygen or the nitrogen of the carbostyril nucleus, that is, whether the benzylated intermediates were of one or the other isomeric forms I and II:

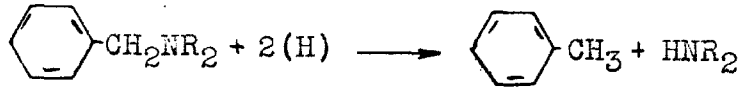


(I)

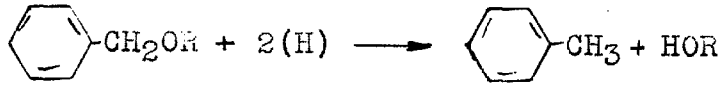


(II)

where Y is $-NO_2$, $NH_2$ and $-NH.CH_2CH_2CH_2.N(C_2H_5)_2$. Either isomer would be expected to be capable of reduction by palladium oxide and hydrogen, the reaction



being as general (21) as



By comparing the absorption spectra of 6-methoxy-1-methyl-8-nitro-2-quinolone, 2,6-dimethoxy-8-nitroquinoline and the "unknown" benzylated compound where Y was $-NO_2$, the isomeric form I was indicated.

## Experimental Part[1]

6-Methoxy-8-aminocarbostyril. A suspension of 67.5 g. of 6-methoxy-8-nitrocarbostyril and 1.0 g. of platinum oxide in 500 ml. of absolute ethanol was shaken with hydrogen at 1 atm. and room temperature. After 4 hours 21 lt. of hydrogen had been taken up, and the rate of hydrogen uptake had decreased to 1 ml./min. Theory required 23.0 lt. The suspension was diluted with 400 ml. of water and filtered. The residue was dissolved in 1 lt. of hot 20% hydrochloric acid, the suspension filtered hot and the filtrate brought to pH 8 with concentrated ammonium hydroxide. The precipitate was filtered and dried to give 53.0 g. (91%) of 6-methoxy-8-aminocarbostyril. The compound was a greyish brown amorphous powder, which could be recrystallized only with difficulty from butanol or methyl cellosolve to give brown crystals, melting above 300°.

Anal. Calcd. for $C_{10}H_{10}O_2N_2$ (190.2): C, 63.14; H, 5.30; N, 14.73.

Found: C, 63.06; H, 5.72; N, 14.73.

2-Benzyloxy-6-methoxy-8-nitroquinoline. 83.7 g. of 6-methoxy-8-nitrocarbostyril was dissolved in 1670 ml. of

[1] All melting points are corrected; microanalyses by Dr. G. Oppenheimer and G. A. Swinehart.

10 wt.% sodium hydroxide, and 480 ml. of benzyl chloride was added to the hot solution. The mixture was stirred vigorously on the steam bath for 8 hours, cooled and allowed to stand overnight. Two layers had formed. The lower, light yellow aqueous layer was syphoned off, and the organic layer, which had set to a black semisolid, was boiled up with 1½ lt. of ethanol. The ethanolic solution was chilled, filtered and the residue recrystallized from ethanol to give 80 g. (68%) of faintly yellow crystals, m.p. 139-140°.

Anal. Calcd. for $C_{17}H_{14}O_4N_2$ (310.3): C, 65.80; H, 4.55; N, 9.03.

Found: C, 65.89; H, 4.73; N, 8.88.

The results of the absorption spectra which were taken to indicate the structure of this compound are summarized in the following Table(I). The solvent used was ethanol, and the concentration of the different compounds in that medium was

| | |
|---|---|
| 6-methoxy-1-methyl-8-nitro-2-quinolone: | 0.216 millimole/lt. |
| 2,6-dimethoxy-8-nitroquinoline : | 0.216 |
| 2-benzyloxy-6-methoxy-8-nitroquinoline: | 0.187 |

Table (I)

| Compound | Maximum | | Minimum | |
|---|---|---|---|---|
| | $\lambda$ (mμ) | $E_{molal}$ | $\lambda$ (mμ) | $E_{molal}$ |
| 6-methoxy-1-methyl-8-nitro-2-quinolone | 373 | 4860 | 307 | 1430 |
| 2,6-dimethoxy-8-nitroquinoline | 349 | 5530 | 297 | 1310 |
| 2-benzyloxy-6-methoxy-8-nitroquinoline | 351 | 4110 | 297 | 1000 |

All measurements were made on a Beckman spectrophotometer.

2-Benzyloxy-6-methoxy-8-aminoquinoline. 61.0 g. of 2-benzyloxy-6-methoxy-8-nitroquinoline and 225 g. of iron by hydrogen were suspended in a solution of 6.7 ml. of 20% hydrochloric acid in 670 ml. of 96% ethanol. The suspension was refluxed with constant mechancial stirring for 6 hours. At the end of that period the suspension was filtered and the residue washed with 350 ml. of 96% ethanol. The filtrate and washings were combined and the solvent stripped off in vacuo at 100°. The residual oil was dark brown and solidified on cooling to yield 45.3 g. (82%) of crude product. It was purified by distilling it in vacuo under nitrogen. The pure product came over at 210-212°/0.2 mm. as a light yellow oil which solidified readily to yield 35.2 g. (64%) of faintly yellow crystals. One recrystallization from 70% ethanol gave colorless needles which were analytically pure and melted at 86-87°.

Anal. Calcd. for $C_{17}H_{16}O_2N_2$ (280.3): C, 72.83; H, 5.75; N, 9.99.

Found: C, 72.95; H, 5.90; N, 10.58.

2-Benzyloxy-6-methoxy-8-(3-diethylaminopropylamino)-quinoline. A solution of 35.2 g. (0.125 mole) of 2-benzyloxy-6-methoxy-8-aminoquinoline, 51.6 g. (0.63 mole) of sodium acetate and 23.3 g. (0.125 mole) of 1-diethylamino-3-chloropropane hydrochloride in 470 ml. of 66% ethanol was refluxed on the steam bath for 5 days, with an additional 23.3 g. of 1-diethylamino-3-chloropropane hydrochloride added each day. At the end of that time the solution was concentrated to 300 ml. and diluted to 1 lt. with water. It was made alkaline with 150 ml. of 25 wt.% sodium hydroxide, saturated with potassium carbonate and extracted three times with 75 ml. portions of ether. The ether extracts were dried over potassium carbonate, the solvent removed and the residual oil distilled in vacuo under nitrogen. 40.2 g. (81%) of condensation product came over at 244-246°/0.06 mm.

The base was dissolved in 124 ml. of ethanol and a solution of 28.5 ml. of hydriodic acid (sp.g. 1.7) in 124 ml. of ethanol was added. The solution warmed up and became red, while crystals appeared almost at once. The suspension was chilled at 5° for 2 hours and filtered. The residue was recrystallized from ethanol to give 45.3 g. (68.5%) of colorless needles, m.p. 124-125°(dec.).

Anal. Calcd. for $C_{24}H_{33}O_2N_3I_2$ (649.4): C, 44.39; H, 5.12; N, 6.47.

Found: C, 44.46; H, 5.41; N, 6.65.

6-Methoxy-8-(3-diethylaminopropylamino)-carbostyril. 11.5 g. of 2-benzyloxy-6-methoxy-8-(3-diethylaminopropylamino)-quinoline[1] was dissolved in 200 ml. of absolute ethanol. To the solution was added 8 ml. of glacial acetic acid and 1.2 g. of palladium oxide[2]. The suspension was shaken under hydrogen at 1 atm. and room temperature. After 80 minutes, 0.95 lt. of hydrogen had been absorbed, and the rate of hydrogen uptake had decreased to 1 ml./min. It may be noted as characteristic of this catalyst that there was a 4 minute lag initially, and that in the following 7 minutes 0.4 lt. of hydrogen were absorbed. Theory required 0.4 lt. of hydrogen for the catalyst and 0.73 lt. for the base, a total of 1.13 lt.

The solution was filtered from the catalyst and 15.5 ml. of hydriodic acid (sp.g. 1.7) in 310 ml. of absolute ethanol was added. The solution was allowed to stand at 5° for 24 hours. At the end of that time the yellow crystals were filtered and recrystallized from ethanol to yield

1 This experiment was performed 8 hours after the base had been distilled from the condensation mixture.

2 Prepared by Dr. M. Rapport of these laboratories.

11.5 g. (91%) of faintly yellow crystals, m.p. 234-235° (dec.), of 6-methoxy-8-(3-diethylaminopropylamino)-carbostyril hydriodide.

Anal. Calcd. for $C_{17}H_{26}O_2N_3I$ (431.4): C, 47.33; H, 6.07; N, 9.74.

Found: C, 47.19; H, 5.99; N, 9.91.

On shaking the hydriodide with 6N sodium hydroxide, a colorless oil was obtained which redissolved in N sodium hydroxide. The free base was not investigated further.

## SUMMARY

Four compounds related to pamaquine have been synthesized in order to determine the effect of a 2-substituent in the quinoline ring on the antimalarial activity and toxicity of this type of drug.

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# PART II.

## Isomorphism in Relation to Serological Specificity.

## INTRODUCTION

The specificity of physiologically active substances has long been recognized in such fields as immunology, enzymatic catalysis and chemotherapeutic action. In immunology particularly, the systematic investigations of K. Landsteiner and others (1) have gradually given rise to the concept that the size and shape of such substances is of fundamental importance. Under the instigation of L. Pauling, stress has now been laid upon the importance of intermolecular forces in biological reactions, and an important parameter of this aspect of the problem is the size and shape of the reacting molecule or the biological agent (2).

Granting that biological agents are highly specific towards differences in size and shape of a molecule with which they react, the next questions which arise are: can a biological agent differentiate between molecules of the same size and shape, regardless of their chemical nature ? and how much can the shape of a molecule be varied before the biological agent is able to " notice the difference " ? In answering these questions, it must be remembered that the specificity is confined only to that part of a molecule which is involved in a biological reaction. The answer to the first question is

then: a biological agent generally is incapable of such differentiation, provided the binding forces between the biological agent and the molecules is of the same nature (i.e. mainly van der Waals attraction, or coulombic attraction, etc.). The second question cannot be answered definitely, since the specificity varies from system to system, but in general small variations in the shape of a molecule change its activity considerably. Thus in the investigations of Landsteiner, which were later supplemented by quantitative studies in These Laboratories (3), it was shown that the substitution of a methyl for a hydrogen in a hapten may lower a hapten inhibition constant to one tenth of the original value (4). The activities of the vitamin nicotinamide and of the analeptic agent Coramin are destroyed by the introduction of 2-methyl groups into their pyridine nuclei (5,6). On the other hand, 2-methylnaphthoquinone (7) and 2-methylthionaphthoquinone (2) both have vitamin K activity. Here the absence of the phytyl group present in the vitamin itself shows that this part of the molecule is not involved in the biological reaction; yet the substitution of a thiophene ring for a benzene ring did not destroy the activity. Indeed the replaceability of the benzene ring by the thiophene ring, and the pyridine ring by the thiazole ring, in various biological systems has been demonstrated in

numerous cases (2, 8-12).

In this connection it is interesting to note that camphor and pinacol, despite their different chemical nature, have approximately similar odors, because they have in common a quasi-globular shape (13).

This dependence of biological activity on shape, its variation with change in shape, and the fact that substances with similar shape react similarly with biological agents (vide supra) (all regardless of chemical structure provided we restrict our discussion to non-polar parts of a molecule) suggest that the criterion of isomorphism (see below) may be applied to such substances. In other words, substances which replace each other in one another's crystal lattice (forming solid solutions) because of similarity in external shape should be expected to act similarly as biological agents, by the same criterion. The idea has been the subject of some investigation, principally by Erlenmeyer and Lettré.

However the questions which must first be answered are : is solid solution formation observed, provided the components have similar size and shape, regardless of the chemical nature of the components? and: how much can a molecule be varied before solid solution formation is no longer attained?[1] These questions were purposely phrased

[1]This question composes the study of morphotropy, so-called by Groth in 1870 (16).

in terms analogous to those on page 36.

In the discussion of these problems, we shall have to use the term isomorphous, which in the past has been used with perhaps more connotations and interpretations than any other. For our purposes, we shall define it as follows: Two substances which, because of certain metrically and energetically similar lattice planes and plane spacings, form solid solutions[1] are called isomorphous[2]. The definition is almost cyclical, since we are considering a priori only those pairs where analogy is expected from consideration of the molecular size and form. However it is only these pairs which are of real interest to us, and we shall avoid artificial classifications (17) and terms like anomalous isomorphism (14, 17-19). Such pairs would by implication have similarly sized molecules and polarization properties.

For a study of morphotropy, organic compounds are best suited, since non-polar constituents can be gradually varied to assume various sizes and shapes.

One of the first of such studies was performed by Ciamician (22, 23), who concluded that organic ring systems with the same number of rings form isomorphous pairs,

[1] Other criteria which we could have chosen are overgrowth and parallel growth.

[2] Neuhaus (14) called this "partielle Isomorphie", Kofler (15) "Massenisomorphie", Weygand (20, 21) "Correspondenz".

i.e. the pairs benzene-thiophene and fluorene-phenanthrene. His experimental results are not to be trusted, however ( Jaeger (38); This Thesis).

Grimm (24, 25) proposed in his "Hydridverschiebungssatz" that isomorphously replaceable groups ("pseudoatoms") could be arranged periodically as the hydrides of non-metallic elements; thus N≡ and CH≡ ; O=,NH= and $CH_2$=, etc., are isomorphously equivalent. This theory, while being supported by an abundance of experimental evidence, is conjectural and has many exceptions; nevertheless it was the basis for the arguments used by Erlenmeyer (8-11) in his attempts to correlate structure and physiological activity.

Other workers (26-32) have shown that the valence angle of pseudoatoms is of importance in considerations of isomorphism ( thus diphenylmethane and diphenyl ether are not isomorphous whereas fluorene and diphenylene oxide are).

Lettré (33), in a study of the isomorphous replaceability of different groups in substituted benzoic acids, found that -H is not isomorphous with -Cl, -Br, -I, $-CH_3$, -OH, $-OCH_3$, or $-NO_2$;[1] that $-CH_3$ is isomorphous with -Cl and -Br but not with -I; that -Cl, -Br and -I are isomorphous; and that $-NO_2$, -OH and $-OCH_3$ are not isomorphous with any group[2]. This isomorphous replaceability is res-

[1] but benzoic acid is isomorphous with p-fluorobenzoic acid (34).

[2] exceptions:the pairs o-nitrobenzoic acid vs. o-toluic, o-chlorobenzoic and o-bromobenzoic acids form solid solutions.

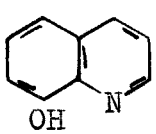
tricted to the benzoic acids, and in another type of compound these groups may or may not be isomorphous. The abnormal behavior of the $-NO_2$, $-OCH_3$ and -OH groups (cf. also footnote 2, p.40) may be attributed to intermolecular hydrogen bonding .

Finally it may be mentioned that stereoisomers of the same compound usually are not isomorphous (16a, 35).

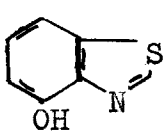
The questions concerning morphotropy which we have asked above may now be answered. Solid solution formation is generally observed, provided the components have approximately similar lattice planes and spacings, and regardless of their chemical nature. The extent of morphotropy is definitely a functions of the type of molecule in question, but, in general, small variations may preclude the formation of solid solutions.

Thus almost complete analogy is attained between the two problems which we are attempting to correlate: isomorphism and serological specificity.

Evidence for such a correlation is abundant. To mention a few examples: thiophene and benzene are isomorphous and can generally replace each other in biological systems (9, 12). 8-hydroxyquinoline (I) and 4-hydroxybenzothiazole (II) are isomorphous (39) and thiazole and pyridine

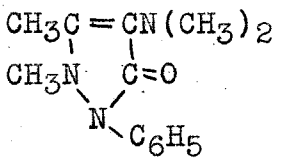



(I)

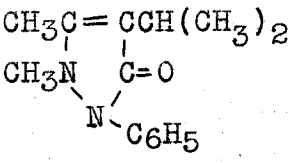



(II)

can generally replace each other in biological systems (10)[1]. Globular molecules of the camphor type are isomorphous and have similar odors (13). Pyramidone (I) and isopropyl antipyrine (II) are isomorphous and both



(I)



(II)

powerful antipyretics (36). Phosphoric and arsenic acid salts are isomorphous and antigens with arsonic and phosphonic acid haptens crossreact (3). Finally, the substituted benzoic acids which are isomorphous (33) crossreact to about the same extent (4).[2]

It must be kept in mind that: a) in biological reactions only part of the molecule may be involved (and specific) whereas in the crystal the same molecule is completely surrounded by others. It is therefore isomorphism which is the more delicate criterion. b) <u>In vivo</u>, the molecule is in solution, and thus may have a different effective form than in the crystal. The hy-

1 The phase relationship of the pair thiazole-pyridine is not known. While nicotinic acid and 5-thiazolecarboxylic acid form solid solutions (This Thesis), the following pairs are not isomorphous: nicotinamide vs. 5-thiazolecarboxamide (40); 2,2'-dithiazolyl vs. 2,2'-dipyridyl (41); 4,4'-dithiazolyl vs. 2,2'-dipyridyl (41); 2,2'-dithiazolyl vs. 4,4'-dithiazolyl (41).

2 exceptions: the o-nitrobenzoic acid systems (footnote 2, p.40)

drogen bonding and charge of a molecule (especially an acidic molecule) may cause the criterion of isomorphism to break down when applied to biological specificity.

It is therefore not surprising that many substances which crossreact biologically[1] are not isomorphous; and that the absence of isomorphism does not mean the absence of crossreactivity. We may however state the hypothesis: Two substances which are isomorphous will generally crossreact (and its corollary: the absence of biological crossreactivity generally means the absence of isomorphism).

As stated, the hypothesis is too qualitative to be more than a working rule. It would be of interest to correlate semi-quantitatively the mutual solubility (in the solid state) of two substances, and their hapten inhibition constants. Since, however, such a program would involve the preparation of many antisera, and since, furthermore, morphotropy usually causes a change from complete solubility to insolubility[2], it was decided that the working rule (vide supra) should first be investigated more systematically.

For this purpose we chose the group of simple aromatic heterocyclic systems, such as furan, thiazole etc. The

[1] the term being used in its broadest sense, i.e. substances which have similar biological activity (inhibition to that activity included).

[2] For a fairly complete list of phase relationships, cf. (37).

efforts of Erlenmeyer and others (8-12) to correlate isomorphism and biological activity were restricted mainly to the systems benzene-thiophene and pyridine-thiazole. Landsteiner and Scheer (42) showed that 2-thiophenecarboxylic acid inhibited benzoic acid extremely well; that nicotinic acid, furoic acid, picolinic acid and 2-pyrrolecarboxylic acid all inhibited benzoic acid to an intermediate extent.

The substances chosen for this research were carboxylic acids. Not only are these substances soluble at serological pH, but their melting points lie in a range (100-300°) convenient for the ready determination of phase relationships.

Specifically, it was our intention that this research should investigate the following problems, which are of interest to the study of morphotropy as well as immunology:

a) Are the carboxy derivatives of the heterocyclic ring systems benzene, furan, thiophene, pyrrole, pyridine, pyrazine and thiazole isomorphous ?

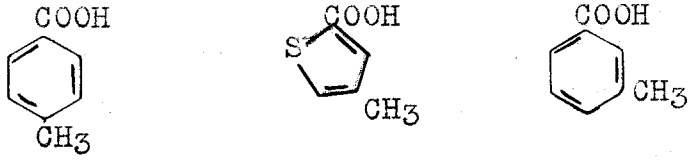
Of the simple rings, only the pairs benzene-thiophene (solid solution (43)) and benzene-pyridine (normal (45)) have been investigated. Of the derivatives of these ring systems (not counting condensed ring systems), the investigations have been restricted to the derivatives of pyridine and thiazole, mentioned on p. 42 (footnote 1) and

to a number of systems containing the pyrrole, the furan and the thiophene ring (22, 23)[1]. This latter investigation is highly unreliable (38).

b) What is the effect of changing the position of the carboxyl group on the ring, i.e. are the changed and original molecules isomorphous ?

Voerman (46) reported that 2- and 3-thiophenecarboxylic acids formed partial solid solutions. It would be interesting to investigate the isomorphism of 2-, 3- and 4-pyridinecarboxylic acids. The results of this investigation are part of This Thesis.

c) If the sulfur atom in thiophene is sterically and electronically analogous to a vinyl group (e.g. thiophene vs. benzene), then it would be of special interest to test the phase relationship of the pairs p-toluic acid vs. 5-methyl-2-thiophenecarboxylic acid, m-toluic acid vs. 4-methyl-2-thiophenecarboxylic acid and o-toluic acid vs. 3-methyl-2-thiophenecarboxylic acid. Especially crucial would be the second of these pairs, along with the pair p-toluic acid vs. 4-methyl-2-thiophenecarboxylic acid:




This last experiment was unfortunately made impossible

[1] cf. also (20) concerning chalcones, thiophene-chalcones and furan-chalcones.

for the time being, since the small yield of 4-methyl-2-thiophenecarboxylic acid could not be obtained in sufficient purity to warrant the determination of phase equilibria.

d) Keeping the heterocyclic ring constant, will substituents which are usually isomorphous retain that property ? This was tested on the -Br and -$CH_3$ derivatives of 2-thiophenecarboxylic acid.

e) If these heterocyclic acids were to be used as haptens in inhibition experiments against anti-$X_p$, anti-$X_m$ and anti-$X_o$, would there be a dependence of the inhibition constant on the results of a)-d), thus giving added weight to the hypothesis that substances which are isomorphous will crossreact ?

The hapten inhibition experiments which are necessary were rendered partly superfluous by the general absence of isomorphism in pairs containing benzoic acid as one of the components (cf. Discussion of Results). Other hapten inhibition experiments which were contemplated have been held up for reasons beyond the control of the author.

## I. Techniques and apparatus for the determination of phase diagrams

The three principal methods of determining temperature-composition diagrams are 1) the cooling curve method, 2) the capillary method, and 3) the hot stage method. An adequate review of the scope of these methods has been published (47).

The relative advantages of the three methods have been compared by Grimm et al. (24) in a fairly exhaustive study of forty-five pairs of substances. His findings show that method 1) gives extremely uncertain results at the s-phase boundary. This fact, coupled with the fact that thermal analysis requires relatively large amounts of material (of the order of one gram) and hence is useless as a micromethod, leaves for consideration only the other two methods. In the present investigation, a combination of both was used: the capillary rested on a hotstage. This has the following advantages of both methods: (a) Decomposition and sublimation can be satisfactorily observed, and at the same time a fairly accurate determination of the thawing point can be made despite initial sublimation. (b) No temperature correction is needed for a properly constructed setup. (c) The initial heating may be very rapid, and may be controlled with great ease. (d) The use of a microscope permits detailed observation of the melting process. A polarizing attachment facilitates observing the change from anisotropy to isotropy.

The microtechnique developed by Kofler (48-52), while more elegant than the hotstage-capillary method, requires photographic attachments and considerable practice. We therefore thought it more expedient to use the more conventional method for this research.

A. Apparatus.

The apparatus consists essentially of a melting-point block mounted on a polarizing microscope. The block was patterned after the one described by Vold and Doscher (53). I wish at this point to express my indebtedness to Dr. Doscher for valuable advice personally given me on the construction of the block and modifications thereof.

The block is machined from "Sil-O-Cel C-22" Celite-Magnesia bricks (Marine Eng. and Supply Co., Los Angeles); details of its construction may be found in reference (53). Minor modifications include a) the use of a rectangular (1"x 9/16"x 1/2") copper strip, instead of the circular strip described in the paper (53), in order to heat the capillary more uniformly; b) the outside of the block was painted with 40 Be. sodium silicate solution and dried in the oven at 130° for two hours. This prevents cracking or chipping of the otherwise fairly brittle Sil-O-Cel.

Heating was accomplished electrically by means of a

no.26 Nichrome wire, looped through the block and embedded in asbestos fiber. Heating was controlled by means of a variac, in series with a 20 ohm heating element.

The samples rested next to the junction of a no.30 B&S gage iron-constantan thermocouple, on top of a small glass plate. The e.m.f. (0.05 mv./ °C) was measured by means of a Leeds and Northrup student potentiometer and a box-type galvanometer with a sensitivity of 0.03 $\mu$a/mm., permitting readings of the accuracy of 0.2°C.

The thermometer was looped twice within the air-space, in order to avoid temperature corrections.

The temperature was computed from standard calibration tables. The apparatus is usable from room temperature to 295°C (corresponding to 16 mv.), the cold junction being at 0°C.[1]

The 32 mm. (4x) objective, in conjunction with an 8x eyepiece, was found to give ample magnification. Observation of the melting process was facilitated by the use of a selenite compensator.

In order to permit a controlled temperature rise at any given temperature, a series of temperature-time curves were plotted for a number of variac voltages.

[1] At higher temperatures, the capillary was immersed in an oil bath, and the melting point observed by the conventional method.

B. Preparation of the mixtures

(a) Preparation of the pure components

The following reagents (EKC white label) were recrystallized from water to constant melting point.

p-Toluic acid, m.p. 177-178°

m-Toluic acid, m.p. 110-111°

o-Toluic acid, m.p. 104-105°

p-Bromobenzoic acid, m.p. 252-253°

Nicotinic acid, m.p. 233°

Benzoic acid, m.p. 121-122°

Pyrazinecarboxylic acid, m.p. 224-226° (dec.)

Picolinic acid, m.p. 136-137°

Furoic acid, m.p. 132-133°

The following acids were prepared by different series of reactions.

Isonicotinic acid was prepared by passing hydrogen sulfide through a suspension of its copper salt (kindly supplied by Dr. D. R. Howton). m.p. 312-314° dec. (sealed tube). Reported: 317° (55); 315° (56).

5-Thiazolecarboxylic acid was prepared as follows. Ethyl formate was condensed with ethyl chloroacetate in the presence of potassium ethoxide (57) to give a 39% yield of formyl-chloroacetic acid ethyl ester (58). The condensation product was reacted with thioformamide (59) to give a 25% yield of 5-carbethoxythiazole (60).

Hydrolysis of the ester in ethanolic potassium hydroxide yielded the desired 5-thiazolecarboxylic acid (60), m.p. 218-220° (dec.)(reported 218° (61)).

2-Thiophenecarboxylic acid was prepared by iodinating thiophene (Socony-Vacuum) in the presence of mercuric oxide (62) and converting the resulting 2-iodothiophene into the desired acid by the Grignard synthesis (63), the overall yield being 15%. Successive recrystallizations from water and ligroin-benzene gave colorless needles, m.p. 127-128°.

3-Thiophenecarboxylic acid was prepared by the following series of reactions. Ethyl crotonate (64) was prepared by the esterification of crotonic acid (EKC practical) with ethanol in the presence of sulfuric acid, in a 56% yield. Treatment of the ester with potassium cyanide and barium hydroxide resulted in a 70% yield of methylsuccinic acid (65). The sodium salt of this acid was heated with phosphorus trisulfide to give a 23% yield of 3-methylthiophene (66). The procedure for the ring closure was based on the preparation of thiophene by Phillips (67) and comments by Steinkopf (68). Oxidation of 3-methylthiophene with alkaline potassium permanganate (69, 70) gave a 3.7% yield of 3-thiophenecarboxylic acid. Successive re-

crystallizations from water, ligroin-benzene and subsequent sublimation gave colorless platelets, m.p. 137-138°.

3-Methyl-2-thiophenecarboxylic acid (71) was prepared by iodinating 3-methylthiophene (cf. p. 51), preparing the Grignard reagent of the resulting 2-iodo-3-methylthiophene, forming the carbon dioxide adduct, and hydrolyzing, to give the desired acid (m.p. 146-147° after three recrystallizations from water). The yield on the basis of 3-methylthiophene was 44%.

5-Bromo-2-thiophenecarboxylic acid , m.p. 140-141° was prepared in a 34% yield by the direct bromination of 2-thiophenecarboxylic acid in glacial acetic acid (72).

5-Methyl-2-thiophenecarboxylic acid was prepared as follows. Levulinic acid was heated with phosphorus trisulfide to give a 8.5% yield of 2-methylthiophene (73), the procedure of Phillips (67) being employed. Iodination (cf. (62)) of that compound gave a 80% yield of 5-iodo-2-methylthiophene (74). This compound gave a 55% yield of 5-methyl-2-thiophenecarboxylic acid (74), m.p. 138-139°, by the Grignard synthesis.

4-Methyl-2-thiophenecarboxylic acid could not be purified sufficiently to warrant its use as a component.

It was prepared as follows. Ethyl 2-bromopropionate (75) was prepared in a 77% yield by refluxing 2-bromopropionic acid and ethanol in the presence of sulfuric acid. The condensation of this ester with acetoacetic ester in the presence of sodium ethoxide resulted in a 66% yield of ethyl 2-aceto-3-methylsuccinate (75). The hydrolysis of the condensation product by 3N hydrochloric acid gave a 73% yield of α-methyllevulinic acid (75) which, on heating with phosphorus trisulphide in the usual fashion, gave a 18.5% yield of 2,4-dimethylthiophene (71, 76). Oxidation of this compound with alkaline potassium permanganate (71, 76) gave a 4.7% yield (0.45 g.) of crude 4-methyl-2-thiophenecarboxylic acid, m.p. 95-108°. Recrystallization from benzene, sublimation and four recrystallizations from ligroin raised its melting point to 110-119° (reported (76) 118-119°). Since only 0.1 g. of material was left, further attempts at purification were abandoned.

2-Pyrrolecarboxylic acid was prepared as follows. Pyrrole was prepared in a 31% yield by the pyrolysis of ammonium mucate (77). 2-Pyrrolecarboxylic acid (78, 79) was obtained in a 24% yield by treating pyrrole with methyl magnesium iodide, forming the carbon dioxide adduct and hydrolyzing (a procedure described in detail by Fischer (80)). The acid melted at 190° (dec.).

(b) Preparation of samples of the mixtures

Weighed amounts of the two components are loosely mixed in 2 ml. pyrex beakers, and then thoroughly ground up with the flattened end of a small stirring rod.[1] The average mixture weighs 10 mg.

In the case of the acids investigated (many of which sublime and decompose), this method of preparing samples is superior to the melting-solidifying-crushing technique (for a critical analysis of preparation of samples cf. (24)).

Two melting point tubes are then filled with the mixture and sealed about 15 mm. from the end. The two samples give a check on the homogeneity of the mixture.

C. Observational procedure

(a) Beginning of melting (thawing point)

In this, as in the other cases, the heating rate was $2\pm1^{\circ}$/min. The thawing point caused much difficulty in the beginning, because transmitted light was used, and the amount of liquid (especially in mixtures of composition close to one of the pure components) was too small to be detected. The technique which finally gave reproducible

[1] Care must be taken in weighing the individual components into the beaker, so that the resulting mixtures will be fairly evenly distributed over the composition range. On the average, 9 to 10 such mixtures are prepared per diagram, except when one of the components is available in only very small quantities.

results consisted in observing the beginning of melting by bright reflected light. By observing the tip of the capillary, the thawing point can be very accurately noted. Sometimes, as in the case of partial solid solution formation, the first droplets resolidify; this phenomenon can, with some practice, be recognized unequivocally.

(b) End of melting (melting point)

This point is readily determined as the disappearance of the last crystal. The polarizing microscope facilitates this observation, transmitted light being used.

(c) Decomposition

In many cases, decarboxylation, demonstrated by the evolution of bubbles, is observed before all of the material has melted. This has the effect of lowering the liquidus, but it has no effect on the position of the s-phase boundary (cf. Discussion of Results).

D. Reliability of results

The accuracy of the method, as judged by the reproducibility of the results, is $\pm 2^{\circ}$ for the thawing and melting points and $\pm 4^{\circ}$ for the decomposition points (beginning of decomposition). In order to compare the results of the method with reported results, two typical phase diagrams were plotted, both of which had been reported by Lettré et al. (54). These authors used both the capillary method and the hot stage method, their results

being the average of several determinations. In the preparation of their samples they used the melting-resolidifying-crushing technique. The results of the comparison are reported graphically in figs. I and II. The check is satisfactory.

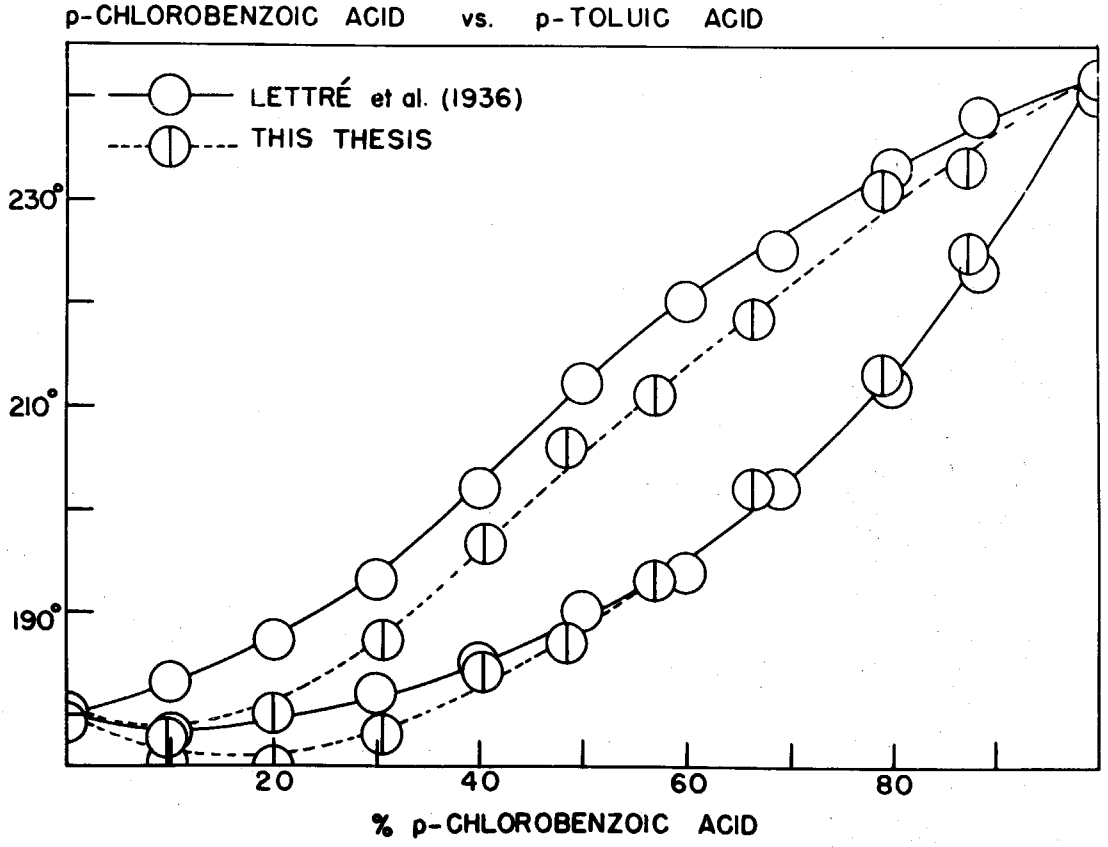



Fig. I

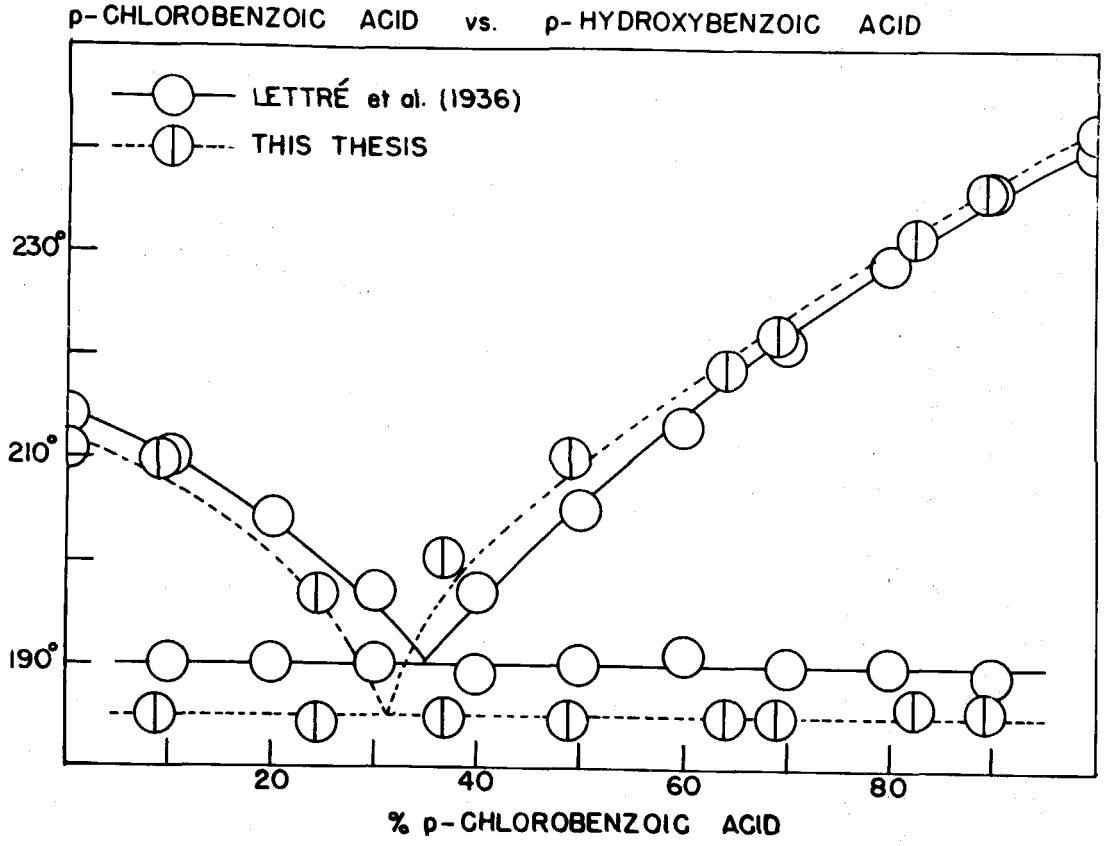



Fig. II

E. Example of a typical determination

The results of all the determinations will be reported in terms of the temperature-wt.% composition coordinates of the points only. The following, in tabular form, are the data leading to the final results. The example chosen is the pair Benzoic acid (A) vs. Furoic acid (B). Table I gives the results of the weighing of the mixtures; table II gives the results of the determination of the various melting ranges corresponding to the different mixtures.

Table I

Weighings

| Beaker no. | Wt. empty (g.) | Wt. plus A (g.) | Wt. plus B (g) | Net wt. A (mg) | Net wt. B (mg) | Total wt. A plus B | Wt.% A |
|---|---|---|---|---|---|---|---|
| 1 | 1.4969 | 1.5059 | 1.5073 | 9.0 | 1.4 | 10.4 | 86.5 |
| 2 | 1.4542 | 1.4628 | 1.4653 | 8.6 | 2.5 | 11.1 | 77.5 |
| 3 | 1.3680 | 1.3751 | 1.3786 | 7.1 | 3.5 | 10.6 | 66.9 |
| 4 | 1.3519 | 1.3585 | 1.3635 | 6.6 | 5.0 | 11.6 | 57.0 |
| 5 | 1.5100 | 1.5153 | 1.5209 | 5.3 | 5.6 | 10.9 | 48.6 |
| 6 | 1.5730 | 1.5777 | 1.5842 | 4.7 | 6.5 | 11.2 | 42.0 |
| 7 | 1.4797 | 1.4834 | 1.4925 | 3.7 | 9.1 | 12.8 | 28.9 |
| 8 | 1.4832 | 1.4862 | 1.4970 | 3.0 | 10.8 | 13.8 | 21.7 |
| 9 | 1.3942 | 1.3954 | 1.4058 | 1.2 | 10.4 | 11.6 | 10.4 |

## Table II

Melting ranges

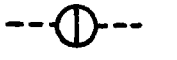
| Beaker no. | Tube no. | THAWING POINT | | | MELTING POINT | | |
|---|---|---|---|---|---|---|---|
| | | MV. | Aver. | °C | MV. | Aver. | °C |
| 1 | 1 | 4.48 | 4.48 | 85.1 | 5.80 | 5.87 | 110.8 |
| | 2 | 4.48 | | | 5.94 | | |
| 2 | 1 | 4.42 | 4.48 | 85.1 | 5.60 | 5.58 | 105.5 |
| | 2 | 4.53 | | | 5.56 | | |
| 3 | 1 | 4.44 | 4.47 | 85.0 | 5.00 | 5.06 | 96.0 |
| | 2 | 4.49 | | | 5.12 | | |
| 4 | 1 | 4.45 | 4.47 | 85.0 | 5.00 | 5.02 | 95.2 |
| | 2 | 4.48 | | | 5.05 | | |
| 5 | 1 | 4.52 | 4.50 | 85.5 | 5.89 | 5.78 | 109.2 |
| | 2 | 4.48 | | | 5.67 | | |
| 6 | 1 | 4.47 | 4.49 | 85.3 | 6.05 | 6.08 | 114.5 |
| | 2 | 4.50 | | | 6.10 | | |
| 7 | 1 | 4.46 | 4.47 | 85.0 | 6.50 | 6.46 | 121.5 |
| | 2 | 4.47 | | | 6.42 | | |
| 8 | 1 | 4.45 | 4.48 | 85.1 | 6.60 | 6.60 | 124.0 |
| | 2 | 4.50 | | | — | | |
| 9 | 1 | 4.47 | 4.52 | 85.8 | 6.81 | 6.76 | 127.2 |
| | 2 | 4.55 | | | 6.70 | | |

## II. Phase relationships of pairs of different carboxylic acids.

The data given on the following pages are plotted as phase diagrams, the coordinates being temperature and wt.% composition. The symbols for the points are

point on phase boundary.

beginning of decomposition.



point not representing an equilibrium condition (such as melting point after decomposition has set in).

initial melting with subsequent resolidification.

Excepting a few cases, no line has been drawn through points not representing an equilibrium condition.

The diameter of the circles and the height of the triangles indicates the precision of the measurements.

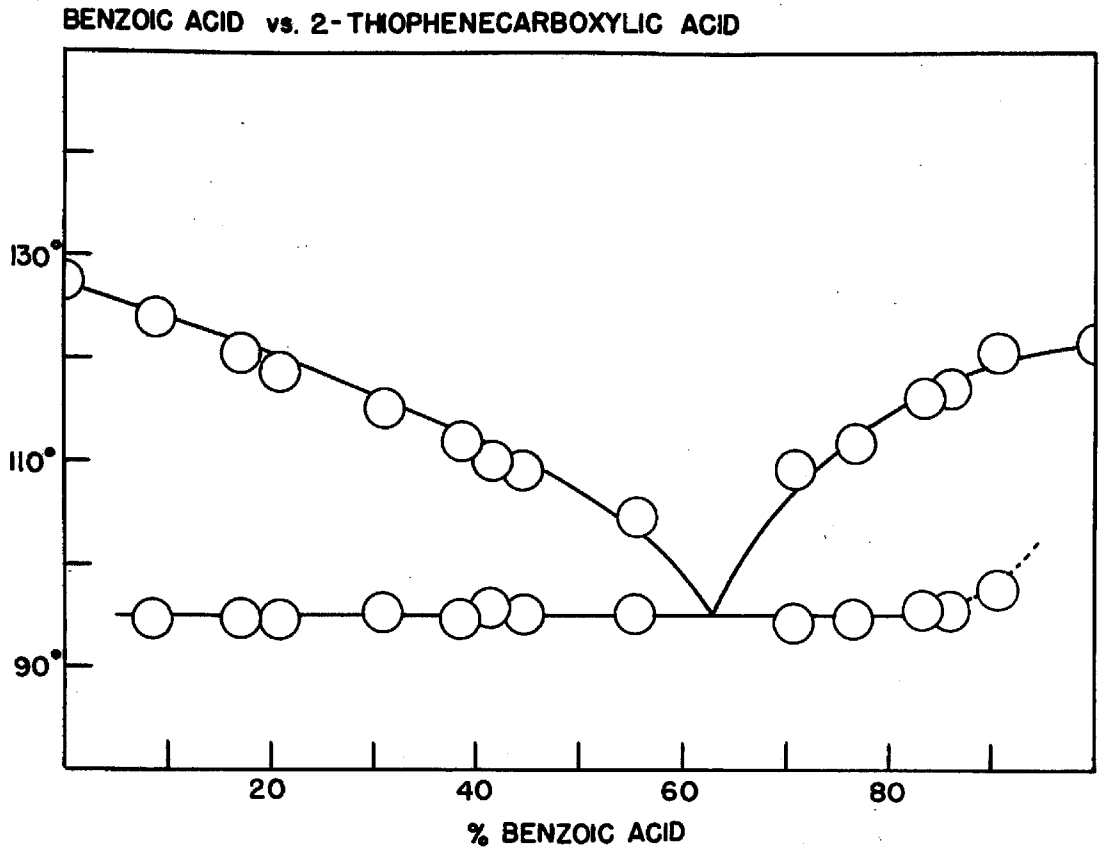
In the tabulations which accompany each phase diagram, the percentage compositions refer to the component indicated on the diagram. The abbreviations designate, respectively:

Th.p. - Thawing point

M.p. - Melting point

Dec.p.-Decomposition point

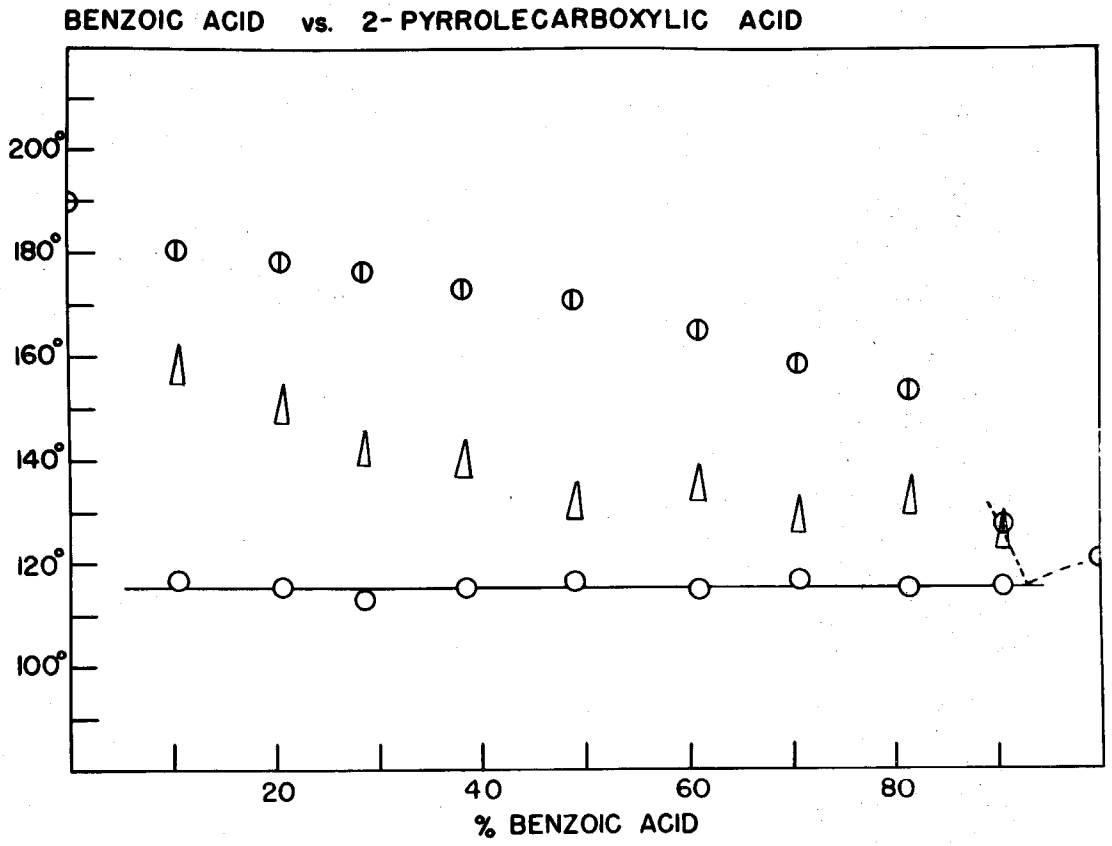
A. Data




Benzoic acid (A) vs. 2-Thiophenecarboxylic acid

| % A | 0 | 8.4 | 17.1 | 20.7 | 30.8 | 38.3 | 41.5 | 44.5 |
|---|---|---|---|---|---|---|---|---|
| Th.p. | 127 | 94.6 | 94.8 | 94.8 | 95.4 | 94.8 | 95.8 | 95.2 |
| M.p. | 128 | 123.8 | 120.4 | 118.6 | 115.2 | 112.0 | 110.2 | 109.2 |

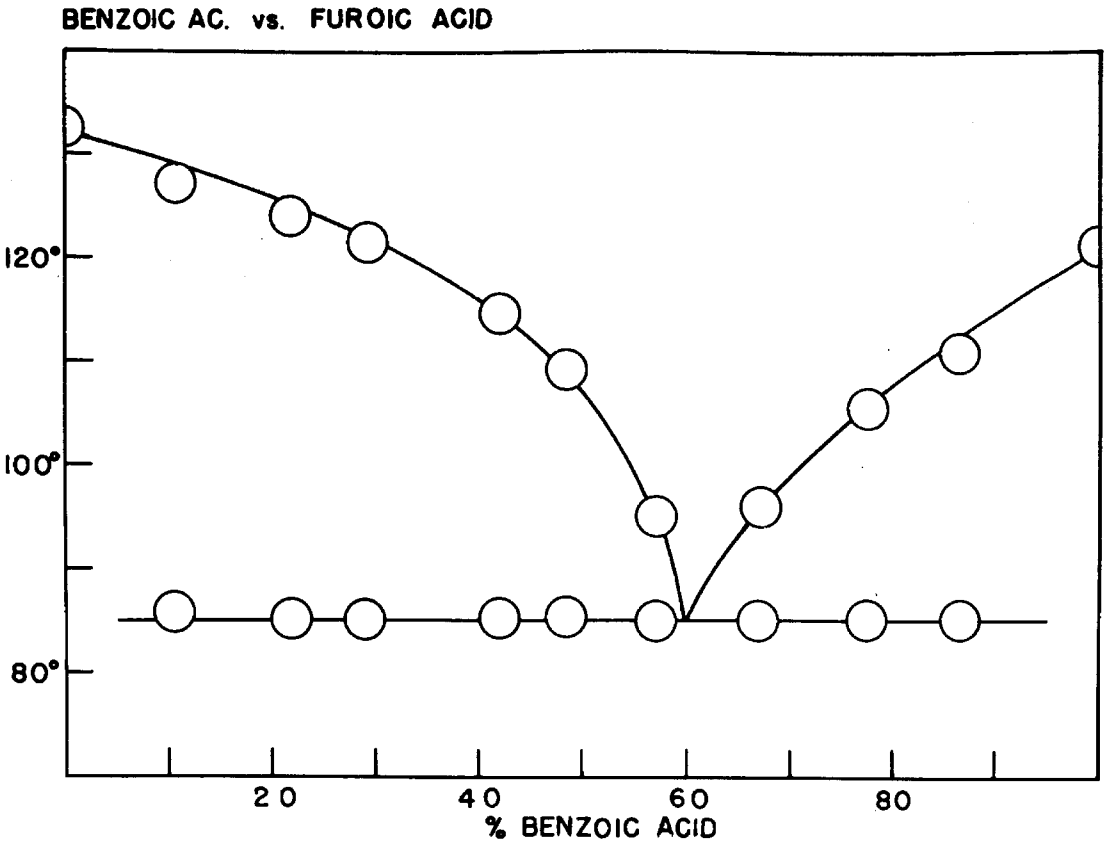
| % A | 55.5 | 71.0 | 76.7 | 83.5 | 86.0 | 90.3 | 100 |
|---|---|---|---|---|---|---|---|
| Th.p. | 95.4 | 94.4 | 94.8 | 95.6 | 95.6 | 97.6 | 121 |
| M.p. | 104.8 | 109.2 | 111.6 | 116.2 | 117.0 | 120.6 | 122 |




Benzoic acid (A) vs. 2-Pyrrolecarboxylic acid

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| % A | 0 | 10.3 | 20.6 | 28.7 | 38.3 | 49.0 | 61.1 | 70.7 |
| Th.p. | 190 | 116.8 | 115.6 | 113.2 | 115.6 | 116.4 | 115.0 | 116.8 |
| Dec.p. | 190 | 158.4 | 150.6 | 142.4 | 140.6 | 132.4 | 136.0 | 129.6 |
| M.p. | 190 | 180.4 | 178.4 | 176.2 | 172.8 | 171.2 | 165.0 | 158.2 |

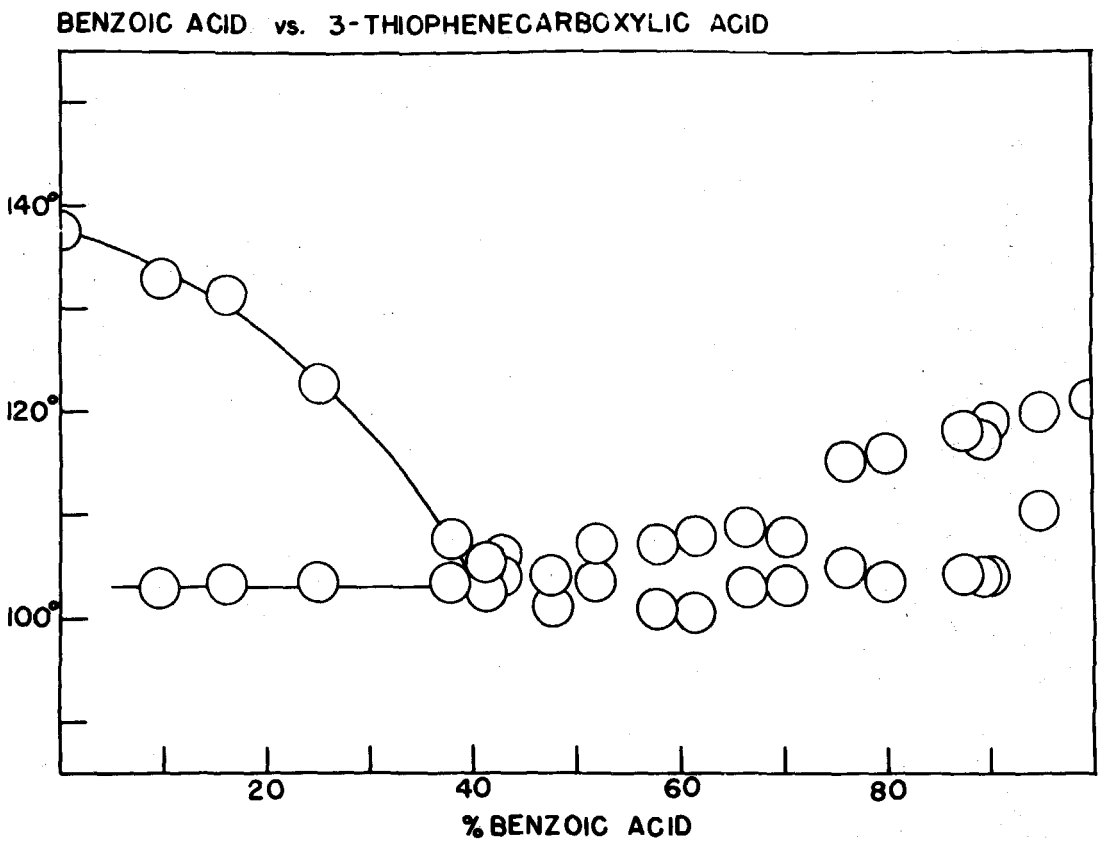
| | | | |
|---|---|---|---|
| % A | 81.4 | 91.0 | 100 |
| Th.p. | 115.4 | 115.6 | 121 |
| Dec.p. | 133.8 | 127.0 | |
| M.p. | 153.2 | 127.6 | 122 |




Benzoic acid (A) vs. Furoic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 10.4 | 21.7 | 28.9 | 42.0 | 48.6 | 57.0 |
| Th.p. | 132 | 85.6 | 85.1 | 85.0 | 85.3 | 85.5 | 85.0 |
| M.p. | 133 | 127.2 | 124.0 | 121.5 | 114.5 | 109.2 | 95.2 |

| | | | | |
|---|---|---|---|---|
| % A | 66.9 | 77.5 | 86.5 | 100 |
| Th.p. | 85.0 | 85.1 | 85.1 | 121 |
| M.p. | 96.0 | 105.5 | 110.8 | 122 |

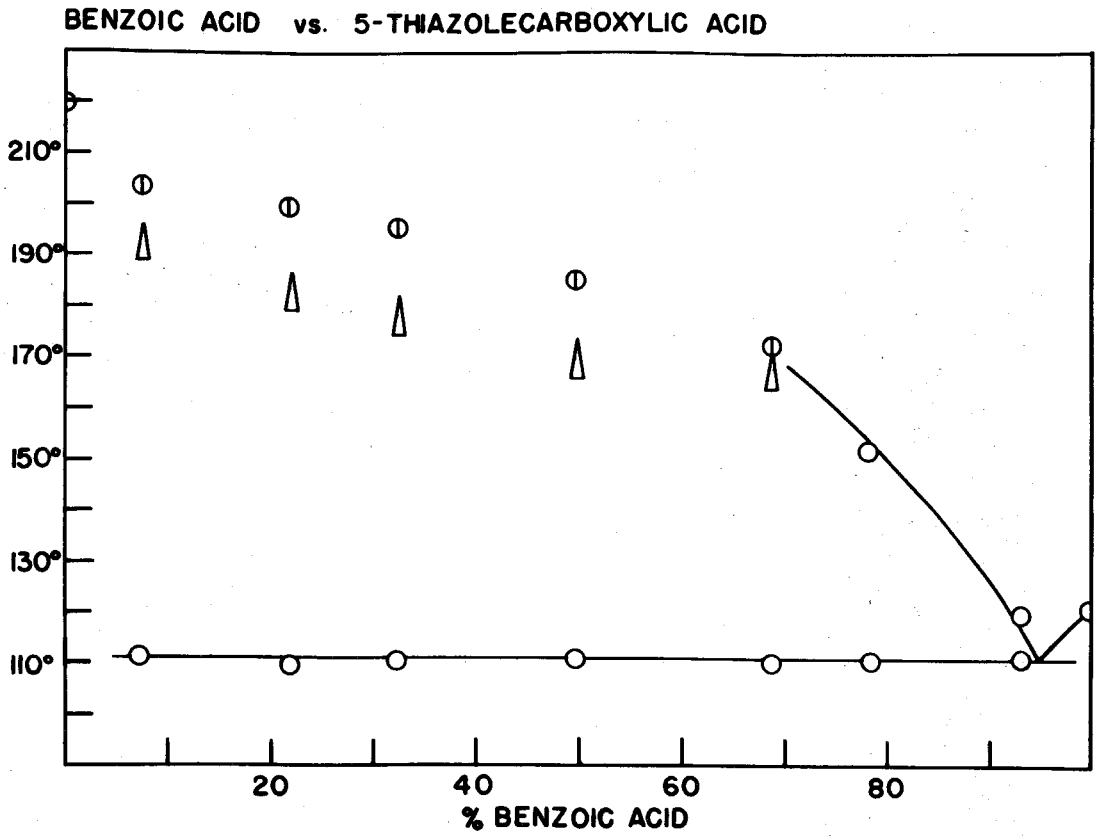



Benzoic acid (A) vs. 3-Thiophenecarboxylic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 9.5 | 15.9 | 25.0 | 37.8 | 41.4 | 42.8 |
| Th.p. | 137 | 102.9 | 103.2 | 103.5 | 103.3 | 102.6 | 104.0 |
| M.p. | 138 | 132.6 | 131.2 | 122.6 | 107.8 | 105.4 | 106.0 |

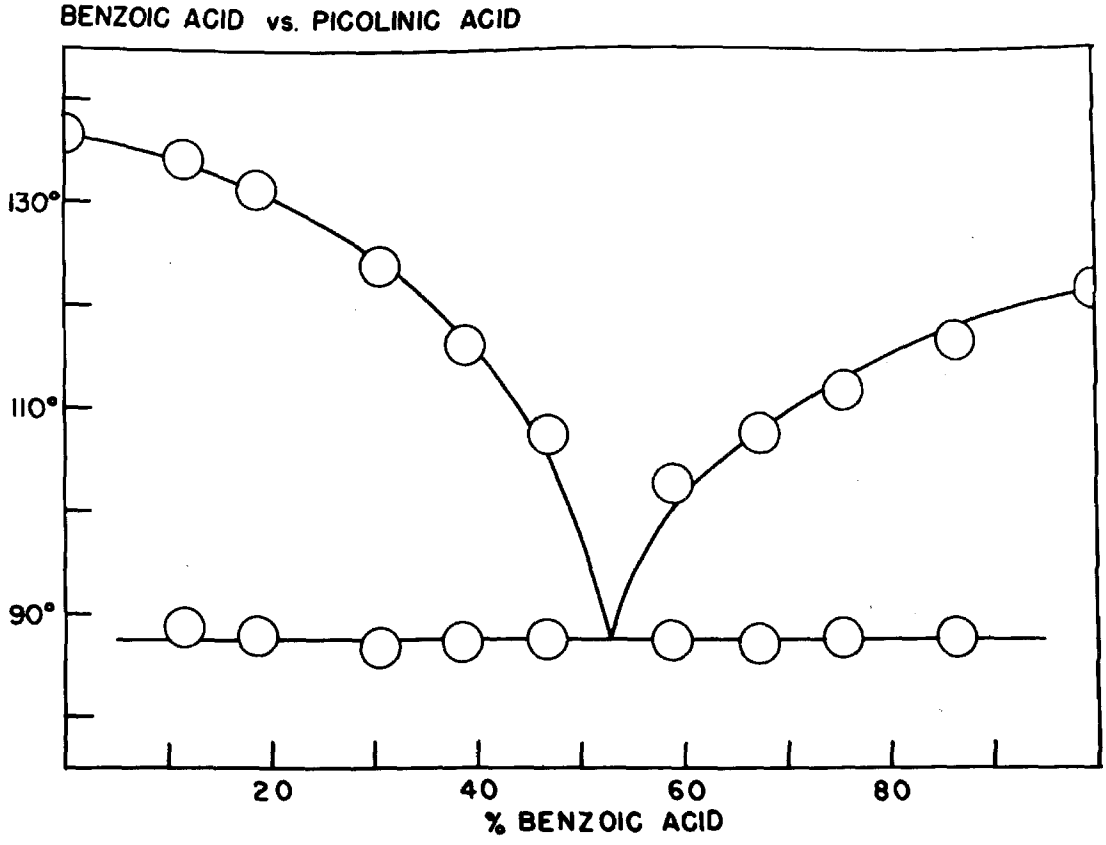
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 47.7 | 52.0 | 57.8 | 61.5 | 66.2 | 70.2 | 76.1 |
| Th.p. | 101.0 | 103.6 | 101.0 | 100.6 | 103.0 | 103.2 | 105.0 |
| M.p. | 104.2 | 107.2 | 107.0 | 108.0 | 108.8 | 108.0 | 115.4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| % A | 79.4 | 80.0 | 87.5 | 90.0 | 95.0 | 100 |
| Th.p. | 104.1 | 103.6 | 104.4 | 104.2 | 110.6 | 121 |
| M.p. | 117.2 | 116.0 | 118.2 | 119.0 | 120.0 | 122 |




Benzoic acid (A) vs. 5-Thiazolecarboxylic acid

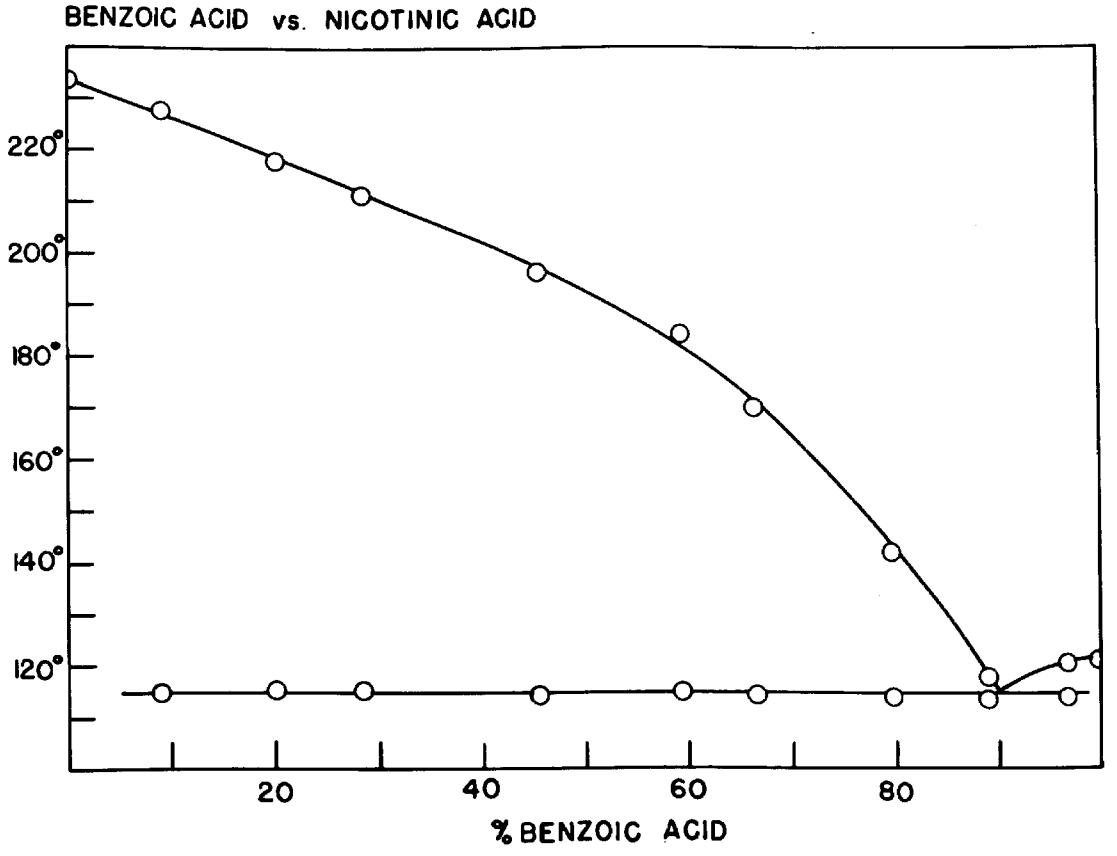
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| % A | 0 | 7.6 | 22.0 | 32.7 | 50.0 | 69.0 | 78.5 | 93.3 | 100 |
| Th.p. | 218 | 111.4 | 109.6 | 111.0 | 111.2 | 110.6 | 111.0 | 111.6 | 121 |
| Dec.p. | 218 | 192.8 | 183.6 | 178.6 | 169.6 | 167.8 | | | |
| M.p. | 220 | 203.5 | 199.4 | 195.4 | 185.0 | 172.4 | 152.0 | 120.0 | 122 |




Benzoic acid (A) vs. Picolinic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 11.6 | 18.6 | 30.3 | 38.3 | 46.5 | 58.8 |
| Th.p. | 136 | 88.4 | 87.6 | 86.4 | 87.0 | 87.2 | 87.4 |
| M.p. | 137 | 134.2 | 131.0 | 123.8 | 116.0 | 107.4 | 102.4 |

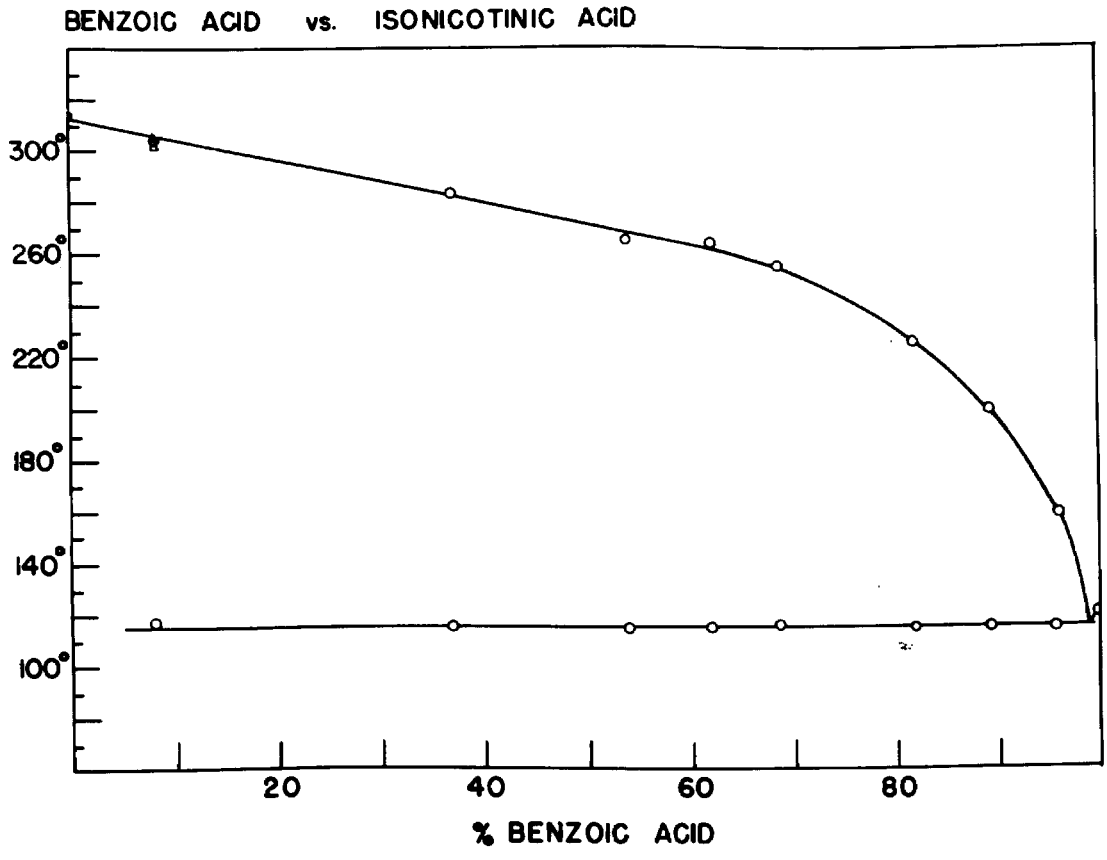
| | | | | |
|---|---|---|---|---|
| % A | 67.2 | 75.5 | 86.6 | 100 |
| Th.p. | 87.0 | 87.6 | 87.6 | 121 |
| M.p. | 107.4 | 111.4 | 116.2 | 122 |




Benzoic acid (A) vs. Nicotinic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 9.0 | 20.0 | 28.6 | 45.4 | 59.5 | 66.6 |
| Th.p. | 233 | 115.0 | 115.4 | 115.4 | 114.2 | 115.0 | 114.6 |
| M.p. | 233 | 227.6 | 217.6 | 211.2 | 195.8 | 184.0 | 169.8 |

| | | | | |
|---|---|---|---|---|
| % A | 79.8 | 89.0 | 96.8 | 100 |
| Th.p. | 114.0 | 113.6 | 114.0 | 121 |
| M.p. | 142.2 | 117.8 | 120.4 | 122 |

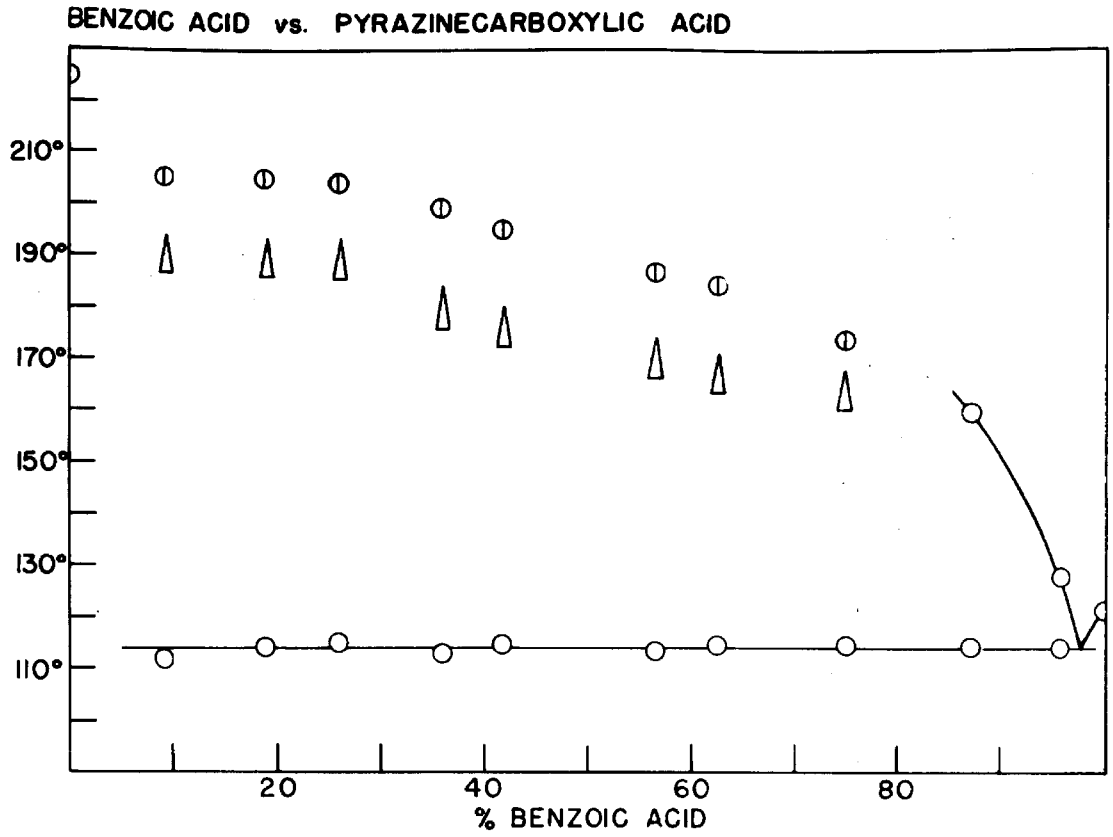



Benzoic acid (A) vs. Isonicotinic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 8.1 | 36.8 | 53.9 | 61.8 | 68.4 | 81.8 |
| Th.p. | 312 | 118.6 | 115.4 | 115.0 | 115.0 | 115.0 | 114.8 |
| M.p. | 314 | 304* | 282.8 | 265.4 | 264.2 | 255.4 | 225.2 |

| | | | |
|---|---|---|---|
| % A | 89.4 | 96.1 | 100 |
| Th.p. | 115.4 | 115.4 | 121 |
| M.p. | 199.4 | 158.8 | 122 |

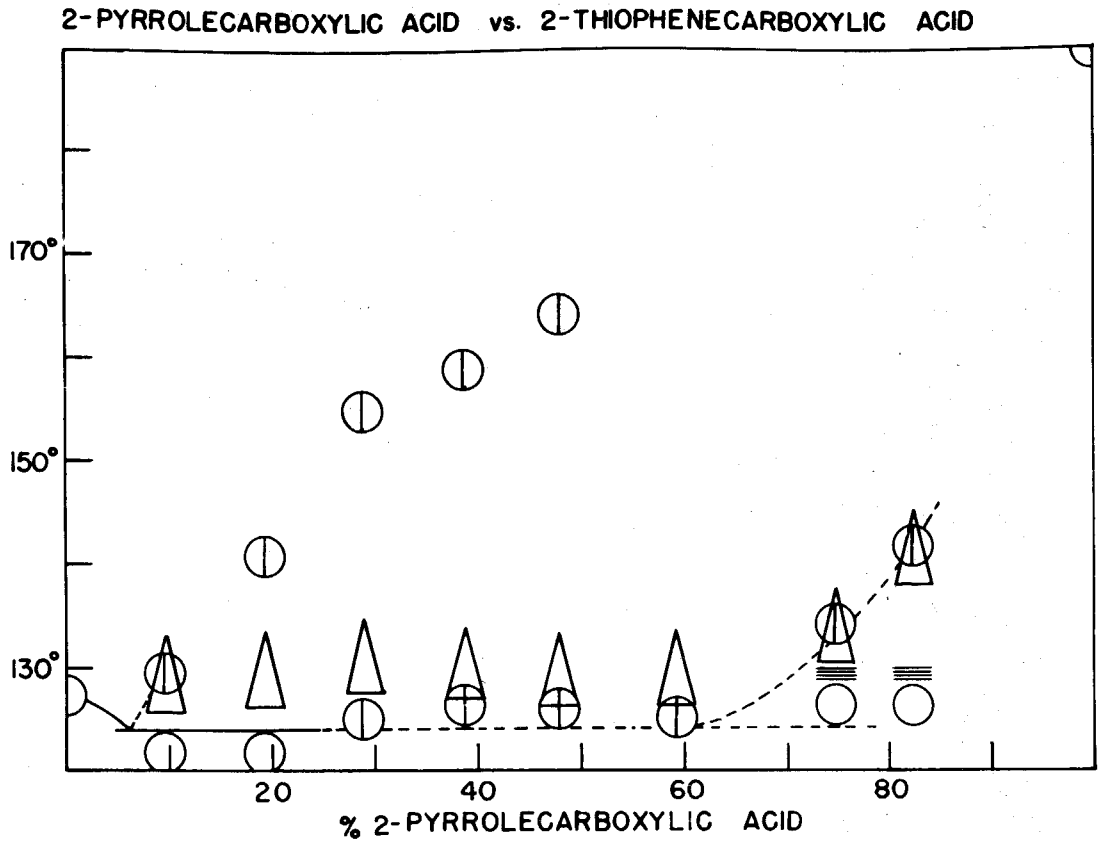
* dec.




Benzoic acid (A) vs. Pyrazinecarboxylic acid

| % A | 0 | 9.1 | 18.8 | 25.8 | 35.8 | 41.8 | 56.6 |
|---|---|---|---|---|---|---|---|
| Th.p. | 224 | 111.8 | 114.0 | 115.0 | 113.0 | 114.6 | 113.6 |
| Dec.p. | 224 | 189.8 | 189.0 | 188.6 | 179.8 | 176.0 | 170.6 |
| M.p. | 226 | 205.0 | 204.2 | 203.2 | 198.4 | 194.2 | 186.2 |

| % A | 62.6 | 75.0 | 87.2 | 95.8 | 100 |
|---|---|---|---|---|---|
| Th.p. | 114.4 | 114.6 | 114.4 | 114.0 | 121 |
| Dec.p. | 167.2 | 164.2 | | | |
| M.p. | 184.0 | 173.4 | 159.4 | 127.8 | 122 |

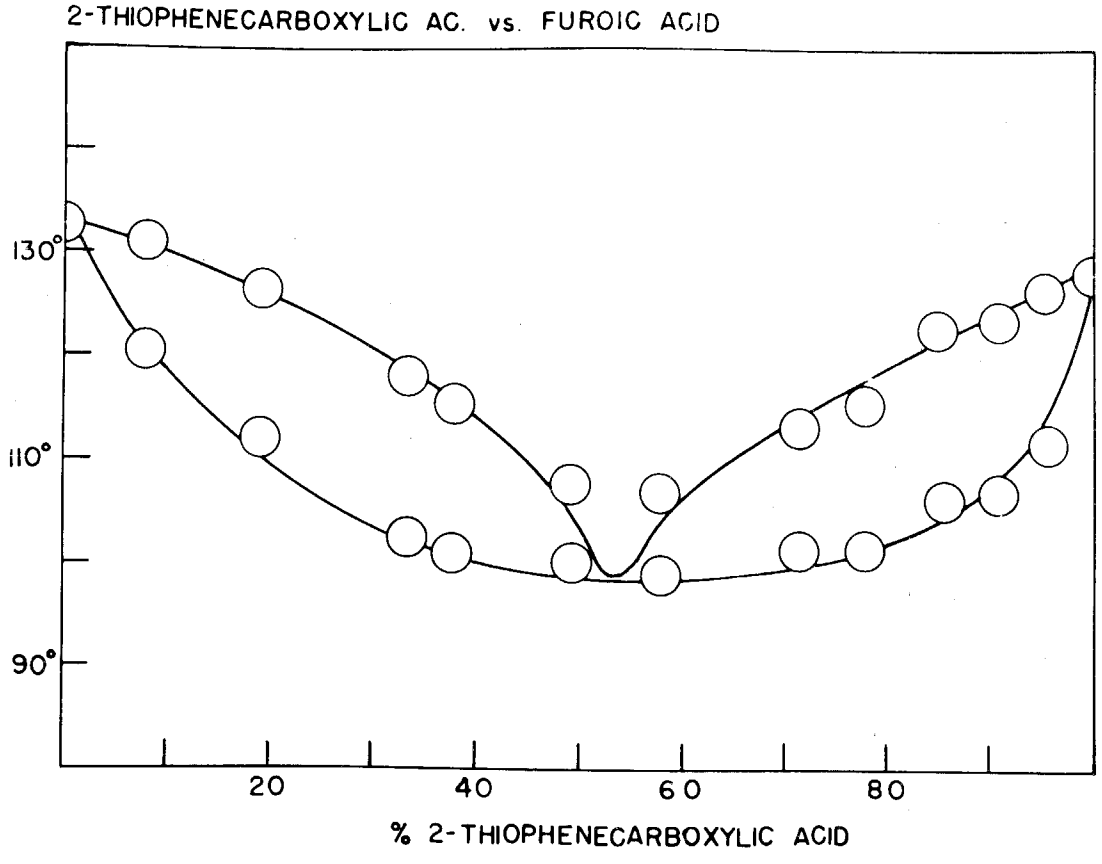



2-Pyrrolecarboxylic acid (A) vs. 2-Thiophenecarboxylic acid

| % A | 0 | 9.7 | 19.4 | 29.0 | 38.7 | 48.2 | 59.4 |
|---|---|---|---|---|---|---|---|
| Th.p. | 127 | 121.8 | 121.8 | 125.0 | 126.4 | 126.0 | 125.2 |
| Dec.p. | | 129.4 | 130.0 | 131.2 | 130.6 | 129.8 | 130.0 |
| M.p. | 128 | 129.4 | 140.6 | 154.6 | 158.4 | 164.0 | |

| % A | 75.5 | 82.6 | 100 |
|---|---|---|---|
| Th.p. | 134.2* | 141.6* | 190 |
| Dec.p. | 134.2 | 141.6 | 190 |
| M.p. | | | 190 |

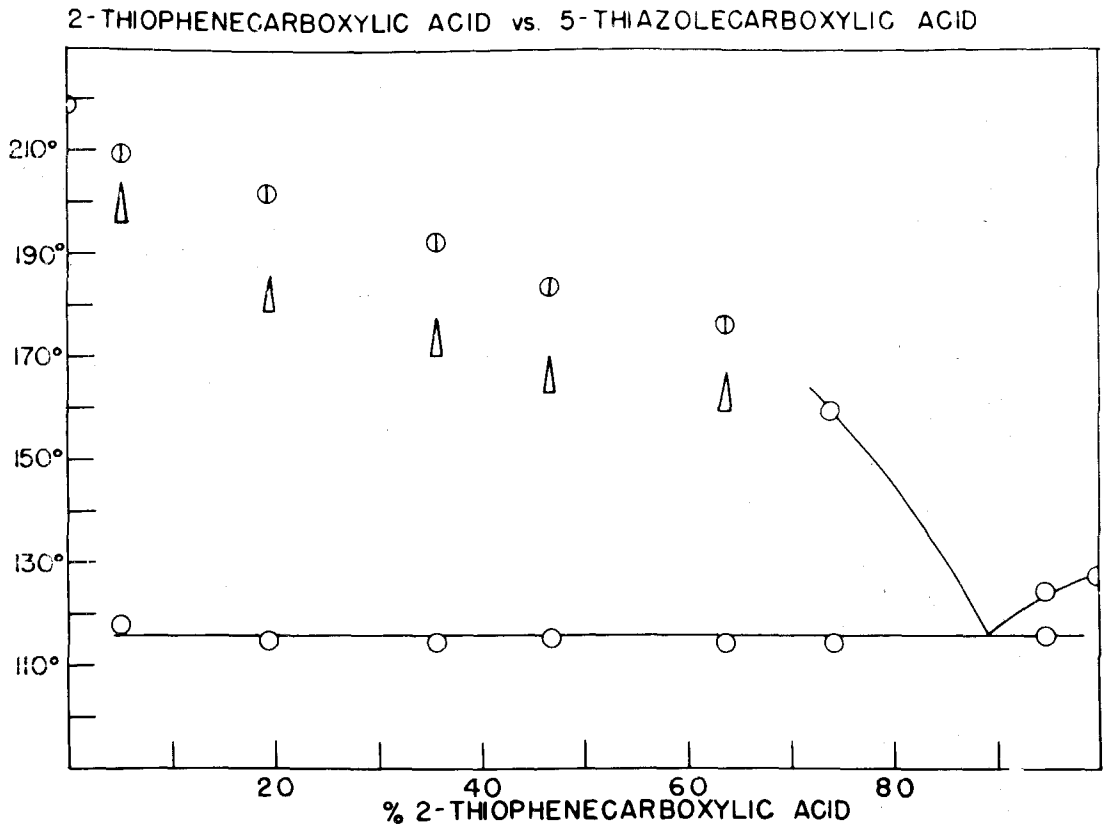
* Initially melted at 126.4 , the resolidified.




2-Thiophenecarboxylic acid (A) vs. Furoic acid

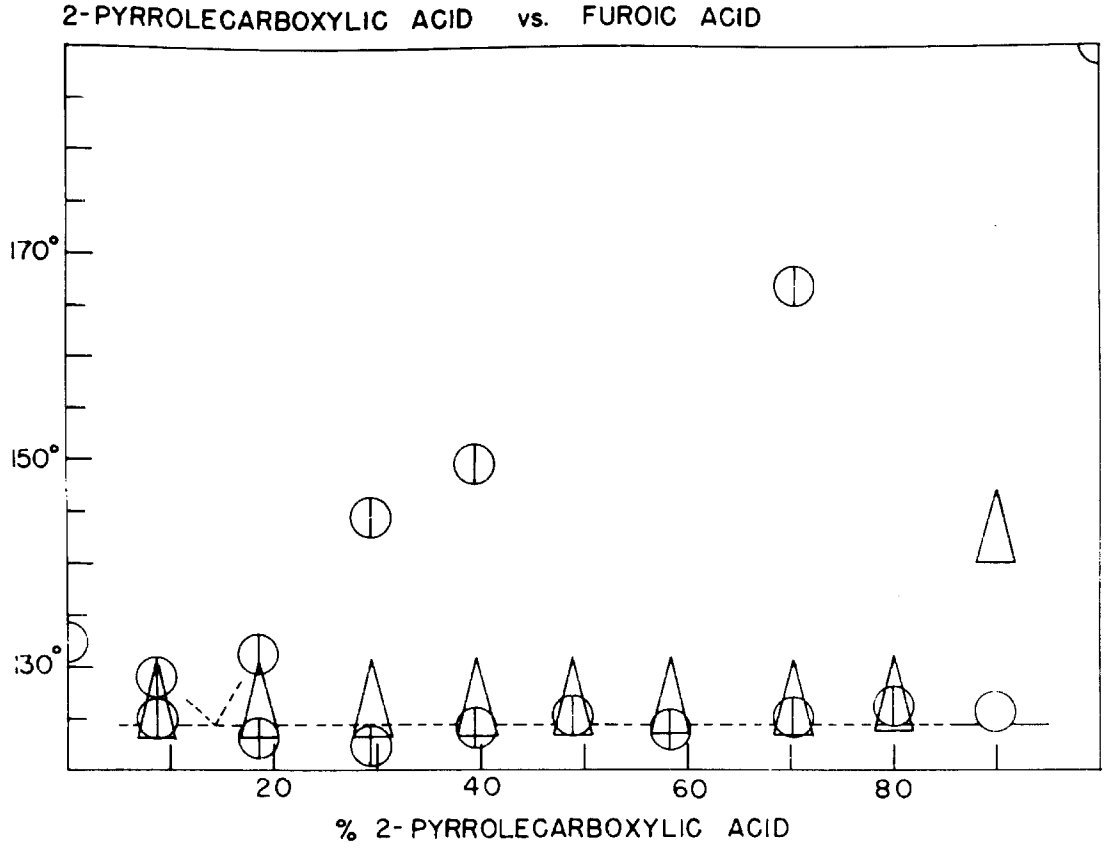
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 7.8 | 18.8 | 33.3 | 37.8 | 49.2 | 57.9 |
| Th.p. | 132 | 120.5 | 112.0 | 102.2 | 100.9 | 100.0 | 98.8 |
| M.p. | 133 | 131.0 | 127.2 | 118.0 | 115.2 | 107.6 | 106.8 |

| | | | | | | |
|---|---|---|---|---|---|---|
| % A | 71.5 | 78.0 | 85.2 | 90.8 | 95.5 | 100 |
| Th.p. | 101.2 | 101.1 | 106.1 | 106.7 | 111.4 | 127 |
| M.p. | 113.0 | 115.2 | 122.6 | 123.4 | 126.3 | 128 |




2-Thiophenecarboxylic acid (A) vs. 5-Thiazole-carboxylic acid

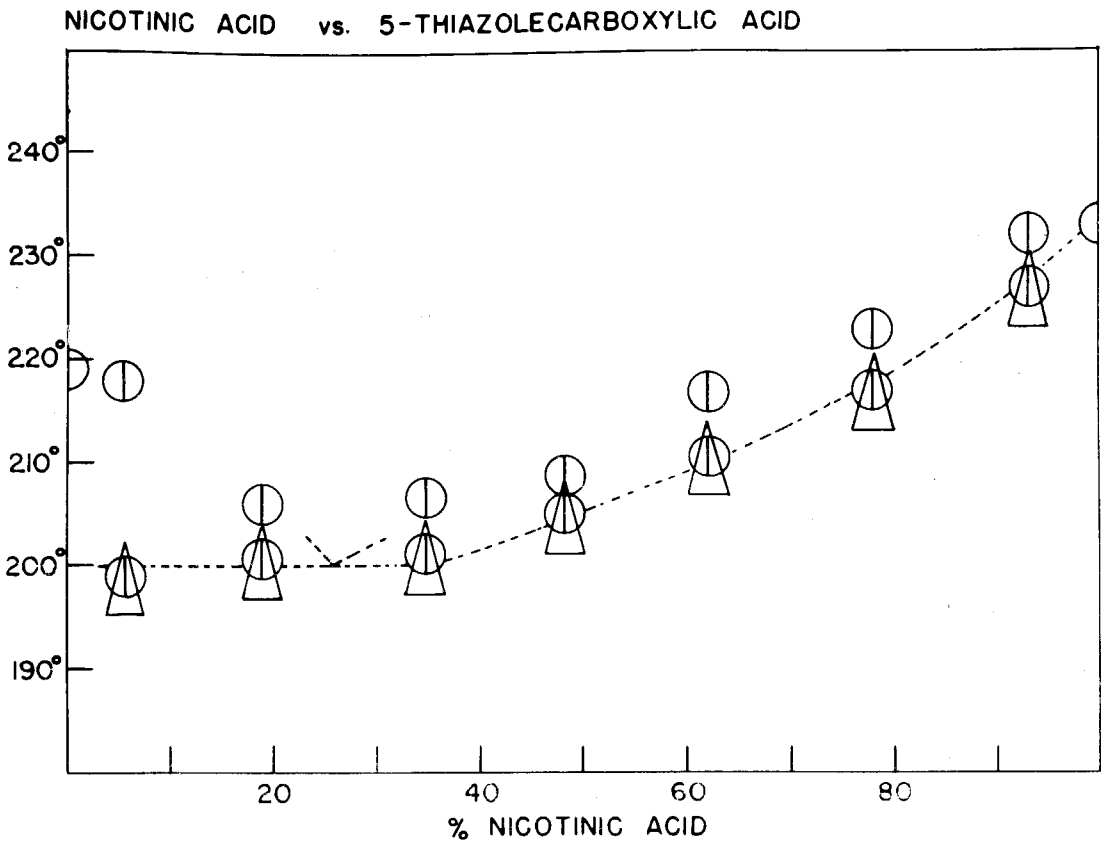
| % A | 0 | 5.2 | 19.4 | 35.9 | 46.8 | 63.8 | 74.1 | 95.0 | 100 |
|---|---|---|---|---|---|---|---|---|---|
| Th.p. | 218 | 118.2 | 115.0 | 114.8 | 115.4 | 114.2 | 114.2 | 116.0 | 127 |
| Dec.p. | 218 | 200.4 | 182.6 | 174.8 | 166.8 | 163.4 | | | |
| M.p. | 220 | 209.4 | 201.8 | 192.2 | 183.6 | 176.2 | 159.6 | 124.6 | 128 |




2-Pyrrolecarboxylic acid (A) vs. Furoic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 8.7 | 16.6 | 20.6 | 39.8 | 43.0 | 58.5 |
| Th.p. | 132 | 125.2 | 126.2 | 132.6 | 134.0 | 135.4 | 134.0 |
| Dec.p. | | 127 | 127 | 127 | 127 | 127 | 127 |
| L.p. | 136 | 129.2 | 131.4 | 144.6 | 149.6 | | |

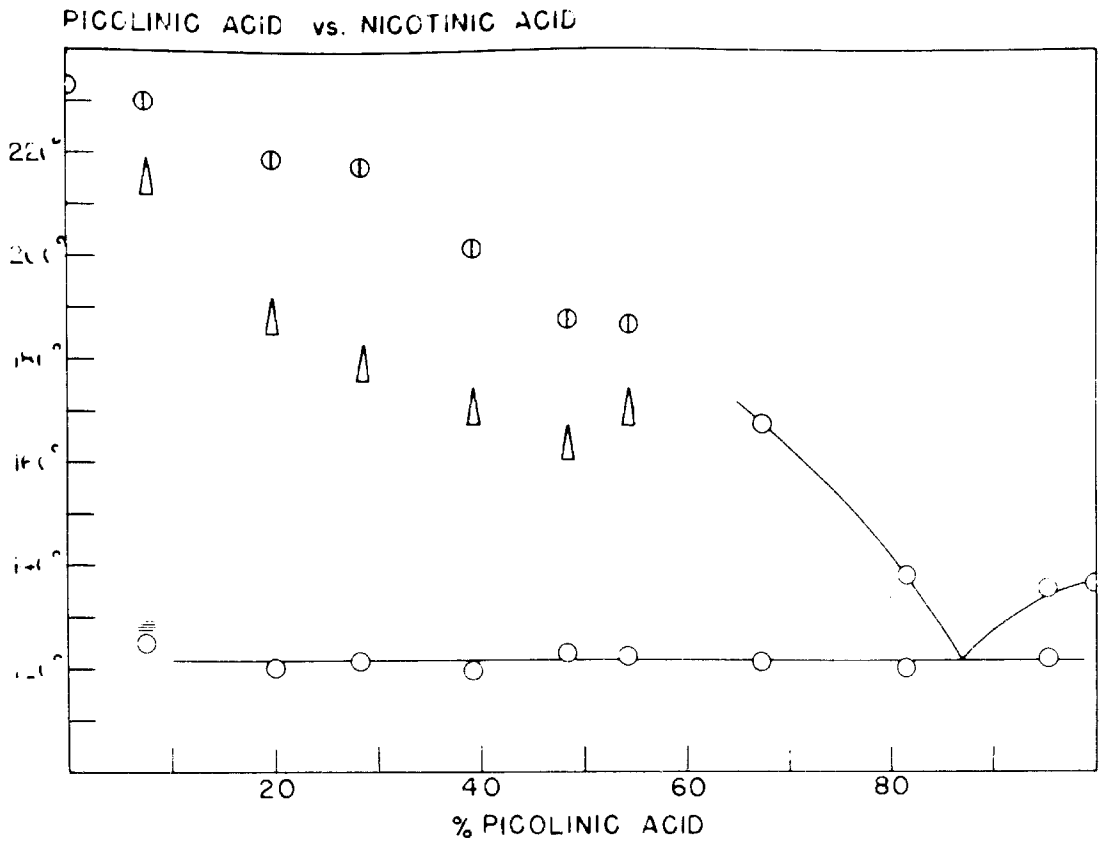
| | | | | |
|---|---|---|---|---|
| % A | 70.5 | 80.2 | 90.0 | 100 |
| Th.p. | 125.2 | 126.4 | 125.6 | 190 |
| Dec.p. | 127 | 127 | 143.8 | 190 |
| L.p. | 136.8 | | | 190 |




Nicotinic acid (A) vs. 5-Thiazolecarboxylic acid

| % A | 0 | 5.9 | 19.0 | 34.8 | 48.3 | 62.3 | 77.8 | 93.3 | 100 |
|---|---|---|---|---|---|---|---|---|---|
| Th.p.* | 218 | 199.0 | 200.8 | 201.4 | 205.0 | 210.8 | 217.4 | 227.0 | 233 |
| M.p. | 220 | 209.8 | 206.0 | 206.6 | 208.8 | 217.0 | 225.0 | 232.4 | 253 |

* identical with dec.p. (except for 100% coordinate)

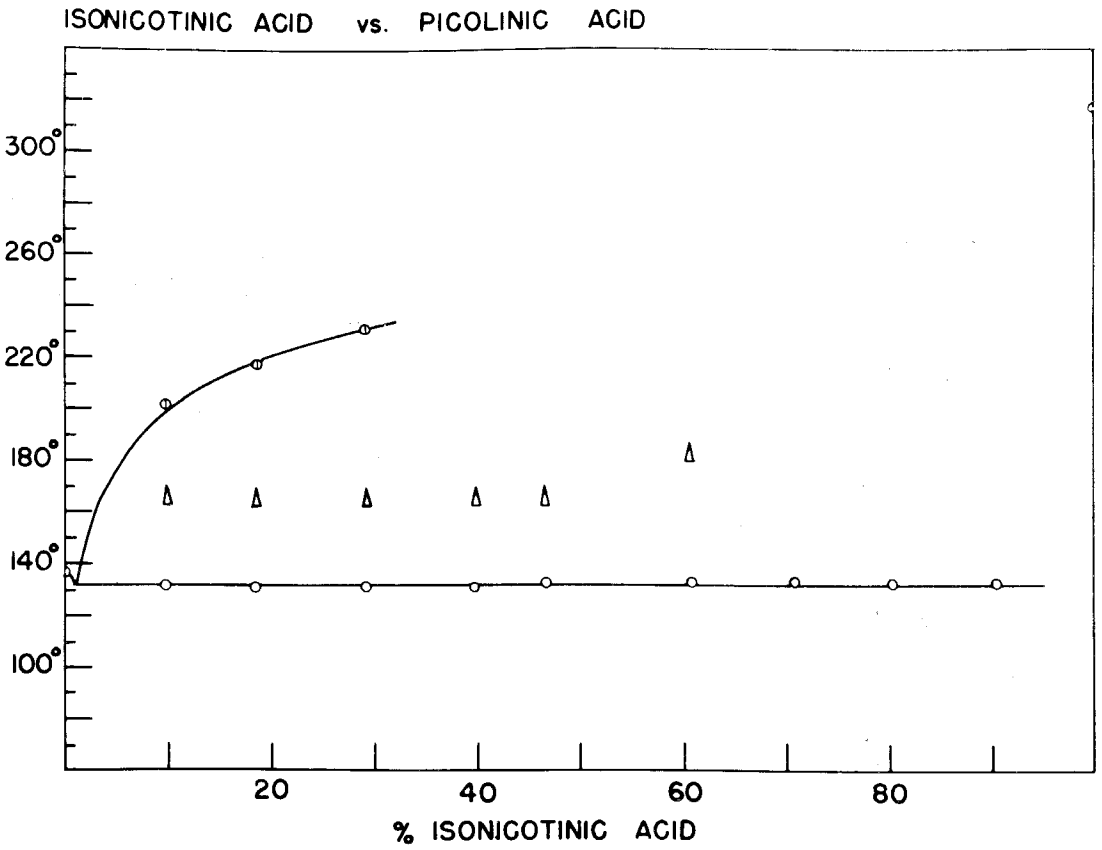



Picolinic acid (A) vs. Nicotinic acid

| % A | 0 | 7.5 | 20.0 | 28.4 | 39.3 | 48.6 | 54.2 |
|---|---|---|---|---|---|---|---|
| Th.p. | 233 | 125* | 120.4 | 121.6 | 119.8 | 123.0 | 122.2 |
| Dec.p. | | 215.8 | 189.0 | 180.0 | 171.6 | 164.2 | 170.8 |
| M.p. | 233 | 230.2 | 219.2 | 217.4 | 201.2 | 188.0 | 186.8 |

| % A | 67.3 | 81.6 | 95.5 | 100 |
|---|---|---|---|---|
| Th.p. | 121.6 | 120.2 | 122.2 | 136 |
| Dec.p. | | | | |
| M.p. | 167.8 | 138.2 | 136.0 | 137 |

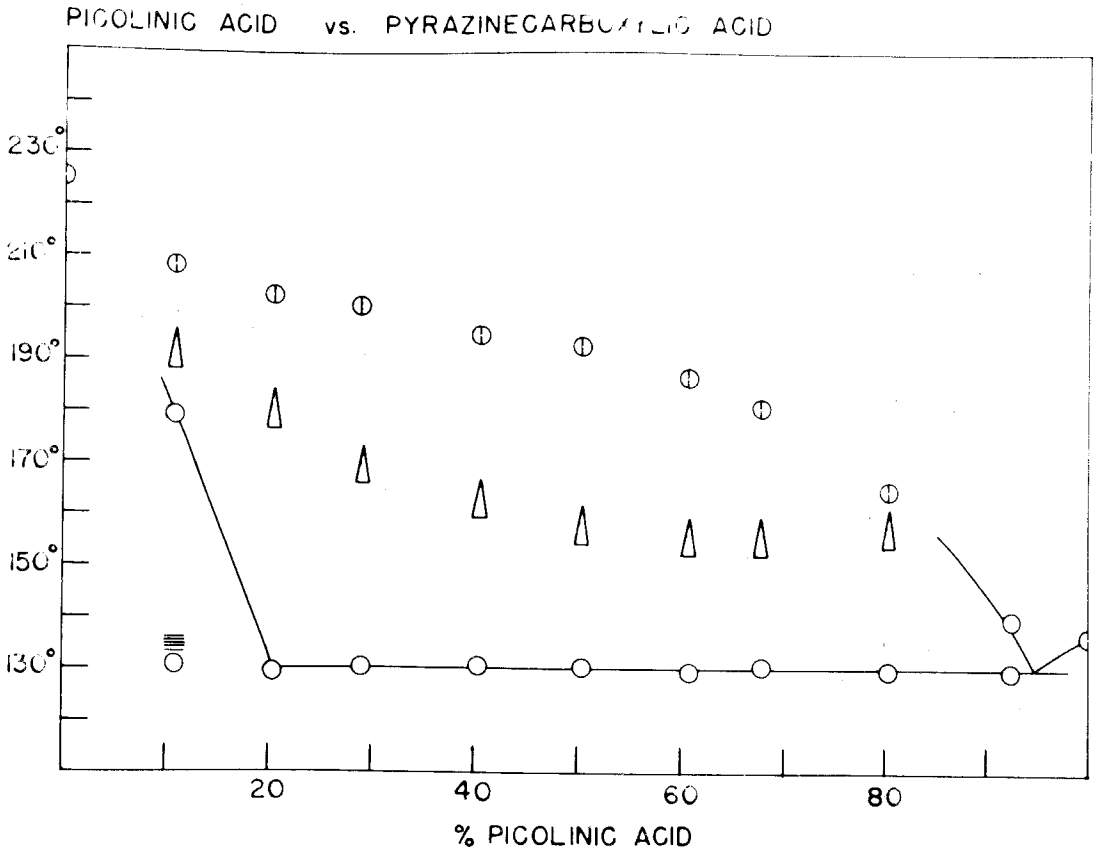
* resolidifies




Isonicotinic acid (A) vs. Picolinic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 9.5 | 18.4 | 29.3 | 39.8 | 46.7 | 60.8 |
| Th.p. | 136 | 132.0 | 131.4 | 131.2 | 131.2 | 132.4 | 132.4 |
| Dec.p. | | 166 | 166 | 166 | 166 | 166 | 184.0 |
| M.p. | 137 | 200.8 | 216.8 | 231.2 | | | |

| | | | | |
|---|---|---|---|---|
| % A | 70.8 | 80.5 | 90.5 | 100 |
| Th.p. | 132.4 | 132.4 | 132.4 | 312 |
| Dec.p. | | | | |
| M.p. | | | | 314 |

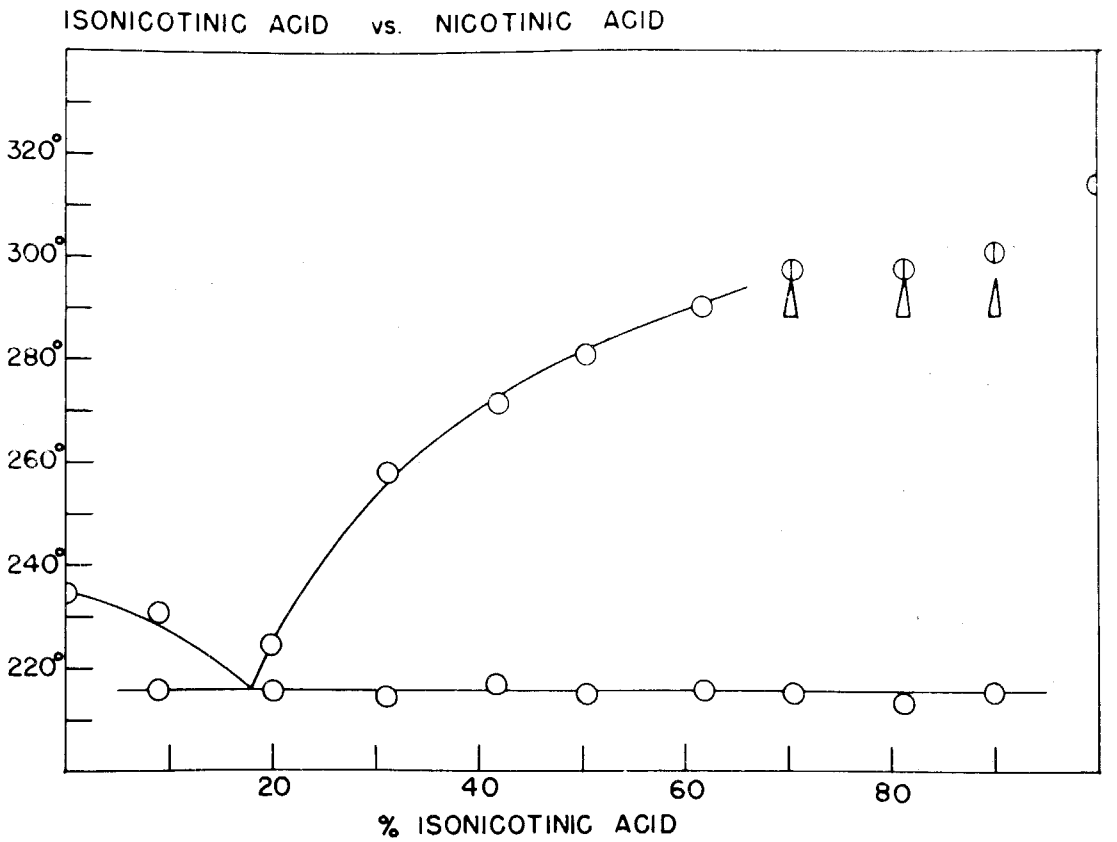



Picolinic acid (A) vs. Pyrazinecarboxylic acid

| % A | 0 | 10.8 | 20.4 | 29.0 | 40.4 | 50.5 | 60.8 |
|---|---|---|---|---|---|---|---|
| Th.p. | 224 | 179.4* | 129.8 | 130.6 | 130.8 | 130.4 | 129.6 |
| Dec.p. | 224 | 192.2 | 180.4 | 169.6 | 163.0 | 158.4 | 156.0 |
| M.p. | 226 | 208.8 | 202.6 | 200.2 | 194.8 | 192.4 | 186.6 |

| % A | 68.0 | 80.3 | 92.4 | 100 |
|---|---|---|---|---|
| Th.p. | 130.6 | 129.8 | 129.4 | 136 |
| Dec.p. | 156.0 | 157.8 | | |
| M.p. | 180.8 | 164.2 | 139.6 | 137 |

* initially melted at 131.4, then resolidified.

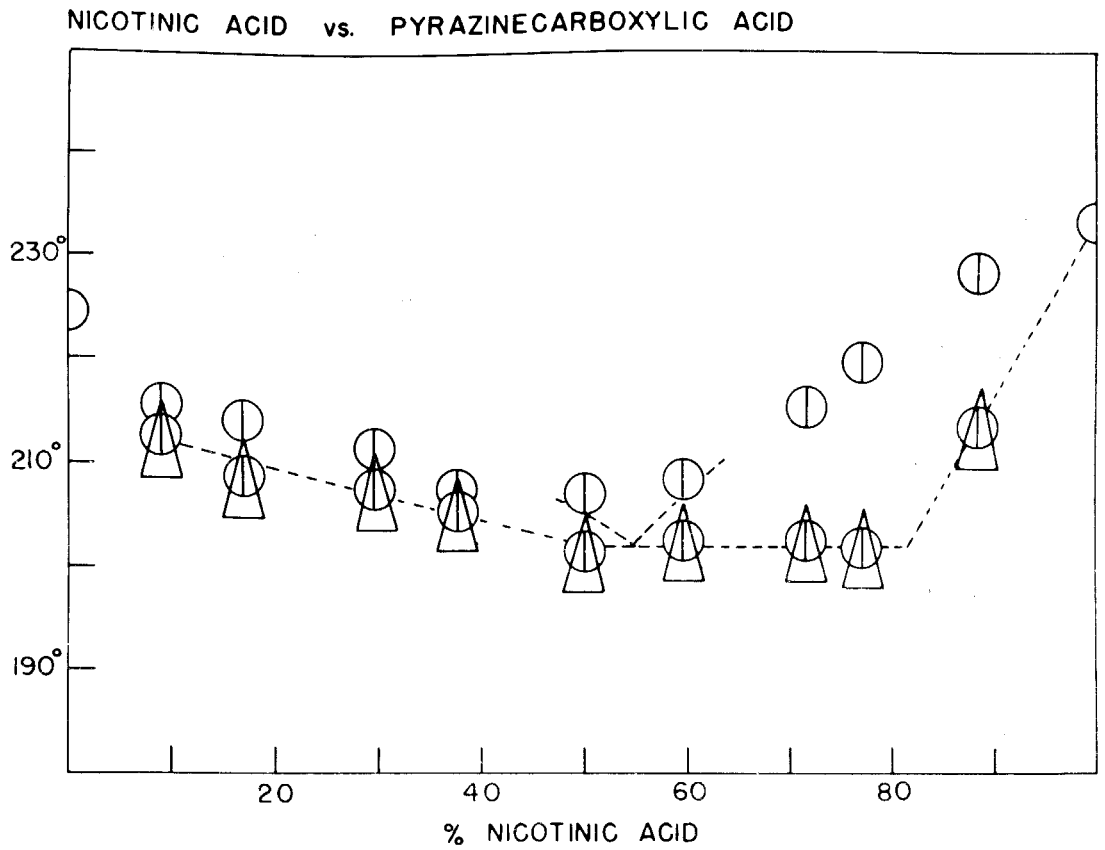



Isonicotinic acid (A) vs. Nicotinic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 9.0 | 20.0 | 31.1 | 41.7 | 50.5 | 61.7 |
| Th.p. | 233 | 215.8 | 215.6 | 214.0 | 217.0 | 215.0 | 215.6 |
| M.p. | 235 | 251.0 | 224.6 | 258.4 | 271.0 | 280.2 | 290.0 |

| | | | | |
|---|---|---|---|---|
| % A | 70.5 | 81.2 | 90.0 | 100 |
| Th.p. | 215.0 | 213.2 | 215.2 | 312 |
| M.p. | 297* | 297* | 300* | 314 |

* dec. at 292.

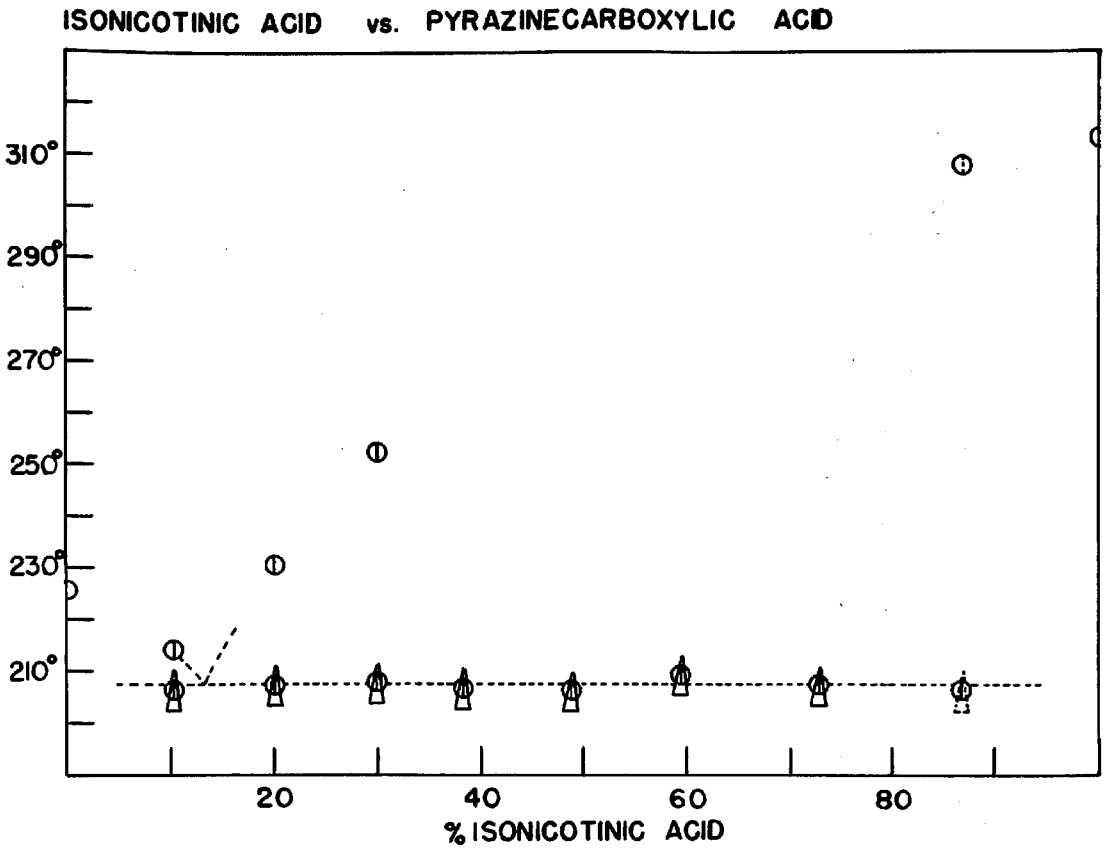



Nicotinic acid (A) vs. Pyrazinecarboxylic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 8.9 | 17.1 | 29.7 | 37.7 | 50.0 | 59.6 |
| Th.p.* | 224 | 212.8 | 208.8 | 207.8 | 205.2 | 201.2 | 202.6 |
| M.p. | 226 | 215.6 | 214.0 | 211.6 | 207.6 | 207.0 | 208.6 |

| | | | | |
|---|---|---|---|---|
| % A | 71.5 | 77.1 | 86.3 | 100 |
| Th.p.* | 202.6 | 202.0 | 215.8 | 235 |
| M.p. | 215.2 | 219.8 | 228.6 | 255 |

* identical with dec.p. (accepting the 100% coordinate)

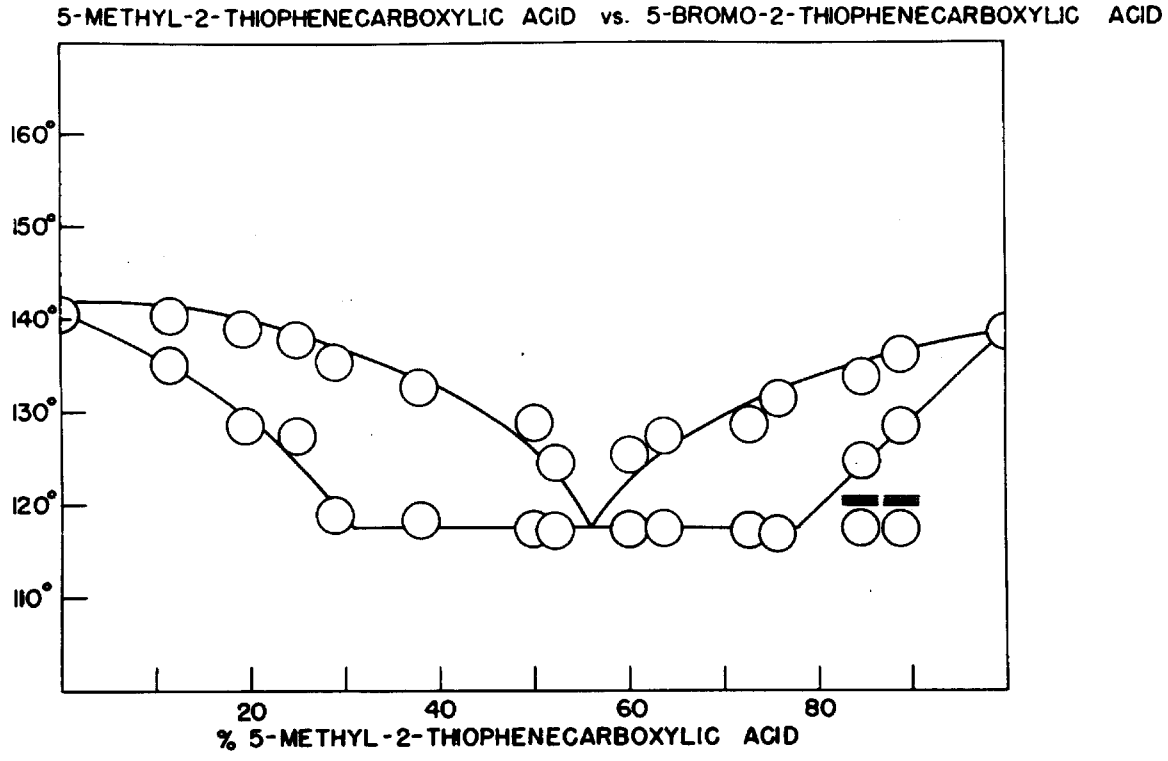



Isonicotinic acid (A) vs. Pyrazinecarboxylic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 10.3 | 20.2 | 30.0 | 38.5 | 49.0 | 59.5 |
| Th.p.* | 224 | 206.8 | 207.4 | 208.2 | 207.0 | 206.8 | 209.4 |
| M.p. | 226 | 214.2 | 230.8 | 252.2 | | | |

| | | | |
|---|---|---|---|
| % A | 72.8 | 86.8 | 100 |
| Th.p.* | 207.6 | 206.8 | 312 |
| M.p. | | 308 | 314 |

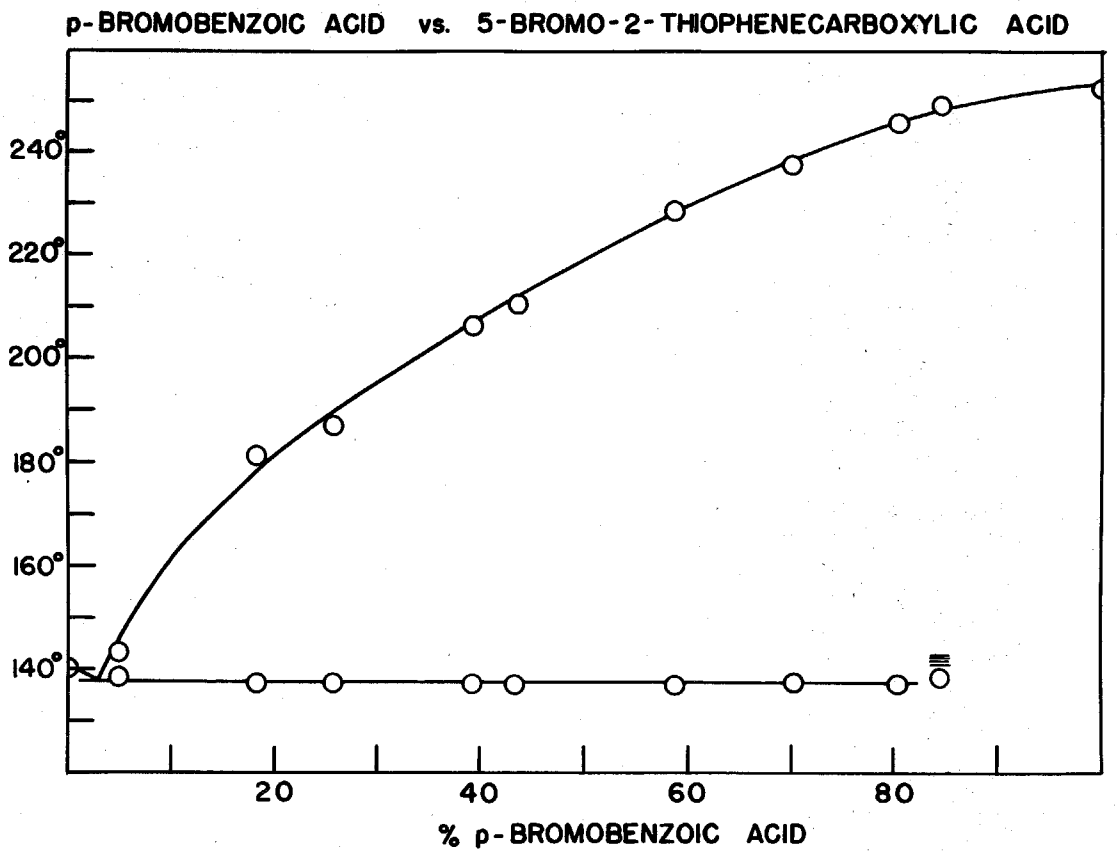
*identical with dec.p.




5-Methyl-2-thiophenecarboxylic acid (A) vs. 5-Bromo-2-thiophenecarboxylic acid

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| % A | 0 | 11.8 | 19.7 | 25.2 | 28.8 | 37.9 | 50.0 | 52.3 |
| Th.p. | 140 | 135.0 | 128.6 | 127.4 | 119.0 | 118.2 | 117.2 | 117.2 |
| M.p. | 141 | 140.2 | 139.0 | 137.8 | 135.4 | 133.0 | 129.0 | 124.8 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 60.2 | 64.0 | 72.8 | 75.9 | 84.8 | 88.8 | 100 |
| Th.p. | 117.2 | 117.4 | 117.2 | 117.0 | 124.8 | 128.6 | 138 |
| M.p. | 125.2 | 127.6 | 128.8 | 131.4 | 133.6 | 136.0 | 139 |

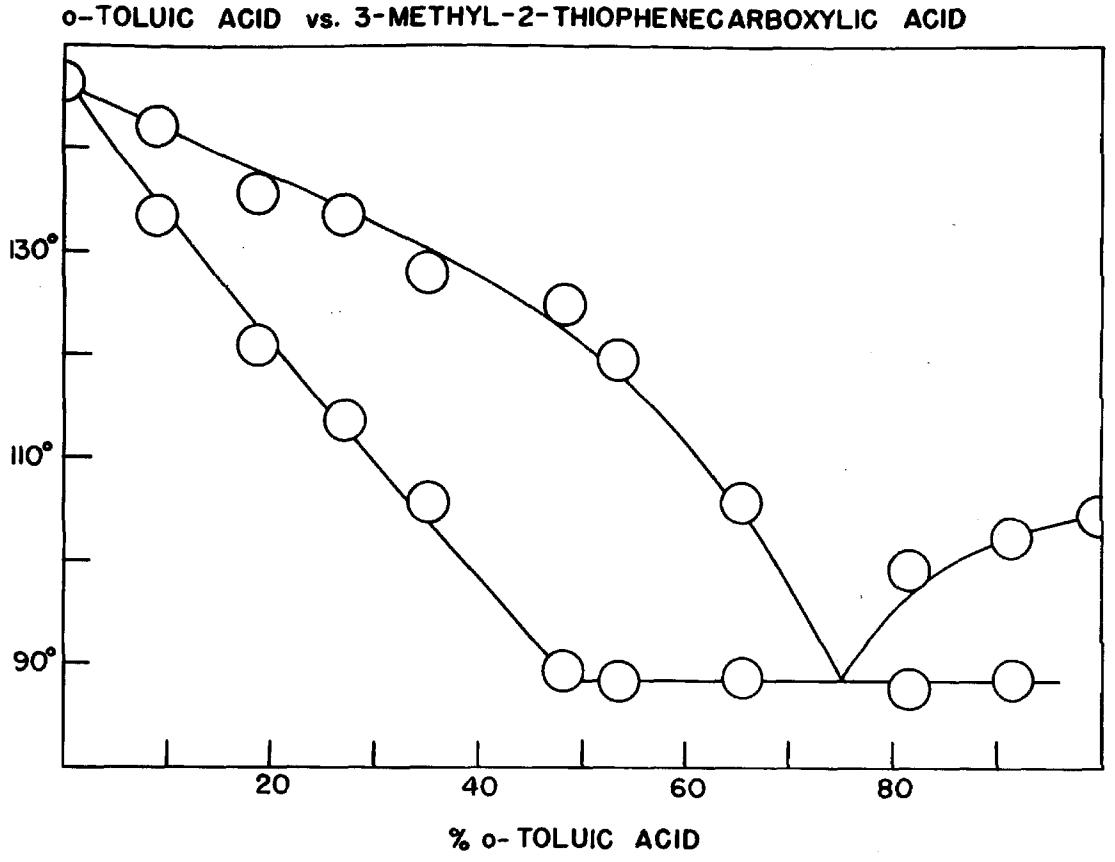



p-Bromobenzoic acid (A) vs. 5-Bromo-2-thiophene-carboxylic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 5.0 | 18.4 | 25.7 | 39.3 | 43.4 | 58.8 |
| Th.p. | 140 | 139.0 | 137.6 | 137.6 | 137.8 | 137.6 | 137.4 |
| M.p. | 141 | 143.8 | 181.6 | 187.6 | 206.6 | 210.4 | 228.4 |

| | | | | |
|---|---|---|---|---|
| % A | 70.2 | 80.6 | 84.6 | 100 |
| Th.p. | 137.8 | 137.8 | 137.8* | 252 |
| M.p. | 237.8 | 245.6 | 249.0 | 253 |

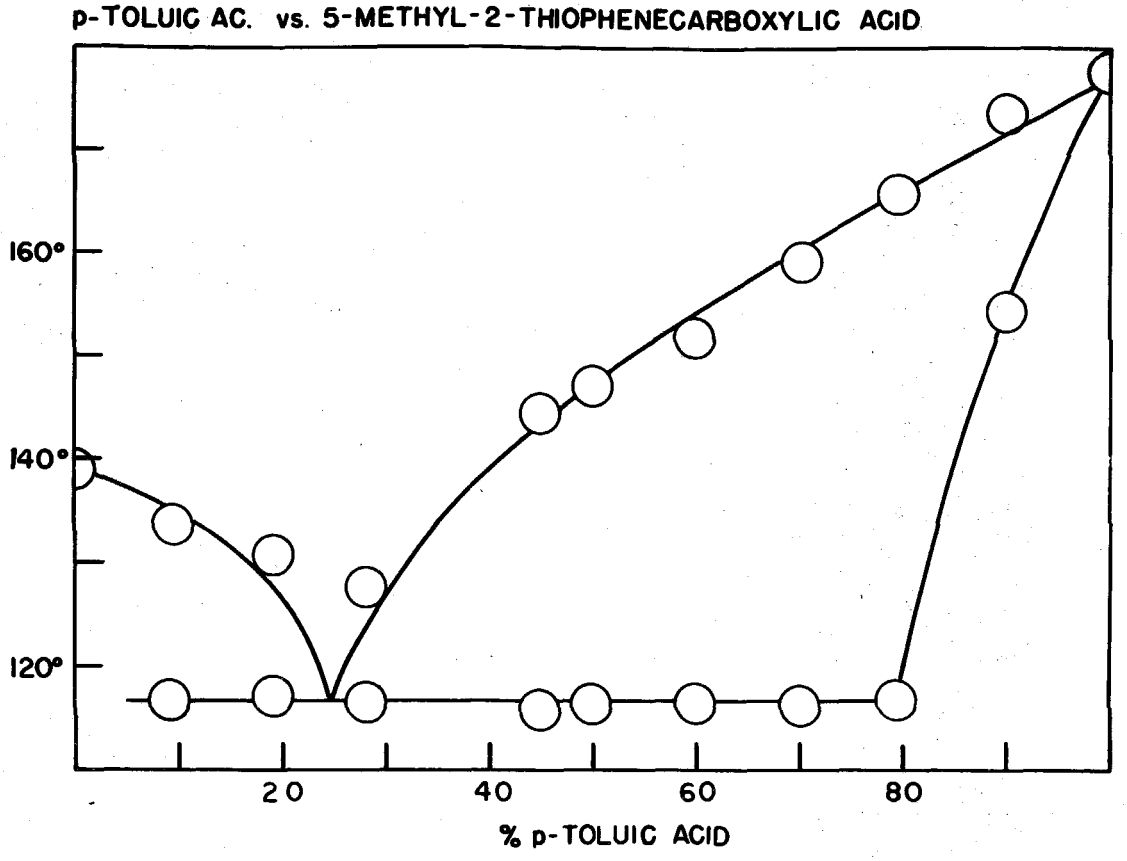
* resolidifies




o-Toluic acid (A) vs. 3-Methyl-2-thiophenecarboxylic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 9.0 | 18.8 | 27.1 | 35.1 | 48.1 | 53.5 |
| Th.p. | 146 | 133.2 | 121.0 | 113.6 | 105.6 | 89.2 | 88.2 |
| M.p. | 147 | 142.0 | 135.6 | 133.4 | 127.8 | 124.8 | 119.6 |

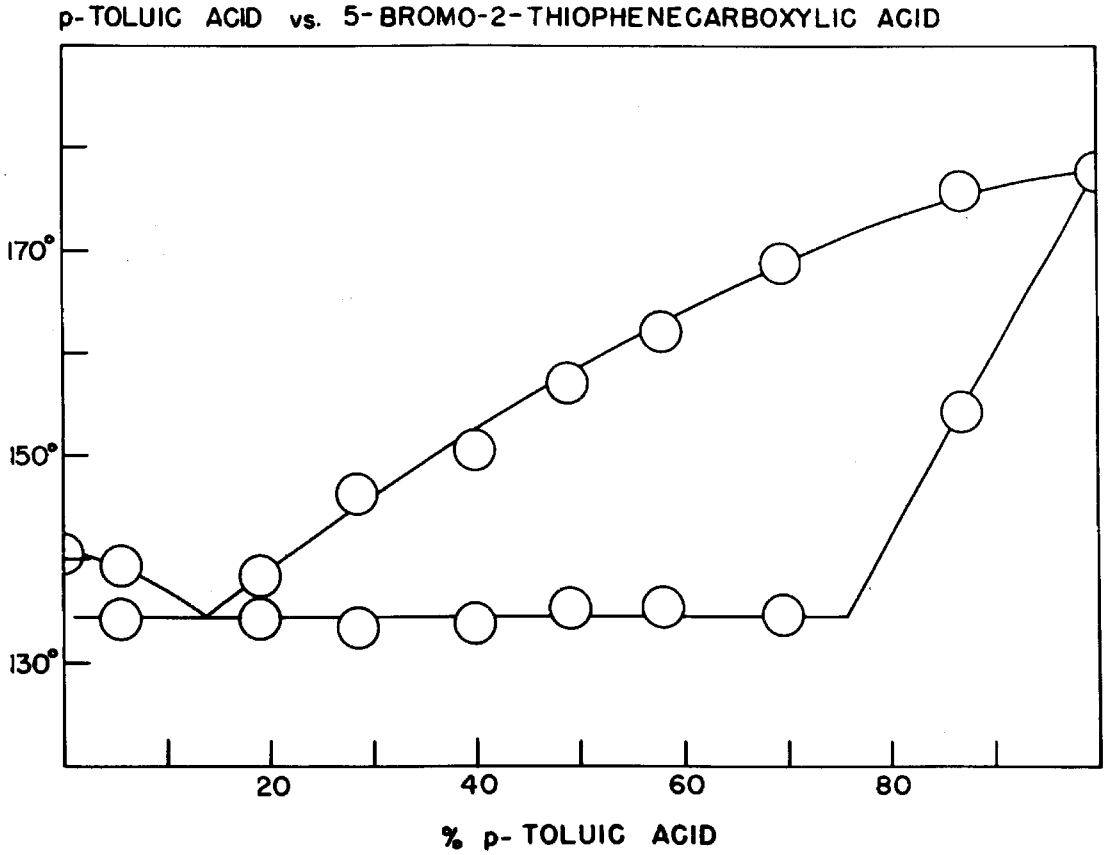
| | | | | |
|---|---|---|---|---|
| % A | 65.2 | 81.6 | 91.5 | 100 |
| Th.p. | 88.4 | 87.6 | 88.4 | 104 |
| M.p. | 105.6 | 99.0 | 102.2 | 105 |




p-Toluic acid (A) vs. 5-Methyl-2-thiophenecarboxylic acid

| % A | 0 | 9.4 | 19.2 | 27.9 | 45.0 | 50.0 | 60.0 |
|---|---|---|---|---|---|---|---|
| Th.p. | 138 | 116.6 | 117.0 | 116.2 | 115.6 | 116.2 | 116.4 |
| M.p. | 139 | 133.2 | 130.4 | 127.4 | 144.4 | 147.0 | 151.8 |

| % A | 70.3 | 79.5 | 90.0 | 100 |
|---|---|---|---|---|
| Th.p. | 116.2 | 116.8 | 154.2 | 177 |
| M.p. | 159.0 | 165.4 | 173.4 | 178 |




p-Toluic acid (A) vs. 5-Bromo-2-thiophenecarboxylic acid

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % A | 0 | 6.6 | 19.0 | 28.5 | 39.8 | 49.1 | 58.0 |
| Th.p. | 140 | 134.2 | 134.2 | 133.6 | 135.8 | 135.2 | 135.4 |
| M.p. | 141 | 139.6 | 138.2 | 146.2 | 150.6 | 157.0 | 162.0 |

| | | | |
|---|---|---|---|
| % A | 69.6 | 86.9 | 100 |
| Th.p. | 134.6 | 154.2 | 177 |
| M.p. | 168.8 | 175.8 | 178 |

B. Interpretation of data

Benzoic acid (A) vs. 2-thiophenecarboxylic acid.

A eutectic at 63% A and 95°. There is an indication of solubility at ca. 90% A.

Benzoic acid (A) vs. 2-pyrrolecarboxylic acid.

A eutectic at 93% A and 115°. Decomposition in the region 0-90% A at ≥130° makes the liquidus indeterminate. No indication of solid solution formation.

Benzoic acid (A) vs. furoic acid.

A eutectic at 60% A and 85°. No indication of solid solution formation.

Benzoic acid (A) vs. 3-thiophenecarboxylic acid.

A eutectic exists at 40% A and 103°, and there is an indication of solubility at ca. 90% A. The region 40-80% A does not lend itself to ready interpretation. However there might be another eutectic at ca. 64% A and 103°, and an addition compound at ca. 53% A (m.p. 109°). A 1:1 compound would be at 49% A.

Benzoic acid (A) vs. 5-thiazolecarboxylic acid.

A eutectic at 95% A and 111°. Decomposition in the region 0-70% A at ≥170° makes the liquidus indeterminate. No indication of solid solution formation.

Benzoic acid (A) vs. Picolinic acid.

A eutectic at 53% A and 115°. No indication of solid solution formation.

Benzoic acid (A) vs. nicotinic acid.

A eutectic at 90% A and 115°. No indication of solid solution formation.

Benzoic acid (A) vs. isonicotinic acid.

A eutectic at ca. 99% A and 115°. No indication of solid solution formation.

Benzoic acid (A) vs. pyrazinecarboxylic acid.

A eutectic at ca. 98% A and 114°. Decomposition in the region 0-80% A at ≥165° makes the liquidus indeterminate. No indication of solid solution formation.

2-Pyrrolecarboxylic acid (A) vs. 2-thiophenecarboxylic acid.

A eutectic at ca. 5% A and 124°. Decomposition at the solidus makes the phase boundaries indeterminate. Solid solution formation begins at 60-70% A.

2-Thiophenecarboxylic acid (A) vs. furoic acid.

Type III solid solution formation (44) with a minimum at 54% A and 100°. The diagram might also be interpreted as type V solid solution formation with a eutectic at 54% A and 100° and a solubility gap at 38-77% A.

2-Thiophenecarboxylic acid (A) vs. 5-thiazolecarboxylic acid.

A eutectic at 89% A and 116°. Decomposition in the region 0-70% A at ≥165° makes the liquidus indeterminate. No indication of solid solution formation.

2-Pyrrolecarboxylic acid (A) vs. furoic acid.

A eutectic at 15% A and 124°. Decomposition at the

solidus makes the phase boundaries indeterminate. No indication of solid solution formation.

Nicotinic acid (A) vs. 5-thiazolecarboxylic acid.

Type V solid solution formation with a eutectic at 26% A and 200°, and a solubility gap at 0-35% A. Decomposition at the solidus makes the phase boundaries indeterminate.

Picolinic acid (A) vs. nicotinic acid.

A eutectic at 87% A and 122°. Decomposition in the region 0-60% A at $\geq$ 165° makes the liquidus indeterminate. There is an indication that solid solution takes place at concentrations of $\leq$ 10% A.

Isonicotinic acid (A) vs. picolinic acid.

A eutectic at ca. 2% A and 132°. Decomposition at $\geq$ 165° makes the liquidus indeterminate. No indication of solid solution formation.

Picolinic acid (A) vs. pyrazinecarboxylic acid.

A eutectic at 95% A and 130°. Decomposition in the region 0-85% A at $\geq$ 160° makes the liquidus indeterminate. Solid solution formation at less than 20% A.

Isonicotinic acid (A) vs. nicotinic acid.

A eutectic at 18% A and 215°. Decomposition in the region 70-100% A at $\geq$ 292° makes the liquidus indeterminate. No indication of solid solution formation.

Nicotinic acid (A) vs. pyrazinecarboxylic acid.

Type V solid solution formation with a eutectic at

55% A and 202°, and a gap at 50-82% A. Decomposition at the solidus makes the phase boundaries indeterminate.

Isonicotinic acid (A) vs. pyrazinecarboxylic acid.

A eutectic at 12% A and 207°. Decomposition at the solidus makes the phase boundaries indeterminate. No indication of solid solution formation.

5-Methyl-2-thiophenecarboxylic acid (A) vs. 5-bromo-2-thiophenecarboxylic acid.

Type V solid solution formation with a eutectic at 56% A and 117°, and a gap at 31-77% A.

p-Bromobenzoic acid (A) vs. 5-bromo-2-thiophenecarboxylic acid.

A eutectic at 3% A and 138°. Above 80% A, solid solution formation seems to take place, but the large range makes the determination of resolidification and remelting highly uncertain.

o-Toluic acid (A) vs. 3-methyl-2-thiophenecarboxylic acid.

Type V solid solution formation with a eutectic at 75% A and 88°, and a gap at 48-100% A.

p-Toluic acid (A) vs. 5-methyl-2-thiophenecarboxylic acid.

A eutectic at 25% A and 116°, with solid solution taking place at concentrations $\geq$ 80% A.

p-Toluic acid (A) vs. 5-bromo-2-thiophenecarboxylic acid.

A eutectic at 14% A and 134°, with solid solution taking place at concentrations $\geq$ 75% A.

## DISCUSSION OF RESULTS

The following conclusions can be reached from a study of the phase relationships investigated in this research.

a) Benzoic acid is not isomorphous with any of the heterocyclic acids. In the case of 2- and 3-thiophenecarboxylic acids, there does exist an indication of solubility at about 90% benzoic acid, due, probably, to the remarkable physical similarity of benzene and thiophene (9, 12). This insolubility of benzoic acid with heterocyclic acids, as well as the absence of solid solubility amongst most of the heterocyclic acids, would suggest that the specificity of hydrogen bonding (nature, strength) is significant amongst these acids[1]. It also follows that serological studies using the various heterocyclic acids as haptens against anti-benzoic acid sera cannot be correlated satisfactorily with these solubility studies. In agreement with our results, however, are the results of Landsteiner and Scheer (cf. p. 44) concerning the inhibition of benzoic acid by some heterocyclic acids.

b) While 2-thiophenecarboxylic acid is only ca. 10% soluble in benzoic acid, the 5-substituted (Br, $CH_3$) 2-thiophenecarboxylic acids are about 20% soluble in the corresponding para-substituted benzoic acids. In the case

[1] cf. in this connection the remarks on p. 41 concerning Lettré's work.

of an ortho-substituent, the solubility becomes greater: o-toluic acid is about 50% soluble in 3-methyl-2-thiophenecarboxylic acid. This increase in solubility, which is significant, is another manifestation of the "ortho-effect" (81; This Thesis p.40, footnote 2).

c) The isomorphogeny of Br and $CH_3$ is maintained: 5-bromo-2-thiophenecarboxylic acid is 18% soluble in p-toluic acid. Furthermore, 5-methyl-2-thiophenecarboxylic acid and 5-bromo-2-thiophenecarboxylic acid are soluble in each other.

d) The pyridinecarboxylic and pyrazinecarboxylic acids show an interesting relationship: while isonicotinic acid does not form solid solutions with any of the other acids, picolinic acid forms 10% solid solutions with nicotinic acid and 20% solid solutions with pyrazinecarboxylic acid; in addition, nicotinic acid forms solid solutions with pyrazinecarboxylic acid having but a relatively small solubility gap (50-80% nicotinic acid).

As a first step toward an explanation of these results, let us list some pertinent properties of the acids in question (Table I):

Table I

| | Picolinic acid | Nicotinic acid | Isonicotinic acid | Pyrazinecarb. acid |
|---|---|---|---|---|
| M.p. | 136° | 233° | 312° | 223° |
| Dec.temp.* | ca. 170° | -- | ca. 300° | ca. 170° |
| Log K(82,83) | -5.30 | -4.87 | -4.97 | |
| Sol.$H_2O$ | v.s. | s.h. | s.h. | |
| Sol.EtOH | v.s. | s.h. | sl.s.h. | |
| Sol.$Et_2O$ | v.sl.s. | v.sl.s. | v.sl.s. | |

The behavior of the acid dissociation constant (which, we propose, is actually related to the base constant of a zwitterion type molecule) cannot be explained unless we assume a positive charge on the nitrogen. This at onee suggests a type of intermolecular bonding reminiscent of that of the simple amino acids (84, 85), i.e. partly coulombic, partly hydrogen bonding. To judge from the melting point, decomposition point and solubility data, this intermolecular bonding probably takes place to a much larger extent in isonicotinic acid than in its isomers. Again, the same data suggest that picolinic acid exists as a low order polymer, perhaps as a dimer (intramolecular chelation has been suggested (86, 87) to account for its low decomposition temperature. This is not a necessary assumption). The

* See (g) for a discussion of decarboxylation.

relative positions of the ring nitrogen and the carboxyl may account for the difference in internal arrangement of the crystals. We can thus explain the low solubility of the pyridine carboxylic acids in each other.

The fact that pyrazinecarboxylic acid is much more soluble in nicotinic acid than in picolinic acid suggests that its intermolecular bonding resembles more closely that of nicotinic acid than that of picolinic acid. Strength is lent to this argument by the fact that the melting points of pyrazinecarboxylic acid and nicotinic acid are very close.

(e) While 5-thiazolecarboxylic acid does not form solid solutions with 2-thiophenecarboxylic acid, it is soluble in nicotinic acid (40-100% nicotinic acid). This result clearly indicates that interchanging a =CH- and a -S- in a molecule already highly specifically bonded (such as nicotinic acid) has little effect on the intermolecular array, whereas it may be sufficient otherwise (as in benzoic acid) to prevent isomorphism. It also shows that the interchange of a =CH- and an =N- under those circumstances will prevent isomorphism. The results strongly suggest that, whereas the hetero-N is involved in intermolecular bonding, the hetero-S is not.

In connection with the isomorphism of thiazole and pyridine (cf. p.42) it is of interest to note that many pairs (cf. p.42, footnote 1) do not form solid solutions. An explanation of that fact is not obvious. It is also

noteworthy that 5-thiazolecarboxylic acid decarboxylates quite readily, although it is formally analogous to nicotinic acid.

(f) The interpretation of the phase diagrams which involve as components the 5-membered ring acids (pyrrole-, furan- and thiophenecarboxylic acids) is not straightforward. 2-Pyrrolecarboxylic acid appears not to be isomorphous with the other two acids although slight solubility is indicated with 2-thiophenecarboxylic acid. However 2-thiophenecarboxylic acid forms solid solutions with furoic acid. This result is unexpected (especially in view of the insolubility of 2-thiophenecarboxylic acid and benzoic acid) and not readily interpretable.

(g) The decarboxylation of many of the acids offers some interesting results.

The acids for which decomposition is observed are picolinic acid, pyrazinecarboxylic acid, 2-pyrrolecarboxylic acid, 5-thiazolecarboxylic acid and isonicotinic acid. The following are the conclusions drawn from the decomposition behavior of these acids.

(1) Decarboxylation, as judged by the evolution of gas, takes place only when a liquid phase has been established. While it is not out of the question that a surface effect is involved, it seems more likely that the acids simply decarboxylate most readily when they are in the

liquid state or in solution.

(2) At small concentrations of the decarboxylating component, the decomposition begins at a fairly definite temperature, the decarboxylation temperature. As the concentration of the decarboxylating component increases, the decarboxylation temperature begins to rise also, corresponding to the fact that enough liquid has to be present to start decarboxylation.

The decarboxylation temperature is independent of the other components and may be above or below the melting point of the decarboxylating component. For the acids in question, we may construct the following Table I.

Table I

| Carboxylic acid | m.p.[1] | decarboxylation temperature |
|---|---|---|
| 2-Pyridine- | 135° | ca. 170° |
| Pyrazine- | 225° | ca. 170° |
| 2-Pyrrole- | 190° | ca. 130° |
| 5-Thiazole- | 220° | ca. 170° |
| 4-Pyridine- | 315° | ca. 300° |

[1] rounded off

The two conclusions elaborated above explain completely the phase diagrams which involve decomposition.

# SUMMARY

a) In connection with a study on the relation between serological specificity and solid solubility, twenty-five binary phase relationships have been investigated, the components being aromatic carboxylic acids.

b) In agreement with the strong inhibition of benzoic acid by 2-thiophenecarboxylic acid, the thiophenecarboxylic acids form very limited solid solutions with benzoic acid, which is not isomorphous with any of the other heterocyclic acids investigated. Isomorphism is noted with some methyl and bromo substituted benzoic and thiophenecarboxylic acids.

c) The phase behavior of pairs involving picolinic, nicotinic, isonicotinic and pyrazinecarboxylic acids may be explained on the basis of a difference in hydrogen bonding in crystals of these acids.

d) The isomorphism of thiazole and pyridine has been substantiated.

e) The study of the decarboxylation behavior of some of the acids investigated leads to some fundamental conclusions, involving the existence of a decarboxylation temperature.

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# PART III [1]

## A Study on the Hammick Reaction

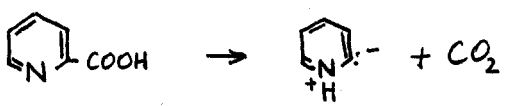
[1] Part of this work was done in collaboration with Dr. C. McCloskey.

# INTRODUCTION

The Hammick reaction (1, 2) proceeds formally according to the scheme

$$PyCOOH + R_1\text{-}CO\text{-}R_2 \rightarrow PyC(OH)R_1R_2 + CO_2$$

where Py- stands for the $\alpha$-pyridyl radical. Of a large number of decarboxylating agents tried (2), Ashworth et al. found that only picolinic, quinaldinic and isoquinaldinic acids underwent the reaction. Their results, i.e. that the carboxyl must be $\alpha$ to the ring nitrogen, which itself must be tertiary, led them to the conclusion that the reaction was of the nature of a cyanohydrin addition reaction, i.e. the first step



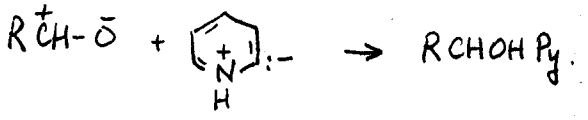
yielding a carbanion formally resembling the cyanide ion. Their sparse experimental evidence has since been amply enlarged by thorough experiments done in this laboratory by Drs. Buchman, Golding and Sargent (3). The following Table I summarizes their main results. Often much ketone, instead of carbinol, was isolated. The third column indicates the ratio of carbinol (C) to ketone (K). The symbol C, for example, by itself means that only carbinol was isolated. The yield is the total yield (C + K) based on picolinic acid.

Table I

Aldehyde RCHO

| R- | Yield | C:K |
|---|---|---|
| Phenyl | 34% | C |
| 4-Chlorophenyl | 31 | C |
| 3,4-Dichlorophenyl | 22 | 4:3 |
| 2,6-Dichlorophenyl | 24 | 5:1 |
| 2,4-Dichlorophenyl | 20 | K |
| 1-Naphthyl | 23 | 3:2 |
| 4-Chloro-1-naphthyl | ca. 2 | K |
| 4-Methoxyphenyl | 22 | 8:3 |
| 3,4-Methylenedioxyphenyl | ca. 8 | 2:5 |
| 4-Hydroxy-3-methoxyphenyl | ca. 0 | |
| 4-Hydroxyphenyl | ca. 0 | |
| 2-Furyl | 21 | 4:1 |
| 3-Nitrophenyl | 29 | K |
| 4-Dimethylaminophenyl | ca. 1 | K |

From these data we may draw the conclusion that the Hammick reaction is simply an electrophilic reaction of the carbonyl carbon:



and that, as more electrons are contributed to the ring by various substituents, the positive charge on the carbonyl carbon decreases, causing the aldehyde molecule to be less reactive with a concurrent decrease in yield. It is interesting to note that, as the yield decreases, the ratio C:K decreases also, in general. This can be understood if we make the justifiable assumption (4) that, as the + E effect of the substituents increases, the reduction potential of the resulting pyridyl-arylketones increases. Evidence exists (1, 2) that the yield of carbinol is increased if the reaction takes place under nitrogen[1].

The Hammick reaction, then, is a new type of carbonyl addition reaction. The effect of ring substituents on the yields of carbinol seems to bear little relation to the stability of the corresponding mandelonitrile (Table II):

Table II

| Aldehyde RCHO<br>R- | Dissociation constant of substituted mandelonitrile (5)<br>$K \times 10^2$ | Yield by Hammick reaction (3)<br>(%) |
|---|---|---|
| Phenyl- | 0.47 | 34 |
| 3-Nitrophenyl- | 0.27 | 29 |
| 2-Hydroxyphenyl- | 1.67 | 0 |
| 4-Chlorophenyl- | 1.81 | 31 |
| 4-Methoxyphenyl- | 3.12 | 22 |
| 4-Hydroxyphenyl- | 7.66 | 0 |
| 4-Diethylaminophenyl- | 39.00 | 0 |

[1] We may hence infer that air is the oxydizing agent.

We therefore see no virtue in the formalism employed by Ashworth et al. (2).

We propose the following mechanism.

I. Decarboxylation

$$RCOOH + B^- \rightarrow RCOO^- + BH$$

$$RCOO^- \rightarrow R^- + CO_2$$

Then, in the absence of competing electron acceptors

$$R^- + BH \rightarrow RH + B^-$$

II. Formation of carbinols

$$R^- + R_1R_2CO \rightarrow RR_1R_2CO^-$$

$$RR_1R_2CO^- + BH \rightarrow RR_1R_2COH + B^-$$

The ionization of the acid as a primary step seems important, to judge from the effect of amine catalysis in many cases of decarboxylation (6). Contrary to Ashworth et al., we do not believe that intramolecular chelation is necessary for this purpose. Rather, it is preferable to say that inductive and electromeric effects are at an optimum in picolinic acid (probably a zwitterion) to cause its decarboxylation. It is furthermore superfluous and perhaps misleading to emphasize the analogy between pyridyl and cyanide ion. In support of our thesis we have shown experimentally that isonicotinic acid can also be made to undergo the Hammick reaction.

To summarize, our modified theory differs in two important aspects from the theory proposed by Ashworth et al.(2):

1) The relative positions of the carboxyl and the basic center do not have to be adjacent as in α-imino acids, and are related only in as far as they affect the stability and reactivity of the carbanion.

2) The formalism of the cyanohydrin analogy is totally unnecessary, and the reaction is treated as an event per se, related to carbonyl additions as a whole, but not to the cyanohydrin addition particularly.

In addition to the experiment in which isonicotinic acid was subjected to the Hammick reaction, other, unrelated, experiments were performed[1] in an effort to elucidate the structure of some by-products obtained in the Hammick reaction. We had felt for some time that these by-products might be benzoins, in view of the fact that the carbinols were, according to Ashworth et al. (2), mandelonitrile analogues, and that these might react further with aldehyde to give, finally, the corresponding benzoins (7). We were encouraged in this hypothesis by the isolation of the pyridine analogue of the hypothetical benzoin cyanohydrin, but this compound did not yield benzoin on heating, but rather dissociated into benzaldehyde and pyridylphenylcarbinol. While one of the otherby-products might be a benzoin, the evidence is not conclusive.

[1] Done in collaboration with Dr. C. McCloskey.

A. 1,2-Diphenyl-1-(2-pyridyl)-ethylene glycol.

This compound was obtained[1] as a by-product of the benzaldehyde - picolinic acid condensation. Its structure was suggested by analysis and lead tetraacetate oxidation, and confirmed by synthesis. The glycol was unstable at high temperatures, dissociating into pyridylphenylcarbinol and benzaldehyde, and it was found that an equilibrium existed between these compounds and the glycol at elevated temperatures. Although a quantitative study was not contemplated, it was evident that the dissociation of the glycol was nearly complete at temperatures above 200°. The amounts of glycol formed in the Hammick reaction very nearly equaled that of the equilibrium mixture at the same temperature. This dissociation of the glycol is similar to that of benzpinacol, which is reported to dissociate into benhydrol and benzophenone.[8,9] The formation of benzpinacol by a reverse reaction (by heat alone[2]) has not been shown.

## Experimental Part[3]

Isolation of the glycol from the Hammick reaction mixture.

A mixture of 250 g. of dry picolinic acid and 2 kg. of redistilled benzaldehyde was heated at 160-170° for seventeen hours. The resulting solution was diluted with an equal

1 First noted by Dr. H. Sargent

2 The formation of triphenylglycol, hydrobenzoin and benzpinacol by the illumination of a mixture of benzyl alcohol and benzophenone has been reported (10)

3 Melting points corrected; analyses by Dr. Oppenheimer and staff.

volume of ether and extracted twice with 4 N hydrochloric acid. The extracts were basified with aqueous ammonia, and an oily precipitate formed. One liter of isopropyl ether was added and the crystals which formed at the interface were filtered off, to give ca. 5 g. of product. On recrystallization from toluene it formed white needles, m.p. 191-192° (dec., immersion temperature 175°)[1]. The compound is soluble in 2 N hydrochloric acid, sparingly soluble in hot toluene and insoluble in common organic solvents and water.

Anal. Calcd. for $C_{19}H_{17}O_2N$ (291.3): C, 78.34; H, 5.88; N, 4.81.
Found : C, 78.25; H, 5.79; N, 4.60.

The glycol forms a hydrobromide hemihydrate which crystallizes from acetone in the form of prisms, m.p. 194-196°(dec.)

Anal. Calcd. for $C_{19}H_{17}O_2N.HBr.\frac{1}{2}H_2O$ (381.2):
C, 59.87; H, 5.02; N, 3.68.
Found: C, 59.85; H, 4.93; N, 3.74.

The base, on quantitative titration with lead tetraacetate in glacial acetic acid (11), was found to use up one equivalent of this reagent.

From the isopropyl ether solution there was obtained 108 g. of 2-pyridylphenylcarbinol as previously described (3). An exhaustive investigation of the remaining syrups gave no indication of the presence of benzoin.

1 The melting point varies with the immersion temperature and the rate of heating.

Synthesis of 1,2-diphenyl-1-(2-pyridyl)ethylene glycol.[1]

To the Grignard reagent prepared from 32 g. (0.2 mole) of 2-bromopyridine and 10 g. of fine magnesium turnings was added a hot solution of 15.8 g. (0.075 mole) of benzoin dissolved in 100 ml. of dry thiophene-free benzene. The reaction mixture was refluxed and stirred mechanically for thirty minutes and then poured onto 50 ml. of saturated ammonium chloride solution containing some ice. The reaction flask was washed out with 150 ml. of chloroform and the washings added to the ice mixture. The resulting mixture was stirred well and the solid filtered off, washed with a little alcohol and dried.

The crude material was dissolved in 250 ml. of boiling pyridine and filtered from the unreacted magnesium. The residue was washed with 50 ml. of hot pyridine and the filtrates combined. The pyridine solution was heated to boiling, water added until the glycol was just in solution and on cooling the 1,2-diphenyl-1-(2-pyridyl)ethylene glycol crystallized out. The crystals were filtered off, washed with a little alcohol and dried. There was obtained 8.64 g. (39.6%), m.p. 200-201$^{0}$(rapid heating). A mixed melting point with the compound obtained from the Hammick reaction gave no depression.

Anal. Calcd. for $C_{19}H_{17}O_2N$: C, 78.34; H, 5.88; N, 4.81.
Found : C, 78.16; H, 5.91; N, 4.82.

[1] Performed by Dr. C. McCloskey.

Equilibrium between 2-pyridylphenylcarbinol (A), benzaldehyde (B) and 1,2-diphenyl-1-(2-pyridyl)ethylene glycol(C).

a) Reaction of (A) and (B)

A solution of 18.5 g.(0.1 mole) of highly purified (A) and 53 g. (0.5 mole) of redistilled (B) was heated for nineteen hours at 165-170°. The solution was diluted with 60 ml. of ether and then extracted four times with 25 ml. of 2.5 N hydrochloric acid. The extract was basified with aqueous potassium hydroxide, 50 ml. of isopropyl ether was added and the mixture shaken. The solid material was filtered off and washed with isopropyl ether. There was obtained 330 mg. of (C), m.p. 188° on recrystallization from methyl cellosolve. From the ethereal layer of the filtrate was recovered 8.2 g. of (A).

A second run at 165-170°,using the same quantities of (A) and (B),gave 430 mg. of (C).

Repeating the run at 190-195° (in a sealed tube) with 6.48 g. of (A) and 17.7 ml. of (B), 1 mg. of (C) was obtained.

At 130-135°, using 6.48 g. of (A) and 17.7 ml. of (B), 140 mg. of (C) was obtained.

A reaction of benzoin and picolinic acid at 165° yielded none of the addition compound (C).

b) Dissociation of (C)

1. A solution of 1.0 g. of (C) in 175 ml. of toluene was refluxed for one hour. There was recovered 0.9 g. of unchanged glycol (C).

2. The glycol (0.25 g.) was heated at 220° for one hour.

The odor of (B) was marked. A little toluene was added and the solution extracted with 3 N hydrochloric acid. The extract was basified and the precipitated oil dissolved in a mixture of ligroin (60-70°) and isopropyl ether. On seeding, crystals of (A), m.p. 74-75°, formed.

3. A mixture of 3.96 g. of (C) and 4 ml. of (B) was heated at 165° for eighteen hours. The reaction mixture was cooled to room temperature, an equal volume of ether added and the solution extracted with two 20 ml. portions of 10% hydrochloric acid. The combined extracts were basified with aqueous ammonia, 30 ml. of isopropyl ether added and the mixture shaken. The crystals which formed were filtered to give 35 mg. of starting material (C). The isopropyl ether layer was evaporated to a syrup and dissolved in ligroin (60-70°) containing 15% of isopropyl ether. After standing, crystals were deposited which were separated from the mother-liquor to give 0.65 g. of (A), m.p. 72-73°. The crystals did not depress the melting point of an authentic sample of (A). The combined filtrates were distilled in vacuo to give 1.3 g. of an oil, b.p. 110-120°/2 mm. , and 0.22 g. of high boiling residue. The oil was reduced by the method of Meerwein and Ponndorf to give 1.14 g. of (A). The total yield of (A) was 1.79 g.(79%).

B. A by-product from the Hammick reaction employing 2,4-dichlorobenzaldehyde.

When 2,4-dichlorobenzaldehyde was condensed with picolinic acid in the usual fashion, there was obtained (3) from the neutral fraction, after extraction with base and acid, a small amount of material which was recrystallized from benzene in large, well-formed prisms, m.p. 156-157°. Tests indicated the absence of nitrogen in this compound, and it was tentatively formulated as 2,4,2',4'-tetrachlorobenzoin on the basis of its elementary analysis.

Anal. Calcd. for $C_{14}H_8Cl_4O_2$: C, 48.04; H, 2.30.

Found : C, 48.61; H, 1.92.
48.48 1.76

In an attempt to prepare this compound by the benzoin condensation, 2,4-dichloromandelonitrile was obtained (3). We succeeded in isolating a compound from the benzoin condensation which proved identical with the product from the Hammick reaction. This compound analyzed for one active hydrogen per molecule and formed a dihydroquinoxaline with o-phenylenediamine, but it did not reduce Fehling's solution and was recovered unchanged after boiling with concentrated nitric acid. These facts do not allow for a definite assignment of structure. A more concentrated attack on the problem has unfortunately been delayed so far, other research programs taking priority.

## Experimental Part[1]

### Preparation of 2,4,2',4'-tetrachlorobenzoin(?) by the benzoin condensation.

An attempt to prepare this compound by conventional methods (12) failed. The following method was finally employed.

To a suspension of 27.3 g. of freshly distilled 2,4-dichlorobenzaldehyde in 42 ml. of ethanol was added a solution of 3.3 g. of potassium cyanide in 8 ml. of water. The solution was refluxed forty-five minutes and poured into a solution of 10 g. of sodium bicarbonate in 200 ml. of water. The solution was shaken for thirty minutes and then extracted three times with 50 ml. portions of ether. The ether extracts were evaporated, the residue redissolved in benzene and the solution shaken one hour with a saturated solution of sodium bisulfite. The benzene layer was separated from the aqueous phase and the bisulfite addition compound, dried and fractionated under nitrogen. The first fraction, b.p. 82-83°/0.15 mm., consisted of still unreacted aldehyde. The second fraction consisted of a yellow, viscous oil, b.p. 177-178°/0.15 mm. The yield of this crude 2,4,2',4'-tetrachlorobenzoin(?) was 6.0 g. (22%). The oil slowly solidified, and after four recrystallizations from ethanol gabe very pale yellow crystals, m.p. 156-157°. A sample of this compound did not depress the melting point of a sample obtained from the Hammick reaction.

[1]Melting points are corrected; microanalyses by Dr. Oppenheimer and staff.

Anal. Calcd. for Benzoin, $C_{14}H_8Cl_4O_2$: C, 48.04; H, 2.30.
Calcd. for Benzil, $C_{14}H_6Cl_4O_2$: C, 48.32; H, 1.72.
Found: C, 48.15; H, 1.92.

Anal. (Zerewitinoff)
Calcd. for Benzoin, $C_{14}H_8Cl_4O_2$: M.W. 348
Found: M. W. 325

2,3-Bis-(2,4-dichlorophenyl)-1,4-dihydroquinoxaline(?).

A solution of 0.108 g. of o-phenylenediamine was dissolved in 2 ml. of glacial acetic acid, and this solution added to a hot solution of 0.348 g. of 2,4,2',4'-tetrachlorobenzoin(?). After standing overnight, the precipitated dihydroxyquinoxaline(?) was centrifuged off and recrystallized from ethanol to give large colorless hexagonal prisms, m.p. 144-145°. With concentrated sulfuric acid, the compound gives a blood-red color, purportedly (13) a test for quinoxalines. It is not out of the question that the compound is 2,3-bis-(2,4-dichlorophenyl)-quinoxaline, formed on condensing 2,4,2',4'-tetrachlorobenzil(?) with orthophenylenediamine.

Anal, Calcd. for Dihydroquinoxaline, $C_{20}H_{12}N_2Cl_4$:
C, 56.90; H, 2.87; N, 6.64.
Calcd. for Quinoxaline, $C_{20}H_{10}N_2Cl_4$:
C, 57.17; H, 2.40; N, 6.67.
Found: C, 57.22; H, 2.67; N, 6.51.

C. The main product from the Hammick reaction employing cinchoninaldehyde.[1]

In this Hammick reaction, the ratio of main product to ketone obtained (no carbinol was obtained) was 20:1 (3). The elementary (C,H,N) analysis of the main product at first indicated it to be 4,4'-quinoloin[2], and it formed a hydrochloride which analyzed for 4,4'-quinoloin dihydrochloride dihydrate. However, when its dilute acidic solution was made just basic with dilute sodium hydroxide solution, a solid precipitated which, by its analysis and melting point proved to be the reported (15) 1,2-bis-(4-quinolyl)-ethylene. Further investigation of the main product has not so far been attempted.

[1] Experiments performed by Dr. C. McCloskey and Dr. E. Buchman et al. (3).

[2] Cinchoninaldehyde undergoes the benzoin condensation with the (unusual) formation of 4,4'-hydroquinoloin (14).

D. The Hammick reaction employing decarboxylating acids other than α-imino acids.

The theory of Ashworth, Daffern and Hammick, by which their reaction is restricted to α-imino acids, is based on their conclusions that "... the mere presence of a basic centre in the molecule was insufficient; the decarboxylation of pyridine and quinoline acids other than those containing the carboxyl group α to the nitrogen atom yielded no products of interaction with aldehydes and ketones. Furthermore the nitrogen atom must be tertiary..." (2). While giving no experimental evidence, those workers list in a footnote the acids which did not undergo the reaction. It includes, amongst a total of twenty-six acids, 2-methylquinoline-4-carboxylic acid and cinchophen. To test our more general theory of decarboxylation - carbonyl addition, we decarboxylated isonicotinic acid in the presence of excess benzophenone. The acid has its decarboxylation temperature (cf. part II, this thesis) at ca. 300°, and boiling benzophenone (306°) should therefore be applicable as solvent - carbonyl component. We obtained from the reaction a 3.5% yield of diphenyl-4-pyridylcarbinol, which analyzed correctly and had the reported melting point (16).

In addition we decarboxylated 2-pyrrolecarboxylic acid (decarboxylation temperature ca. 130°) in benzaldehyde, but only a trace (ca. 5 mg.) of a crystalline product was obtained, along with a large quantity of red amorphous product, which was not investigated further. The crystals

did not analyse for phenyl-2-pyrrylcarbinol or dipyrryl-phenylmethane, and were not investigated further.

## Experimental Part[1]

### Diphenyl-4-pyridylcarbinol.

A mixture of 19.8 g. (0.16 mole) of recrystallized isonicotinic acid and 250 g. (1.37 mole) of benzophenone was refluxed for 9½ hours, an air condenser being employed. A sealed-in plunger arrangement helped to scrape sublimed crystals of isonicotinic acid back into the reaction mixture. After 5 hours, ca. 3600 ml. of carbon dioxide had been evolved (90% of the theory). In the subsequent 4½ hours, only 50 ml. more of carbon dioxide was evolved.

The dark brown solution was allowed to cool to room temperature and then diluted with 500 ml. of benzene. This solution was extracted with 2.5 N hydrochloric acid, since more concentrated acid precipitates a tar, which redissolves on dilution with water. The acid extracts were basified and extracted three times with 25 ml. of benzene. About 1 g. of a brown solid (A) separated at the interface. The solid was removed by centrifugation and the benzene layer evaporated to dryness. The residue, on cooling, yielded a suspension of crystals in oil, which was diluted with acetone and centrifuged. The centrifugate consisted of crystals (B). The motherliquors, on standing overnight at

[1] Melting points corrected; microanalyses by Dr. Oppenheimer and staff.

5°, did not yield any further crystals and were not worked up further.

Crystals (B) were washed free of motherliquor with acetone, in which they are insoluble. There was obtained 0.85 g. of tan microscopic prisms, m.p. 192-232°. Four recrystallizations from benzene-pyridine raised its melting point to 237-238°. The pure material consists of colorless microscopic prisms.

Anal. Calcd. for $C_{18}H_{15}ON$ (261.3):

C, 82.73; H, 5.79; N, 5.36.

Found: C, 82.94; H, 5.79; N, 5.09.

The compound is reported to melt at 235° (16).

Solid (A) was dried and recrystallized from benzene-pyridine to yield 0.6 g. of the crude carbinol, m.p. 205°-232°. Thus the total yield of the reaction was 1.45 g. (3.5%).

## $C_{11}H_{11}N_2O_4$(?)

A mixture of 1.3 g. (0.011 mole) of pure 2-pyrrolecarboxylic acid and 10.0 g. (0.095 mole) of benzaldehyde was heated for three hours at 150±5°. At the end of this time, 290 ml. of carbon dioxide had been evolved (81% of the theory). The pyrrole and 5.2 ml. of benzaldehyde were distilled off, and the remaining red, gummy substance allowed to stand under ethanol overnight. By then the gum had solidified to a red, amorphous solid, soluble in ethanol. The solution was norited until it was translucent, the ethanol

stripped off and the residue heated with benzene. From the resulting solution there precipitated out, on cooling, ca. 5 mg. of a crystalline substance, which was extremely soluble in ethanol and insoluble in benzene. Recrystallization of the solid from benzene-ethanol gave colorless platelets, m.p. 192-193°, with a transformation point at 172-173°.

Anal. Calcd. for $C_{11}H_{11}N_2O_4$(?): C, 56.15; H, 4.72; N, 11.91.
Found : C, 55.02; H, 4.76; N, 12.11.

## SUMMARY

A modified theory of the Hammick reaction has been proposed, and partly substantiated by the successful reaction of isonicotinic acid with benzophenone.

Some byproducts obtained in the Hammick reaction have been investigated. The structure of one such by-product has been elucidated, and that of two other byproducts partly, though not conclusively, clarified.

## References


(1) Dyson and Hammick, J. Chem. Soc. 1937, 1724

(2) Ashworth, Daffern and Hammick, J. Chem. Soc. 1939, 809

(3) Unpublished work by Dr. Buchman et al.; Final Report, contract $OEM_{cmr}$-319.

(4) Adkins and Cox, J. Am. Chem. Soc. 60, 1151(1938)

(5) Lapworth et al., J. Chem. Soc. 1928, 2533; 1931, 1976

(6) Kharasch, Reinmuth and Mayo, J. Chem. Ed. 11, 88 (1934). This seems to be the only thorough discussion of decarboxylation and decarbonylation available.

(7) Lapworth, J. Chem. Soc. 1903, 1004

(8) Thörner and Zincke, Ber. 10, 1473(1877)

(9) Valeur, Bull. Soc. chim. 31, 1219(1879)

(10) Ciamician and Silber, Ber. 36, 1576, 1953(1903)

(11) Criegee, Ann. 481, 263(1930)

(12) Hickinbottom, "Reactions of Organic Compounds", p.161, Longmans, Green & Co., New York 1936.

(13) Reference (12), p.294

(14) Phillips, J. Am. Chem. Soc. 68, 2568(1946)

(15) Kaplan, J. Am. Chem. Soc. 63, 2654(1941)

(16) Tschitschibabin and Benewolenskaja, Ber. 61, 547(1928)

# PROPOSITIONS

1. The Hammick reaction (this Thesis) has hithertofore been applied to aldehydes and ketones only. I propose attempts to apply it to esters and nitriles, as a new alcohol and ketone synthesis respectively.

2. (a) It has been shown (this Thesis) that the scope of the Hammick reaction can be extended somewhat. It would be of interest to generalize it to a greater extent by applying it to other negatively substituted acids which do not contain the pyridine ring.

(b) A study of the temperature dependence of the rate constant of decarboxylation of various substituted picolinic acids would be of theoretical interest.

3. (a) The commonly accepted acid strengths of the pyridine carboxylic acids (Ostwald, Z.phys.Chem., 3, 385(1889)) cannot be explained in view of their decarboxylation behavior. I propose that they actually refer to the acid dissociation constant $PyH^{+}COO^{-} \rightarrow PyCOO^{-}+H^{+}$.

(b) The conclusions drawn by Erlenmeyer et al.(Helv.20, 310(1937)) concerning the effect of the ring on the acid strengths of various heterocyclic ring acids are invalidated by the nature of his comparison.

(c) It would be of interest to determine the crystal structures of the three pyridinecarboxylic acids and of pyrazinoic acid.

4. (a) The conclusions drawn by Ciamician (Z.phys.Chem. 18, 51(1895)) concerning the isomorphism of some heterocyclic acids with benzoic acid are in conflict with our results (this Thesis). I propose that complete phase diagrams are necessary in order to draw such conclusions.

(b) The argument offered by Erlenmeyer and Berger (Biochem.Z. 252, 22(1932)), that a basis for the crossreactivity of diphenyl ether and diphenyl methane may be found in the fact that the two compounds form solid solutions, is invalid, since evidently these two compounds form a simple eutectic (Lüttringhaus, Ann. 528, 223(1937)).

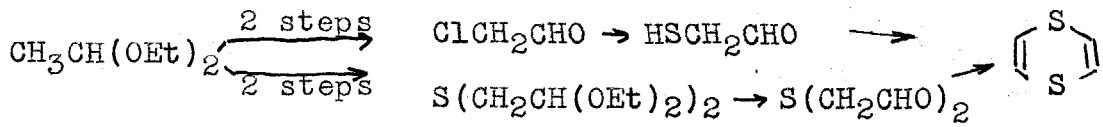
5. (a) The synthesis of 2,4,5-trichloro-3-nitrothiophene, m.p. 86°(Rosenberg, Ber.19, 651(1886)) and of 3,4,5-trichloro-2-nitrothiophene, m.p. 73-76°(Steinkopf et al., Ann. 512, 151(1934)) could not be repeated (Steinkopf et al., Ann. 532, 250(1937)), a product m.p. 70° being obtained in both cases, and neither product depressing the melting point of the other. I propose that this material be submitted to chromatographic analysis, since it may well be the minimum of a series of solid solutions.

(b) Many isomeric halo-derivatives of thiophene are iso-

morphous and have the same melting point (Steinkopf, "Die Chemie des Thiophens", p. 15ff.). I propose that the luminescence analysis presently employed to arrive at the identity of such compounds be replaced by the criterion of chromatographic behavior.

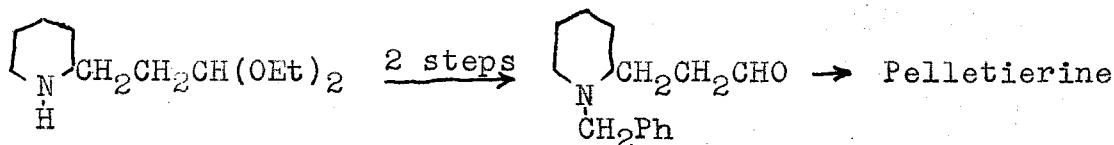
(c) Much difficulty is encountered in finding a substance the derivatives of which lend themselves to a successful study of morphotropy (this Thesis). I propose the homologous series of 2,3,5-trichloro-4-alkylthiophenes as a promising subject for such a study. This, supplemented by an appropriate immunological study, would lead to interesting semi-quantitative results.

6. (a) An electron diffraction study on 1,4-dithiene would be of considerable interest; however the preparation of this compound has met with difficulties so far (Meyer, "Die Thiophengruppe", p. 274). The following alternate syntheses are proposed:



(b) Only 2,5-derivatives of 1,4-dithiene are known. A synthesis for 2,6-derivatives is proposed (cf. Baker et al., J.Am.Chem.Soc. 58, 262(1936)).

7. (a) The extreme sensitivity of Pelletierine to oxidation, heat and pH have rendered its synthesis impossible to date (Spielmann et al., J.Org.Chem. 6, 780(1941)). I propose the following synthesis:



(b) It has been proposed (Spielmann, lo.cit.; Beets, Rec. trav. 62, 553(1943)) that Pelletierine exists largely in the bicyclic carbinolamine configuration. This claim could be readily verified by a measurement of its absorption spectrum.

8. I propose a study of the photolysis of $\omega$-diazoketones in the presence of water, in order to elucidate somewhat the function of the catalyst in the Wolff rearrangement, and in order to find conditions for a variation of the Arndt-Eistert synthesis, in which the rearrangement may take place in the absence of thermal excitation and of catalysts.

9. I propose that the measurement of the heat of formation of fluorosilane would constitute a contribution towards our concept of single bond energies (Pauling, "The Nature of the Chemical Bond").

10. The experimental results of Herz (Z. anorg. allgem. Chem. 187, 379(1930)) concerning the ratio of the temperature coefficient of fluidity to the coefficient of thermal expansion of a liquid can be explained on the basis of Batschinski's theory of viscosity (Z.phys.Chem. 84, 643(1913)).

11. Lest visiting lecturers garner a mistaken impression of the soundness of mind of Gates-and-Crellinites, I propose they be forewarned of the idiosyncrasies of The Sisters.