[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Metalation of Phenoxazine and Some of its Derivatives[1]

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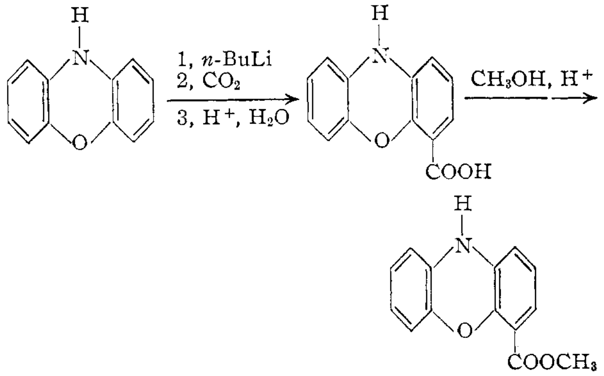
Phenoxazine, 10-ethyl-, and 10-phenylphenoxazine are metalated by *n*-butyllithium to give what probably are 4-substituted carboxylic acids. Attempts to prove the structures by interconversion of the acids were not successful. 10-Ethylphenoxazine-3-carboxylic acid and 10-(4-carboxyphenyl)-phenoxazine were prepared by a halogen–metal interconversion reaction, which established these structures.

The metalation of heterocycles is a means of obtaining a reactive intermediate very useful in the synthesis of many derivatives. This method of making derivatives is especially useful since the substitution often proceeds at positions different from those of normal electrophilic substitution. It was thus considered profitable to determine whether phenoxazine would metalate, and, if possible, determine the position of substitution.

Phenoxazine, 10-ethylphenoxazine and 10-phenylphenoxazine[3] are metalated quite slowly by *n*-butyllithium in ether. Some dimetalation occurs in each case. An attempt was made to produce only the monometalated product[4] by the use of methyllithium, but under the conditions tried only a very small amount of metalation occurred.

The position of metalation was not definitely proven, but it seems quite safe, since much comparative metalation has been done, to assume that metalation probably would occur in the 4-position, next to the oxygen.



The infrared spectra[5] of the carboxylic acids from the carbonation of the metalation products are quite similar, especially in the region 12.0-13.5μ. The band expected for a vicinally trisubstituted benzene was present but weak, and there was no band in the region where 1,2,4-trisubstituted benzenes generally occur. This would indicate substitution in either the 1- or the 4-position. Competitive metalation of dibenzofuran, dibenzothiophene and 9-ethylcarbazole has indicated that the order of ease of metalation for the three hetero atoms is: O > S > N.[6] Despite this fact, it seemed possible that unsubstituted phenoxazine might have metalated *ortho* to the nitrogen, since phenothiazine metalates next to the nitrogen.[7] However, the failure of methyl phenoxazinecarboxylate to react with ethyl iodide in base is evidence against substitution in the 1-position. If the ester group of this compound were in either the 1- or the 3-position, then it would act through conjugation to enhance the acidity of the hydrogen attached to the heterocyclic nitrogen. This would increase the ease of ethylation by ethyl iodide in base. Such ethylations occur readily with 3-nitrocarbazole[8] and 3-nitrophenoxazine[9] but not with unsubstituted phenoxazine.[3]

The carboxylic acid substituted in the 3-position of 10-ethylphenoxazine was prepared from 3-bromo-10-ethylphenoxazine[10] and is different from the acid prepared by metalation of 10-ethylphenoxazine.

Attempts were made to convert phenoxazine-4-carboxylic acid and 10-ethylphenoxazine-4-carboxylic acid to a common derivative by making the methyl ester of each and then ethylating methyl phenoxazine-4-carboxylate. The esters were prepared quite easily from the reaction of the acids with absolute methanol using anhydrous hydrogen chloride as a catalyst. The ethylation was not successful. Two attempts were made. The first using ethyl iodide in base did not yield the desired product since the H–N of the heterocycle was not sufficiently acidic. The second method, using a general procedure for preparing 10-alkylphenoxazine derivatives,[3] involved the use of sodium amide followed by ethyl iodide. The sodium amide appeared to have reacted with the ester group or some other part of the molecule other than the heterocyclic nitrogen. The product which was isolated was not identified.

Experimental[11]

Metalation of Phenoxazine.—A 9.16-g. (0.05 mole) sample of phenoxazine[3] in sodium-dried ether was metalated with 0.12 mole of *n*-butyllithium[12] for 110 hours at room temperature under a dry, oxygen-free nitrogen atmosphere. When the *n*-butyllithium was consumed, as indicated by Color Test IIa,[13] the mixture was poured jet-wise into a Dry

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[2] Du Pont Teaching Fellow, 1956–1957.

[3] H. Gilman and L. O. Moore, THIS JOURNAL, **79**, 3485 (1957).

[4] S. H. Eidt, unpublished Ph.D. Thesis, Iowa State College, Ames, Iowa, 1955, p. 215.

[5] Phenoxazine derivatives substituted in the 3-position have distinctly different spectra in the 12.0–13.5 μ region. See H. Gilman and L. O. Moore, unpublished studies.

[6] H. Gilman and J. W. Morton, in Roger Adams "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 258.

[7] H. Gilman, D. A. Shirley and P. R. Van Ess, THIS JOURNAL, **66**, 625 (1944).

[8] T. S. Stevens and S. H. Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

[9] H. Gilman and L. O. Moore, unpublished studies.

[10] L. O. Moore, unpublished studies.

[11] All melting points are uncorrected.

[12] H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, THIS JOURNAL, **71**, 1499 (1949).

[13] H. Gilman and J. Swiss, *ibid.*, **62**, 1847 (1940).

Ice–ether slurry, and allowed to warm to room temperature. Water was added to dissolve the salt of the acid and the two layers separated. The organic layer was washed with 10% potassium hydroxide, and the combined aqueous solution was washed with fresh ether. The water solution was warmed on a steam-bath to remove any dissolved ether and then acidified with dilute hydrochloric acid. This gave 7.8 g. of crude acid, melting over the range 200–215°. From the ether layer was obtained 4.2 g. of phenoxazine (identified by mixture melting point). The acid was refluxed with 95% ethanol which left a yellow residue, melting over the range 315–320°. Attempts to purify the dibasic acid from this failed. From the ethanol solution was obtained 3.18 g. of monobasic acid, melting over the range 230–240°. This was further purified by recrystallization from toluene, using Norit A to decolorize, to give 0.50 g. of phenoxazine-4-carboxylic acid, m.p. 244–245°.

Anal. Calcd. for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.31; neut. equiv., 227.2. Found: C, 68.89, 68.63; H, 3.88, 4.00; N, 6.14, 6.11; neut. equiv., 228.6.

Metalation of 10-Ethylphenoxazine. Method A. With *n*-Butyllithium.—In the same manner as described above, 10.56 g. (0.05 mole) of 10-ethylphenoxazine[3] was metalated with 0.07 mole of *n*-butyllithium at ether reflux for 42 hours. The crude acid, 8.5 g., was refluxed with 1 l. of absolute ethanol. This left a residue melting over the range 300–305°. Attempts to purify this high melting solid failed, as the neutral equivalent after several recrystallizations and triturations using acetic acid indicated that some monocarboxylic acid was still present. From the ethanol solution was obtained, after several recrystallizations, 3.90 g. of 10-ethylphenoxazine-4-carboxylic acid, m.p. 163.5–165.0°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49; neut. equiv., 255.26. Found: C, 70.45, 70.33; H, 5.38, 5.33; N, 5.27, 5.42; neut. equiv., 253.9.

From the ether solution, left from the extractions, was obtained 3.5 g. of 10-ethylphenoxazine (identified by mixture melting point).

Method B. With Methyllithium.—As described for the metalation of phenoxazine, a 5.28 g. (0.025 mole) sample of 10-ethylphenoxazine was metalated with 0.05 mole of methyllithium[14] at ether reflux for 26 hours. There was isolated after extraction 0.2 g. of a yellow acid, melting over the range 106–206°. Dissolution in base and acidification gave 0.1 g. of product, m.p. 160–163°. A mixture melting point with 10-ethylphenoxazine-4-carboxylic acid was undepressed. From the ether layer was isolated 4.97 g. of 10-ethylphenoxazine (identified by mixture melting point).

Metalation of 10-Phenylphenoxazine. Method A. With *n*-Butyllithium.—As described for the metalation of phenoxazine, 10.0 g. (0.039 mole) of 10-phenylphenoxazine was metalated with 0.07 mole of *n*-butyllithium for 23 hours. There was isolated, after extractions, 8.20 g. of crude acid. The crude mixture was recrystallized from ethanol and toluene to give 0.47 g. of 10-phenylphenoxazine-4-carboxylic acid, m.p. 208–210°.

Anal. Calcd. for $C_{19}H_{13}NO_3$: N, 4.62; neut. equiv., 303.3. Found: N, 4.55, 4.68; neut. equiv., 306.1.

Part of the crude mixture was insoluble in ethanol and was recrystallized from acetic acid three times to give 1.38 g. of product, which very probably is 10-phenylphenoxazine-4,6-dicarboxylic acid, m.p. 332.5–334.0°.

Anal. Calcd. for $C_{20}H_{13}NO_5$: N, 4.03; neut. equiv., 173.7. Found: N, 3.83, 3.99; neut. equiv., 176.9.

From the ether solution, left from the extractions, was obtained 1.10 g. of 10-phenylphenoxazine (identified by mixture melting point).

Method B. With Methyllithium.—As described for the metalation of phenoxazine, 10-phenylphenoxazine (6.48 g., 0.025 mole) was metalated with 0.05 mole of methyllithium at ether reflux for 26 hours. The crude acid, 0.20 g., was dissolved in base and reprecipitated with hydrochloric acid to give 0.10 g. of acid, melting over the range 197–205°. A mixture melting point with 10-phenylphenoxazine-4-carboxylic acid, isolated above, was undepressed. From the ether solution was recovered 6.05 g. of 10-phenylphenoxazine (identified by mixture melting point).

10-Ethylphenoxazine-3-carboxylic Acid.—To a stirred solution of 4.35 g. (0.015 mole) of 3-bromo-10-ethylphenoxazine[15] in 100 ml. of anhydrous ether was added 0.015 mole of *n*-butyllithium. The mixture was stirred for 30 minutes and then poured jet-wise into a Dry Ice–ether slurry. After allowing the mixture to warm to room temperature, water was added to dissolve the salt of the acid. The layers were separated, the ether layer washed with 10% potassium hydroxide, and this wash solution combined with the water layer. There separated on acidification 2.30 g. of crude acid, melting over the range 175–190°. Recrystallization from an ethanol–water mixture and a toluene–petroleum ether (b.p. 60–71°) mixture gave 0.60 g. of acid, m.p. 207.5–210.5°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: N, 5.49; neut. equiv., 255.3. Found: N, 5.42, 5.29; neut. equiv., 258.6.

This acid is different from the acid obtained by metalation of 10-ethylphenoxazine.

10-(4-Carboxyphenyl)-phenoxazine.—In the same manner as described just above, 2.62 g. (0.008 mole) of 10-(4-bromophenyl)-phenoxazine[3] was treated with 0.013 mole of *n*-butyllithium and carbonated to produce 1.1 g. of crude acid, melting over the range 245–255°. The acid was recrystallized twice from an ethanol–water mixture to give 0.56 g. of yellow powder, m.p. 258.5–260.5°.

Anal. Calcd. for $C_{19}H_{13}NO_3$: N, 4.62; neut. equiv., 303.3. Found: N, 4.54, 4.41; neut. equiv., 307.6.

Methyl 10-Ethylphenoxazine-4-carboxylate.—A 0.8-g. sample of 10-ethylphenoxazine-4-carboxylic acid was refluxed for 48 hours in 200 ml. of absolute methanol saturated with hydrogen chloride. The cooled mixture was neutralized with 10% potassium hydroxide, and the yellow oil which separated was extracted with ether. Distillation of the ether left only a small amount of yellow oil which would not crystallize. The infrared spectrum of this oil had the bands expected for methyl 10-ethylphenoxazine-4-carboxylate.

Methyl x-Nitro-10-ethylphenoxazine-4-carboxylate.—In a second attempt to prepare methyl 10-ethylphenoxazine-4-carboxylate using 2.0 g. of the corresponding acid, the ether solution was washed with dilute nitric acid just prior to concentration. As the volume of the ether solution became small, 1.15 g. of a dark red solid separated, melting over the range 135–150°. Several recrystallizations from ethyl acetate gave 0.70 g. of fine, red needles, m.p. 173.5–175.0°. Qualitative tests for both an ester and a nitro group[16] were positive.

Anal. Calcd. for $C_{16}H_{14}N_2O_5$: N, 8.93. Found: N, 8.87, 8.91.

The nitration seemed to occur when the ether was distilled to a low volume. Apparently some of the nitric acid remained from the wash solution.

The position of nitration was not determined, but it appears from the infrared spectrum and from previous work on the nitration of this heterocycle[9] that the product is methyl 3-nitro-10-ethylphenoxazine-6-carboxylate.

Methyl Phenoxazine-4-carboxylate.—A solution of 3.0 g. of phenoxazine-4-carboxylic acid in 200 ml. of absolute methanol saturated with hydrogen chloride was refluxed for 36 hours. From this mixture separated 2.0 g. of a yellow solid, melting over the range 100–112°. Recrystallization from an ethanol–water mixture, using Norit A to decolorize, gave 1.0 g. of yellow needles, m.p. 112.5–114.0°

Anal. Calcd. for $C_{14}H_{11}NO_3$: N, 5.81. Found: N, 6.08, 6.18.

Reaction of Methyl Phenoxazine-4-carboxylate with Ethyl Iodide. Method A.—Methyl phenoxazine-4-carboxylate (0.30 g.) was refluxed for 4 hours in 50 ml. of acetone with 10 ml. of ethyl iodide and 0.2 g. of potassium hydroxide. Work-up of the mixture gave the starting ester as the only isolable material (identified by mixture melting point).

Method B.—To 0.02 mole of sodium amide in liquid ammonia was added 0.5 g. of methyl phenoxazine-4-carboxylate. The solution was stirred for 20 minutes and 25 ml. of ethyl iodide was added. The main solution was yellow

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[14] H. Gilman, E. A. Zoellner and W. M. Selby, THIS JOURNAL, **55**, 1252 (1932).

[15] This compound was prepared by the bromination of 10-ethylphenoxazine. The results of bromination studies will be published later.

[16] H. Gilman and T. N. Goreau, THIS JOURNAL, **73**, 2939 (1951).

and a separate red liquid phase was present at the bottom of the flask. After warming to room temperature, water and ether were added and the layers separated. Distillation of the ether under reduced pressure left a yellow glass which was recrystallized from an ethanol–water mixture to give 0.15 g. of yellow needles melting over the range 90–94°. A mixture melting point with the starting material was depressed. The analysis of the product indicated 9.21 and 9.29% of nitrogen present.

Acknowledgment.—All infrared spectra were obtained by use of the Baird double beam infrared spectrophotometer of the Institute for Atomic Research, Iowa State College. The writers express their appreciation to Robert McCord and E. Miller Layton for the preparation of the spectra.

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[Contribution from the Department of Chemistry of the University of Michigan]

1,5-Diaryl-2,3-pyrrolidinediones. XI. Observations on Synthetic Methods and the Effect of 4-Substituents on Chemical Properties

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A number of 1,5-diphenyl-2,3-pyrrolidinediones with substituents in the 4-position have been prepared and examined. Unlike the parent member of the series, these compounds appear to be extensively, if not fully, enolized and thus also may be characterized as 4-substituted-1,5-diphenyl-Δ^3-2-pyrrolinones. Methods of synthesis are described and contrasted with those for 1,5-diphenyl-2,3-pyrrolidinedione. The thermal decomposition of two of the 4-substituted compounds is described and the major product from each is characterized.

In an earlier paper[2] reference was made to unpublished work by one of us wherein 4-carbomethoxy-1,5-diphenyl-2,3-pyrrolidinedione was decarbomethoxylated to give what was then thought to be 1,5-diphenyl-2,3-pyrrolidinedione (I) but what has recently been unequivocally identified as the isomeric 3-anilino-5-phenyl-2(5H)-furanone.[3] In a later publication[4] reference was made to the unsatisfactory state of this reaction. Subsequently, sporadic investigation of the reaction was intensified with the following results; while the carbomethoxy group readily affords carbethoxy with ethanol (and *vice versa*) attempts at hydrochloric and hydrobromic acid induced hydrolysis lead to not readily characterizable products[5]; basic hydrolysis under mild conditions is essentially without effect, and under drastic conditions affords at best a poor yield of the 3-anil of the desired I. Thus the reported[2] isolation of I was a purely fortuitous isolation of 3-anilino-5-phenyl-2(5H)-furanone.

When it appeared that resistance to hydrolysis coupled with reluctance of the alkali enolates to be alkylated ruled out the 4-carbalkoxy-1,5-diphenyl-2,3-pyrrolidinediones as convenient sources of either I or its 4-substituted analogs, attention was directed to the previously reported "decarboxylation" of the 4-carbalkoxy-1,5-diphenyl-2,3-pyrrolidinediones.[4] The major reactant of their thermal decomposition had not been identified; and since we were working with an enolized β-ketoester, the reaction might well be another instance of thermal "decarbalkoxylation," as first studied by Meerwein[6] (and very recently elegantly applied in steroid synthesis by Johnson and his collaborators[7]).

The reported quantitative evolution of carbon dioxide was observed upon heating 4-carbethoxy-1,5-diphenyl-2,3-pyrrolidinedione (II) in nitrobenzene,[4] with no water known to be present. Consequently, the analogy to Meerwein's reaction was not complete, and an attempt was made to see if ethylene were also produced, and if so, what was produced from the analogous methyl ester. However, collection of the evolved gas over 50% potassium hydroxide, as for a Dumas nitrogen determination,[8] afforded completely negative results. Thus ordinary ester pyrolysis was ruled out, and in spite of the apparent absence of water it appeared that the reaction must resemble Meerwein's, the necessary water being present in the solvent and adsorbed on the solute. The nitrobenzene was removed in an air stream leaving a substance which melted at 166–167° and which showed infrared absorption at 1710 and 1760 cm.$^{-1}$ but none in the hydroxyl region. The same substance was obtained from the analogous methyl ester. Analytical data and a resemblance of the infrared spectrum to those of authentic 2,3-pyrrolidinediones[9] suggested that thermal "decarbalkoxylation" had indeed occurred with production of I. Characterization of the resulting product and details of the "decarbalkoxylation" already have been reported.[10] Thus with the parent member of the series (I) in hand, attention was turned to non-functional 4-substituents.

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[1] Abstracted from the Ph.D. Dissertation of Irene Shuster Covey, University of Michigan, 1957.

[2] W. R. Vaughan and L. R. Peters, *J. Org. Chem.*, **18**, 382 (1953).

[3] (a) W. L. Meyer and W. R. Vaughan, *ibid.*, **22**, 98 (1957); (b) **22**, 1560 (1957).

[4] W. R. Vaughan and D. I. McCane, *ibid.*, **20**, 143 (1955).

[5] See, however, H. H. Wassermann and R. C. Koch, *Chemistry & Industry*, 428 (1957), who appear to have hoped for effective hydrolysis by means of hydriodic acid, but actually achieved hydrolysis, decarboxylation and *reduction* of the 3-carbonyl owing to the hypophosphorous acid present in commercial concentrated hydriodic acid, a most interesting result which has recently been repeated in this Laboratory (W. L. Meyer, private communication).

[6] (a) H. Meerwein, *Ann.*, **398**, 242 (1913); (b) in this study enolizable β-ketoesters were heated at 200° with water in sealed tubes.

[7] (a) W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, This Journal, **78**, 6354 (1956); W. S. Johnson, R. Pappo and W. F. Johns, *ibid.*, **78**, 6339 (1956); (b) these authors appear to favor a direct, homolytic or heterolytic decomposition and propose to study the mechanism.

[8] W. R. Vaughan, W. T. Boyd, D. I. McCane and G. J. Sloan, *Anal. Chem.*, **23**, 508 (1951).

[9] Very kindly furnished by Professor Phillip L. Southwick; *cf.* P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

[10] W. L. Meyer and W. R. Vaughan, *ibid.*, **22**, 1554 (1957).