Condensation of Pyrrocoline with Oxalyl Chloride.—To a solution of 2.0 g. of pyrrocoline in 50 ml. of benzene there was added dropwise with stirring a solution of 2.0 g. of oxalyl chloride in 5 ml. of benzene. The resulting black solution was allowed to stand at room temperature overnight before the material, which precipitated, was collected. Extraction of this dark material with benzene afforded a yellow solid which, on sublimation, gave 400 mg. (15%) of yellow crystals, m.p. 240°. The composition of these crystals are in accord with structure XII.

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 75.15; H, 4.50; N, 9.65.

The filtrate from the above experiment was concentrated to give a green solid. This was digested with dilute aqueous sodium hydroxide and then acidified. The precipitated solid was collected and recrystallized from benzene to give 2.45 g. (80%) of fine yellow prisms, m.p. 174–175°. The composition and properties of these crystals are in accord with those expected for X.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.35; H, 3.75; N, 7.20.

In the above experiment, when the concentration of the original filtrate to give the solid was followed by sublimation, an orange powder, m.p. 90–92°, could be isolated in good yield. This has the correct composition for 3-pyrrocolylglyoxylyl chloride.

Anal. Calcd. for $C_{10}H_6NO_2Cl$: C, 57.82; H, 2.89. Found: C, 58.23; H, 3.6.

Methyl 3-Pyrrocolylglyoxylate (XI).—Treatment of 3-pyrrocolylglyoxylic acid (X) in the solid state with an ethereal solution of diazomethane caused vigorous effervescence of nitrogen. Evaporation of the ether gave a yellow gum which crystallized on trituration with methanol. Further purification could be accomplished either by recrystallization from a benzene–hexane mixture or by sublimation to give yellow crystals, m.p. 67–69°, in good yield.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.05; H, 4.45; N, 6.90. Found: C, 65.25; H, 4.58; N, 6.44.

All attempts to effect a Reformatski reaction between the ester XI and methyl bromoacetate using the usual conditions for this reaction[23] failed.

Cyclization of 3-(2′-Pyridyl)-propanol to give Pyrrocoline.—This has been investigated using the following catalysts: Raney nickel, 5, 10 and 30% palladium-on-charcoal, and a 30% palladium-on-charcoal catalyst prepared by the formaldehyde reductive procedure.[22] Of these the latter catalyst gave pyrrocoline in highest yield, was most consistent and gave relatively small amounts of side products. The main side products identified were carbon monoxide and 2-ethylpyridine. The presence of carbon monoxide was demonstrated by the fact that the effluent gases from the reaction mixture did not contain carbon dioxide but, after passage over hot copper oxide, carbon dioxide was present and the copper oxide was reduced to metallic copper. The presence of 2-ethylpyridine was shown by preparing a picrate of the oil from the steam distillation and showing that the stable picrate, so formed, was identical with an authentic sample of the picrate of 2-ethylpyridine. The formation of carbon monoxide and 2-ethylpyridine was favored using Raney nickel as catalyst and accounted for 25–30% of the 3-(2′-pyridyl)-propanol in this case. The following constitutes a procedure that has been duplicated repeatedly for preparing pyrrocoline.

A mixture of 2.1 g. of a 30% palladium-on-charcoal catalyst[22] and 100 g. of 3-(2′ pyridyl)-propanol was heated at 270–280° for 36 hours in a flask equipped for passing through a continuous stream of nitrogen and for removal of water as formed. At the end of this time the flask was cooled and steam distillation continued until organic material no longer separated from the distillate. When the distillate was allowed to stand in a cold room for 24 hours, pyrrocoline crystallized in the aqueous solution and could be collected by filtration. Sublimation of the crude solid gave 33.3 g. (39%) of white crystals, m.p. 73–74°.

2-(α-Hydroxypropyl)-6-methylpyridine.—To 1.3 l. of a 2.5 *M* ethereal solution of phenyllithium there was added with cooling and stirring a solution of 178 g. of 2,6-lutidine in 500 ml. of dry ether. The solution was allowed to stand at room temperature for 1 hour and then, after cooling the solution in an ice-bath, a solution of 74.4 g. of ethylene oxide in 750 ml. of dry ether was added over a period of 40 minutes. The solution was allowed to stir an additional hour at room temperature and then was decomposed by adding moist ether followed by aqueous 3 *N* hydrochloric acid. The aqueous layer was separated, made basic with concentrated sodium hydroxide solution, and extracted with methylene chloride. After the methylene chloride extract had been dried over sodium sulfate the solution was concentrated and the residual oil distilled. There was obtained 123.5 g. (49%) of a colorless oil, b.p. 75–76° at 0.3 mm. The oil was hygroscopic making it difficult to obtain satisfactory analyses.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 70.46; H, 8.83; N, 9.02.

5-Methylpyrrocoline.—The cyclization of 2-(γ-hydroxypropyl)-6-methylpyridine to 5-methylpyrrocoline was carried out following the same procedure given above for the preparation of pyrrocoline. From 102 g. of 2-(γ-hydroxypropyl)-6-methylpyridine there was obtained 66 g. (75%) of a colorless oil, b.p. 93° at 15 mm. The infrared spectrum of this oil was essentially superimposable with that of an authentic sample of 5-methylpyrrocoline.[20]

(23) "Organic Reactions," Vol. I, edited by R. Adams, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 1.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER, ROCHESTER 20, N. Y.]

The Formation of Pyrrocolines by the Reaction of Dimethyl Acetylenedicarboxylate with Heterocyclic Zwitterions[1]

BY V. BOEKELHEIDE[2] AND K. FAHRENHOLTZ[3]

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The reaction between dimethyl acetylenedicarboxylate and the zwitterionic compounds derived from 1-phenacylpyridinium bromide, 1-phenylacyl-2,5-dimethylpyrazinium bromide and 1-phenylacylpyrindanium bromide leads to the formation of a five-membered ring giving the corresponding pyrrocoline or azapyrrocoline derivatives.

Recently, it was reported that the addition of dimethyl acetylenedicarboxylate to pyrrocoline in the presence of a dehydrogenation catalyst provides a convenient route for the synthesis of cycl[3.2.2]-azine and certain derivatives.[4] Since the Chichibabin reaction is the standard method of preparing substituted pyrrocolines,[5] it seemed that a combination of these two reactions would allow the synthesis of a wide variety of cycl[3.2.2]azine derivatives starting from readily available materials. The

(1) Aided in part by the Office of Ordnance Research, Army Ordnance Contract No. DA-30-069-O.R.D. 2528.

(2) University of Oregon, Eugene, Ore.

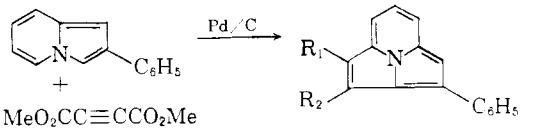
(3) Du Pont Predoctoral Fellow, 1958–1959.

(4) A. Galbraith, T. Small, R. A. Barnes and V. Boekelheide, THIS JOURNAL, **83**, 453 (1961).

(5) A. E. Chichibabin, *Ber.*, **60**, 1607 (1927).

present study was undertaken to try to exploit this possibility.

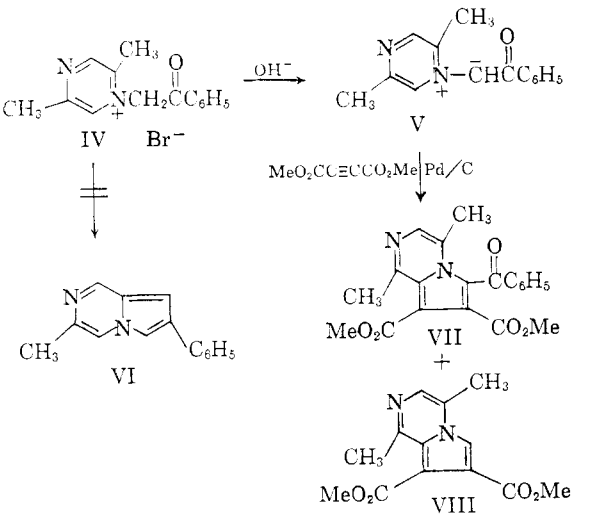
Probably the most common Chichibabin reaction involves the cyclization of an N-phenylacylpyridinium halide and gives a substituted 2-phenylpyrrocoline. Therefore, our initial studies concerned the addition of dimethyl acetylenedicarboxylate to 2-phenylpyrrocoline. This proceeded smoothly in the presence of a 5% palladium-on-charcoal catalyst to give the corresponding cycl[3.2.2]azine derivative I. The structure of I was readily established by its hydrolysis to the dibasic acid II followed by decarboxylation to the known 2-phenylcycl[3.2.2]-azine (III). Thus it was evident that the bulky phenyl group at the 2-position did not offer undue steric hindrance to the addition of dimethyl acetylenedicarboxylate and it seemed probable that other pyrrocolines similarly substituted could be employed.



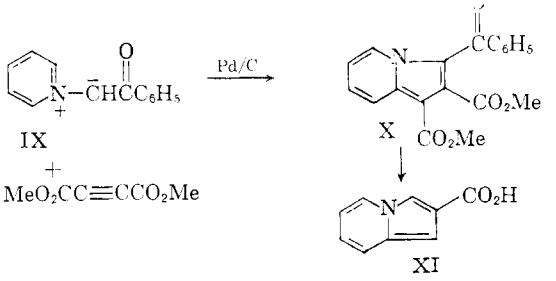
I, $R_1 = R_2 = -CO_2Me$
II, $R_1 = R_2 = -CO_2H$
III, $R_1 = R_2 = -H$

The application of the Chichibabin reaction to 2,5-dimethylpyrazine was next investigated. Formation of 1-phenacyl-2,5-dimethylpyrazinium bromide (IV) followed by treatment with base readily gave the expected zwitterion V but, unfortunately, none of the usual conditions employed in the Chichibabin reaction were effective in converting this on to the expected 2-phenyl-6-methyl-7-azapyrrocoline (VI). With the failure of the desired Chichibabin reaction in this case, attention turned to the possibility of utilizing the zwitterion V. Kröhnke has made an extensive study of the preparation of such zwitterions and their use in various alkylation and acylation reactions.[6] Based on the theory that the initial step in the reaction between pyrrocoline and dimethyl acetylenedicarboxylate is one of electrophilic attack,[4] it would be expected that a zwitterion such as V would be subject to a similar attack which, if followed by cyclization, would yield the corresponding pyrrocoline VII. This has been found to be true. Treatment of V with dimethyl acetylenedicarboxylate in the presence of a 5% palladium-on-charcoal catalyst gives two products having the correct composition for the pyrrocoline derivatives VII and VIII. The latter molecule presumably arises through loss of the benzoyl group either during the reaction or in subsequent work-up. The loss of the benzoyl group was not unexpected since such cleavages were a common experience in Kröhnke's studies.[6b]

Since a lack of suitable reference compounds made a direct proof of structure for VII and VIII rather difficult, the analogous pyridine derivatives were investigated for this purpose. Treatment of the zwitterion IX derived from 1-phenacylpyridinium bromide with dimethyl acetylenedicarboxylate in



the presence of a palladium-on-charcoal catalyst gave a product having the correct composition for X in about 20% yield. It is well known that acyl groups located at the 3-position in pyrrocoline are readily cleaved by acid.[7] Also, 1- and 3-carboxypyrrocolines undergo decarboxylation much more readily than 2-pyrrocolinecarboxylic acids.[8] Thus, as expected, hydrolysis of X followed by treatment with acid gave 2-pyrrocolinecarboxylic acid (XI). Its identity was established by comparison with an authentic sample of 2-pyrrocolinecarboxylic acid prepared by the Chichibabin reaction from 2-picoline and ethyl bromopyruvate.[9]



By analogy, then, the proof of structure of the adduct in the pyridine series provides convincing evidence for the correctness of the postulated structure VII in the pyrazine series. In the case of VIII independent proof was sought that it was related to VII simply by cleavage of the benzoyl group. In Kröhnke's work it was shown that N-methylpyridinium halides can be converted to the corresponding zwitterion and utilized in condensation reactions, although in poorer yield than the phenacyl derivatives.[6b] When 1,2,5-trimethylpyrazinium bromide was converted to the zwitterion XII and treated with dimethyl acetylenedicarboxylate under dehydrogenating conditions, the product formed in 1% yield was identical with VIII.

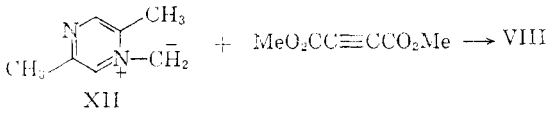
With the assurance that VII and VIII were the correct structures for these adducts, it was of interest to investigate their use in the synthesis of

(6) (a) F. Kröhnke, *Ber.*, **68**, 1177 (1935); (b) F. Kröhnke, *ibid.*, **66**, 604 (1933); (c) for a summary, see F. Kröhnke, *Angew. Chem.*, **65**, 605 (1953).

(7) E. T. Borrows, D. O. Holland and J. Kenyon, *J. Chem. Soc.*, 1069 (1946).

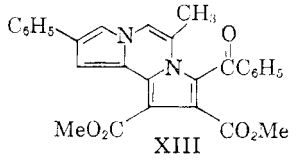
(8) R. H. Wiley and L. H. Knabeschuh, *J. Org. Chem.*, **18**, 836 (1953).

(9) E. T. Borrows and D. O. Holland, *J. Chem. Soc.*, 672 (1947).

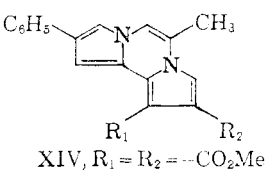


XII

unusual heterocycles. Unfortunately, attempts to effect a base-catalyzed condensation of VII to give the corresponding cycl[3.2.2]azine derivative were unsuccessful. However, both VII and VIII were readily quaternized by treatment with phenacyl bromide and converted by the Chichibabin reaction to XIII and XIV. Apparently, these are the first examples of the fully aromatic dipyrrolo[a,c]pyrazine ring system. Hydrolysis and subsequent decarboxylation of XIV occurred smoothly to give XV. The reaction of XV with dimethyl acetylenedicarboxylate was investigated since there are several ways in which addition might occur, any one of which would lead to highly interesting structures. However, XV was recovered unchanged from these experiments.



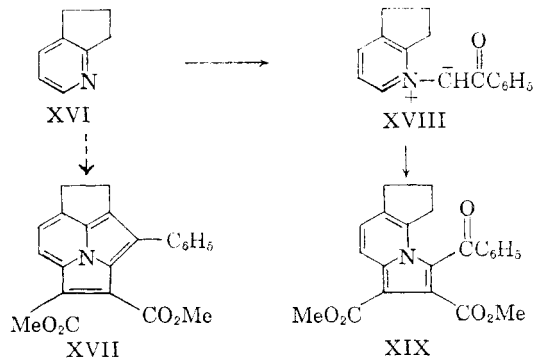
XIII



XIV, $R_1 = R_2 = -CO_2Me$

XV, $R_1 = R_2 = -H$

In the original plans for exploitation of the Chichibabin reaction followed by addition of dimethyl acetylenedicarboxylate, pyrindane (XVI) seemed to be a particularly interesting choice as starting material. In this case the successful application of these two reactions would give the cycl[3.2.2]azine derivative XVII in which three five-membered rings are fused in a contiguous fashion around the central pyridine ring. Rapoport and Smolinsky have provided a brilliant example of the effects of such a strained ring fusion in the case of benzene derivatives by their synthesis of 2,2a,3,3a,4,5-hexahydro-1H-cyclopent[jkl]-*asym*-indacene.[10] A similar study in which the five-membered rings are unsaturated would be especially valuable for investigating the counterbalancing effects of ring strain and resonance energy. However, again attempts to accomplish the Chichibabin reaction with pyrindane were unsuccessful.



XVI XVIII

XVII XIX

When XVIII, the zwitterion derived from pyrindane, was treated with dimethyl acetylenedicarboxylate in the presence of a palladium-on-charcoal catalyst, addition occurred to give the corresponding pyrrocoline derivative XIX. Attempts to convert XIX to XVII by a base-catalyzed condensation were again unsuccessful.

From this study it would appear that the addition of dimethyl acetylenedicarboxylate to heterocyclic zwitterions is general in nature. Although the yields obtained have been low, the products are of unusual structure and would be difficult to prepare by other synthetic procedures.

Experimental[11]

1,2-Dicarbomethoxy-3-phenylcycl(3.2.2)azine (I).—To a solution of 3.86 g. of 2-phenylpyrrocoline[7] and 2.9 g. of dimethyl acetylenedicarboxylate in 100 ml. of toluene there was added 3.0 g. of a 5% palladium-on-charcoal catalyst and the mixture was boiled under reflux in a nitrogen atmosphere for 20 hr. After removal of the catalyst and solvent, the dark residual solid was taken up in benzene and chromatographed over Woelm neutral alumina. From the first benzene eluates there was recovered 0.826 g. of 2-phenylpyrrocoline. Then, the next benzene eluates contained 1.99 g. (38%, based on unrecovered 2-phenylpyrrocoline) of yellow crystals, m.p. 135–137°. Recrystallization of these from acetone gave pale yellow needles, m.p. 139–140°; λ_{max} 238 (log ϵ 4.54), 255 (4.31), 331 (4.23) and 413 mμ (4.06).

Anal. Calcd. for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54; N, 4.20. Found: C, 72.37; N, 4.58; N, 4.43.

1,2-Dicarboxy-3-phenylcycl(3.2.2)azine (II).—A solution of 814 mg. of 1,2-dicarbomethoxy-3-phenylcycl(3.2.2)azine (I) in 50 ml. of a 5% methanolic potassium hydroxide solution was warmed at 50° for 10 hr. After removal of the methanol under reduced pressure, the residual solid was dissolved in water and acidified. The solid, which separated, was collected and recrystallized from methanol to give 724 mg. (97%) of yellow needles, m.p. 202–205° dec.

Anal. Calcd. for $C_{18}H_{11}NO_4$: C, 70.81; H, 3.63; N, 4.59. Found: C, 70.78; H, 3.69; N, 4.86.

2-Phenylcycl(3.2.2)azine (III).—A mixture of 350 mg. of 1,2-dicarboxy-3-phenylcycl(3.2.2)azine (II) and 300 mg. of copper chromite catalyst in 20 ml. of quinoline was heated at 220° in a nitrogen atmosphere until carbon dioxide was no longer evolved. After removal of the catalyst, the solution was poured onto ice and acidified with hydrochloric acid. Extraction of the aqueous solution with ether followed by drying and concentration of the ether extract gave an orange solid. Sublimation of this gave yellow crystals, m.p. 94-95°. A comparison of these crystals with those of an authentic sample of 2-phenylcycl(3.2.2)azine[12] both in their infrared spectra and by a mixture melting point determination showed them to be identical.

1-Phenacyl-2,5-dimethylpyrazinium Bromide (IV).—A mixture of 25.0 g. of phenacyl bromide and 16 ml. of 2,5-dimethylpyrazine was warmed at 55° for 1 hr. during which crystallization was complete. Hot chloroform was added with stirring and the resulting slurry was filtered. The solid, which was collected, was recrystallized from methanol to give 31.7 g. (82%) of white crystals, m.p. 208–210°.

Anal. Calcd. for $C_{14}H_{15}N_2OBr$: C, 54.73; H, 4.92; N, 9.12. Found: C, 54.71; H, 4.98; N, 9.17.

1-Phenacyl-2,5-dimethylpyrazinium picrate was prepared by treating the bromide IV with ethanolic picric acid and was obtained, after recrystallization from the same solvent, as yellow crystals, m.p. 129–130°.

Anal. Calcd. for $C_{20}H_{17}N_5O_8$: C, 52.75; H, 3.76. Found: C, 53.06; H, 3.81.

1,2-Dicarbomethoxy-3-benzoyl-5,8-dimethyl-7-azapyrrocoline (VII).—To a solution of 2.0 g. of 1-phenacyl-2,5-dimethylpyrazinium bromide (IV) in 50 ml. of water excess sodium carbonate was added. The orange solid

(10) H. Rapoport and G. Smolinsky, THIS JOURNAL, **82**, 1171 (1960).

(11) All melting points are corrected. Analyses are by the Micro-Tech Laboratories, Skokie, Ill., and Mr. T. Montzka, University of Rochester.

(12) R. J. Windgassen, Jr., W. H. Saunders, Jr., and V. Boekelheide, THIS JOURNAL, **81**, 1459 (1959).

which separated was taken up in chloroform and passed over a short column of Woelm neutral alumina. Concentration of the chloroform eluate gave an unstable orange solid (m.p. 110°) which was immediately dissolved in 100 ml. of toluene. Addition of 2.5 g. of dimethyl acetylenedicarboxylate caused the orange color of the solution to change to a red brown. Then, 1.5 g. of a 5% palladium-on-charcoal catalyst was added and the mixture was boiled under reflux in a nitrogen atmosphere for 16 hr. After removal of the catalyst and solvent, the dark residual oil was taken up in benzene and chromatographed over Woelm neutral alumina. The benzene eluate containing the first band from the column was concentrated to a yellow solid which, on crystallization from acetone, gave 120 mg. (5.2%) of yellow crystals, m.p. 128–129°. The benzene eluate containing the succeeding bands was reserved (see below).

Anal. Calcd. for $C_{20}H_{18}N_2O_5$: C, 65.56; H, 4.95; N, 7.65. Found: C, 65.74; H, 5.03; N, 7.39.

1,2-Dicarbomethoxy-5,8-dimethyl-7-azapyrrocoline (VIII). (A) From 1-Phenacyl-2,5-dimethylpyrazinium Bromide.—Concentration of the remaining benzene eluate from the above experiment gave a brown oil which, when dissolved in hot ethanol and allowed to cool, deposited a yellow solid. This was recrystallized from methanol and then from benzene to give 280 mg. (16%) of white crystals, m.p. 171–172°; λ_{max} 237 (log ϵ 4.47), 276 (3.49), 287 (3.59), 298 (3.65), 328 (3.68) and 341 mμ (3.69).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.58; H, 5.40; N, 10.59.

The hydrobromide of VIII was prepared by dissolving a sample of VIII in benzene and passing anhydrous hydrogen bromide through the solution. After recrystallization from ethanol, it was obtained as white needles, m.p. 219–221°.

Anal. Calcd. for $C_{13}H_{15}N_2O_4Br$: C, 45.49; H, 4.41; N, 8.16. Found: C, 45.47; H, 4.44; N, 8.16.

(B) From 1,2,5-Trimethylpyrazinium Iodide.—To a solution of 2.0 g. of 1,2,5-trimethylpyrazinium iodide in 50 ml. of water there was added an excess of sodium carbonate and the solution was continuously extracted with 100 ml. of chloroform. In the flask containing the boiling chloroform for the extraction there was added 0.90 g. of dimethyl acetylenedicarboxylate and 1.0 g. of a 5% palladium-on-charcoal catalyst. After the extraction had been allowed to proceed overnight, the chloroform solution was filtered to remove the catalyst and then concentrated. The residual dark gum was taken up in benzene and chromatographed over Woelm neutral alumina. From the benzene eluate there was isolated 23 mg. (1%) of yellow crystals, m.p. 168–170°. A comparison of these with the crystals obtained in (A) both in their infrared spectra and by a mixture melting point determination showed them to be identical.

1,2-Dicarbomethoxy-3-benzoyl-5-methyl-9-phenyldipyrrolo(a,c)pyrazine (XIII).—A solution of 300 mg. of VII and 2 g. of phenacyl bromide in 30 ml. of methanol was allowed to stand at room temperature for 7 days. After the methanol had been removed under reduced pressure, the residual gum was dissolved in 25 ml. of water and extracted with ether. Then, an excess of sodium carbonate was added to the aqueous solution causing the appearance of a deep red color. When the color had faded to yellow, the solution was extracted with benzene. After the combined benzene extracts had been concentrated to a reasonable volume, it was passed over Woelm neutral alumina. The solid obtained from the benzene eluate was recrystallized from toluene to give 300 mg. (78%) of yellow crystals, m.p. 201–202°.

Anal. Calcd. for $C_{28}H_{22}N_2O_5$: C, 72.09; H, 4.75; N, 6.01. Found: C, 72.68, 71.57; H, 4.94, 4.93; N, 6.12.

An attempt to effect the addition of dimethyl acetylenedicarboxylate to XIII under the conditions used previously for 2-phenylpyrrocoline led to recovery of starting material.

1,2-Dicarbomethoxy-5-methyl-9-phenyldipyrrolo(a,c)pyrazine (XIV).—A solution of 611 mg. of VIII and 465 mg. of phenacyl bromide in 20 ml. of dimethylformamide was heated at 80° for 24 hr. Then the solution was poured into water and extracted with ether. Addition of sodium carbonate to the aqueous solution caused the appearance of a red color which gradually faded to yellow. When the yellow aqueous solution was extracted with chloroform followed by concentration of the chloroform, there was obtained 350 mg. (41%) of a yellow powder, m.p. 197–199°. Recrystallization of this from an ethanol–acetone mixture gave yellow needles, m.p. 201–202°; λ_{max} 254 (log ϵ 4.41) and 280 mμ (4.56), shoulder at 335 mμ (log ϵ 4.00).

Anal. Calcd. for $C_{21}H_{18}N_2O_5$: C, 69.60; H, 5.00; N, 7.73. Found: C, 69.44; H, 5.17; N, 7.82.

Attempts to effect the addition of dimethyl acetylenedicarboxylate to XIV under the conditions used previously for 2-phenylpyrrocoline led to recovery of starting material.

2-Phenyl-6-methyldipyrrolo(a,c)pyrazine (XV).—A solution of 300 mg. of 1,2-dicarbomethoxy-5-methyl-9-phenyldipyrrolo(a,c)pyrazine (XIV) in ethanolic potassium hydroxide was boiled under reflux for 1 hr. After removal of the ethanol under reduced pressure, the residue was dissolved in water and extracted with ether. Acidification caused the precipitation of 295 mg. of a high-melting gray solid. Since no suitable solvent could be found for recrystallization, the dicarboxylic acid was subjected directly to decarboxylation by dissolving it in 20 ml. of quinoline, adding 100 mg. of a copper chromite catalyst, and heating the mixture at 220° under nitrogen until no further evolution of carbon dioxide occurred (12 hr.). The quinoline solution was then diluted with 100 ml. of benzene, the catalyst was removed by filtration, and the filtrate was extracted with 0.5 *N* hydrochloric acid. When the benzene layer was concentrated, there was obtained a dark crystalline mass which, on sublimation at 180° at 2 mm., gave 160 mg. (74%) of a light brown solid, m.p. 194–196°. Recrystallization of this from acetone gave yellow prisms, m.p. 195.5–196.0°.

Anal. Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.75; N, 11.37. Found: C, 83.07; H, 5.58; N, 11.48.

An attempt to effect the addition of dimethyl acetylenedicarboxylate to XV under the conditions used with 2-phenylpyrrocoline led to recovery of starting material.

1,2-Dicarbomethoxy-3-benzoylpyrrocoline (X).—To a solution of 5.0 g. of 1-phenacylpyridinium bromide in 50 ml. of water there was added an excess of solid sodium carbonate. The orange solution was then extracted carefully with chloroform and the combined chloroform extracts were quickly passed over a short column of alumina. Removal of the chloroform under reduced pressure left an unstable, yellow crystalline mass which was immediately dissolved in 100 ml. of toluene. After the addition of 2.56 g. of dimethyl acetylenedicarboxylate and 2.0 g. of a 5% palladium-on-charcoal catalyst to the toluene solution, the mixture was boiled under reflux under a nitrogen atmosphere for 20 hr. After removal of the catalyst, concentration of the toluene filtrate gave a solid. This, on recrystallization from acetone, yielded 1.10 g. (18%) of white crystals, m.p. 165–166°; λ_{max} 235 (log ϵ 4.38), 277 (4.18) and 362 mμ (4.11).

Anal. Calcd. for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.73; H, 4.63; N, 4.58.

3-Benzoylpyrrocoline-2-carboxylic Acid.—A solution of 100 mg. of 1,2-dicarbomethoxy-3-benzoylpyrrocoline (X) in methanolic potassium hydroxide was heated at 50° for 6 hr. After removal of the methanol, the residue was dissolved in water and extracted with benzene. Acidification of the aqueous solution gave a precipitate which was collected and crystallized from acetone. Sublimation of the yellow-green solid gave 59 mg. (75%) of pale yellow crystals, m.p. 164–166°; λ_{max} 232 (log ϵ 4.51), 260 (4.17) and 385 mμ (4.11).

Anal. Calcd. for $C_{16}H_{11}NO_5$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.38; H, 4.60; N, 5.66.

Pyrrocoline-2-carboxylic Acid (XI).—Solution of 130 mg. of 3-benzoylpyrrocoline-2-carboxylic acid in concd. hydrochloric acid gave a red solution which, after boiling under reflux for 1 hr., was concentrated to dryness. The residue was dissolved in aqueous potassium hydroxide solution and acidified. The precipitate, which separated, was collected and sublimed to give 47 mg. (60%) of a pale yellow solid, m.p. 244–246° dec. Comparison of these crystals with an authentic sample of pyrrocoline-2-carboxylic acid prepared by the method of Burrows and Holland[9] both in their infrared spectra and by a mixture melting point determination showed the two to be identical.

N-Phenacylpyrindanium Bromide.—A solution of 10.54 g. of pyrindane[13] and 17.6 g. of phenacyl bromide in 200 ml. of a 1:1 ether–chloroform mixture was allowed to stand at room temperature for 16 hr. The solution was concen-

(13) M. M. Robison, THIS JOURNAL, 80, 6254 (1958).

trated to remove most of the ether and then was heated at 50° for 6 hr. After removal of the chloroform, the residual oil was triturated with ether to induce crystallization. The resulting solid, after recrystallization from an ethanol–ethyl acetate mixture, gave 28 g. of white needles, m.p. 168–169.5°.

Anal. Calcd. for $C_{16}H_{16}NOBr$: C, 60.39; H, 5.07; N, 4.40. Found: C, 60.44; H, 5.20; N, 4.18.

1,2-Dicarbomethoxy-3-benzoyl-5,6-trimethylenepyrrocoline (XIX).—To a solution of 2.0 g. of N-phenacylpyrindanium bromide in 50 ml. of water there was added an excess of solid sodium carbonate and the solution was extracted carefully with chloroform. The combined chloroform extracts were passed over a short column of Woelm neutral alumina and the chloroform eluate was concentrated under reduced pressure. The resulting unstable orange solid was taken up in toluene and 0.90 g. of dimethyl acetylenedicarboxylate and 2.0 g. of a 5% palladium-on-charcoal catalyst were added. The mixture was boiled under reflux for 6 hr. under a nitrogen atmosphere. After removal of the catalyst and solvent, the residual dark gum was taken up in benzene and chromatographed over Woelm neutral alumina. Concentration of the benzene eluate afforded yellow crystals which, after recrystallization from ethanol, gave 165 mg. (7%) of yellow prisms, m.p. 160.5–161.5°, λ_{max} 246 (log ϵ 4.49), 282–290 (4.03), 334 (4.12) and 371 mμ (3.89).

Anal. Calcd. for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71. Found: C, 70.02; H, 5.12; N, 4.21.

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A Correlation of Some Electrophilic Substitution Reactions of Cycl[3.2.2]azine[1]

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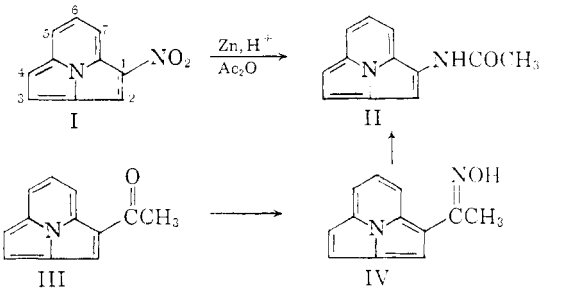
The monosubstitution products from the Friedel–Crafts reaction and from nitration of cycl[3.2.2]azine have been interrelated to show that the substituent group is introduced at the same position in each case. A further correlation with the adduct from pyrrocoline and methyl propiolate provides evidence that this is the 1-position as predicted from M.O. calculations.

Recently, a synthesis of cycl[3.2.2]azine was described and, as qualitative evidence for its aromatic character, it was found that the molecule readily underwent electrophilic substitution—nitration, bromination and the Friedel-Crafts reaction.[4] From simple molecular orbital calculations it was predicted that electrophilic substitution should occur most readily at the 1-position, radical attack at the 2- or 5-positions, and nucleophilic attack at the 5-position.[4] The present study was undertaken to try to test these predictions and to correlate the positions of substitution in various electrophilic reactions.

Nitration of cycl[3.2.2]azine proceeded in high yield to give a mononitro derivative I, as previously described.[4] However attempts to effect the reduction of the nitrocycl[3.2.2]azine to the corresponding amino derivative, either by catalytic hydrogenation or chemical means, were unsuccessful. The products from these experiments were too unstable to permit characterization. This behavior is reminiscent of that observed in attempts to prepare aminopyrroles and aminoazulenes[5,6] and so was not entirely unexpected. Schulze and Heilbronner were successful in preparing 1-aminoazulene by hydrosulfite reduction of the azo coupling product of azulene.[7] Unfortunately, attempts to obtain similar azo coupling products with cycl[3.2.2]azine have not proved fruitful. However, the procedure used by Anderson, Nelson and Tazuma[6] for the reductive acetylation of 1-nitroazulene was applicable and gave the corresponding acetamidocycl[3.2.2]azine (II) in good yield.



The acylation of cycl[3.2.2]azine under Friedel–Crafts conditions gives both mono- and diacyl derivatives. The monoacyl derivative III was readily converted to the corresponding oxime IV and this, in turn, underwent a Beckmann rearrangement to give an acetamido derivative. The fact that the acetamidocycl[3.2.2]azine from the Beckmann rearrangement was identical with that obtained from reductive acylation of the nitrocycl[3.2.2]azine establishes that both the Friedel–Crafts reaction and nitration lead to substitution at the same position.

Alternatively, the monacetyl derivative of cycl[3.2.2]azine (III) was degraded to the corresponding acid V using sodium hypoiodite. Treatment of V with methanolic hydrogen chloride readily gave a well-defined, crystalline ester VI. The same ester was obtained from the direct condensation of pyrrocoline and methyl propiolate. From our present knowledge of the addition of dieneophiles to pyrrocoline,[8] it would be anticipated that the addition of methyl propiolate would lead to 1-carbomethoxycycl[3.2.2]azine (VI). For example, the reaction of pyrrocoline with methyl phenylpro-

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