tetrachloride and heated to reflux. Pyridine (20 g., 0.25 mole) was added slowly and the heating continued for 3 hr. Silver chloride was filtered from the mixture and the solvent was evaporated leaving 11.6 g. of a dark "oil 1." Oil 1 was treated with methanolic potassium hydroxide (as in the preparation of III) and when worked up yielded another oil (3.0 g.) which distilled at 70° (0.3 mm.) as a colorless liquid, $n^{25}D$ 1.5305. The picrate had m.p. 123–124°. *Anal.* Calcd. for $C_{17}H_{18}N_4O_7$: C, 52.31; H, 4.65. Found: C, 52.29; H, 4.78.

In several of the preliminary attempts to isolate N-benzoyl-2-(1-hexynyl)-1,2-dihydropyridine from oil 1, the following observations were made. An ether solution of oil 1 was first washed with aqueous acid, bicarbonate solution then dried and evaporated. The residue was distilled at 135–143° (0.1–0.3 mm.) to give a clear liquid which generally darkened rapidly on standing. Benzoic acid was often isolated from the distillate or on the walls of the distillation apparatus. The distillate reacted rapidly with aniline depositing benzanilide, m.p. 162–163°. Another portion of the distillate with phenylhydrazine reagent gave the phenylhydrazone of 2-pyridinaldehyde which crystallized from ethanol and had m.p. 173–174° (lit.[29] m.p. 173–176°).

The presence of phenyl 1-hexynyl ketone in the distillate was also established both by the infrared spectrum and the preparation of the DNP, m.p. 145–147° (lit.[3] m.p. 156°). Its m.p. was not depressed when mixed with the DNP, m.p. 149–152°, prepared from authentic phenyl 1-hexynyl ketone.

N-*p*-Nitrobenzoyl-2-phenylethynyl-1,2-dihydropyridine.—To *p*-nitrobenzoyl chloride (9.3 g., 0.05 mole) and pyridine (4.8 g., 0.05 mole) in 100 ml. of refluxing carbon tetrachloride was slowly added finely ground silver phenylacetylide (10.5 g., 0.05 mole). After 12 hr., the mixture was filtered and washed three times with hot carbon tetrachloride. The residue, 10.3 g., contained 3 g. of silver phenylacetylide. The yield of crude product was 90%. It crystallized from carbon tetrachloride and had m.p. 173–174°. *Anal.* Calcd. for $C_{20}H_{14}N_2O_3$: C, 72.71; H, 4.27. Found: C, 72.29; H, 4.27.

N-*m*-Nitrobenzoyl-2-phenylethynyl-1,2-dihydropyridine.—To *m*-nitrobenzoyl chloride (14.1 g., 0.075 mole) and silver phenylacetylide (15.9 g., 0.075 mole) in 200 ml. of refluxing carbon tetrachloride-pyridine (23.7 g., 0.3 mole) was added. After 5 hr. the mixture was worked up to give 22.2 g. of m.p. 135–140°, in 90% yield. Recrystallization from carbon tetrachloride gave yellow needles, m.p. 144–145°. *Anal.* Calcd. for $C_{20}H_{14}N_2O_3$: C, 72.71; H, 4.27. Found: C, 72.75; H, 4.36.

Attempt to Prepare N-*p*-Anisoyl-2-phenylethynyl-1,2-dihydropyridine.—When *p*-anisoyl chloride was treated with silver phenylacetylide and pyridine in carbon tetrachloride in the usual manner, the dihydropyridine could not be isolated in pure form. Basic hydrolysis, however, led to stilbazole, m.p. 88–90°, in 50% yield (based on *p*-anisoyl chloride); *p*-methoxybenzoic acid, m.p. 176° (lit.[35] m.p. 180–182°) was also isolated.

N-Benzoyl-2-phenylethynyldihydroquinoline.—Silver phenylacetylide (4.2 g., 0.02 mole), benzoyl chloride (3.2 g., 0.022 mole) and 20 ml. of quinoline in 50 ml. of carbon tetrachloride were refluxed overnight and worked up. The oily residue was crystallized from methanol–acetone to give white crystals, m.p. 133–134°, in *ca.* 40% yield. *Anal.* Calcd. for $C_{24}H_{17}ON$: C, 85.93; H, 5.11. Found: C, 85.90; H, 5.22.

2-Phenacylpyridine.—In an attempt to prepare the analog of I from 2-methylpyridine, the phenacylpyridine was produced. Silver phenylacetylide (7 g.), benzoyl chloride (4.5 g.) and 2-methylpyridine (3 g.) were refluxed in carbon tetrachloride in the usual way. Silver chloride (4.5 g.) as well as a dark oil (3.5 g.) contaminated with benzoyl chloride were isolated. On treatment with alcoholic base, the oil gave another liquid as well as benzoic acid. The picrate of 2-phenacylpyridine was prepared from this liquid and had m.p. 176–178° (lit.[33] m.p. 176–177°).

***p*-Chlorobenzoic Anhydride.**—Attempts to prepare the *p*-chlorobenzoyl analog of Ia in the usual way were unsuccessful. Instead, *p*-chlorobenzoic anhydride was obtained, m.p. 195–196°, from acetone (lit.[36] m.p. 193–194°). Prior treatment of the *p*-chlorobenzoyl chloride with thionyl chloride and distillation did not lead to the desired product. Apparently, traces of water or *p*-chlorobenzoic acid remained in the starting material and formed the anhydride, or the desired reaction was very slow and the anhydride was formed during the working up of the products.

(35) J. B. Cohen and H. W. Dudley, *J. Chem. Soc.*, **97**, 1732 (1910).

(36) R. Adams, W. V. Wirth and H. E. French, THIS JOURNAL, **40**, 424 (1918).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER, ROCHESTER, N. Y., AND THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY, NEW BRUNSWICK, N. J.]

The Formation of Cycl[3.2.2]azine Derivatives *via* the Reaction of Pyrrocoline with Dimethyl Acetylenedicarboxylate

BY ANDREW GALBRAITH,[1a,2] THEODORE SMALL,[1a,3] RODERICK A. BARNES[1b] AND V. BOEKELHEIDE[1a,4]

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The reaction of pyrrocoline with dimethyl acetylenedicarboxylate in the presence of a dehydrogenation catalyst gives 1,2-dicarbomethoxycycl[3.2.2]azine (I) plus some 1,2-dicarbomethoxy-3,4-dihydrocycl[3.2.2]azine (XVIII). The evidence for these structures as well as a theoretical consideration of the reaction mechanism is presented.

In their extensive studies on the reaction of heterocyclic amines with dimethyl acetylenedicarboxylate, Diels and his collaborators discovered a series of interesting and unusual products.[5] In the case of the six-membered heterocycles, pyridine and its various derivatives, the reaction involves attack on the nitrogen atom. Originally these products were formulated as zwitterionic compounds, but the recent work of Acheson and Taylor clearly demonstrates that they are quinolizine derivatives.[6a,b] However, with five-membered heterocycles such as pyrrole, the normal course is one of substitution to introduce an α,β-dicarbomethoxyvinyl residue.[7] It was of interest, therefore, to study the case of pyrrocoline in which the nitrogen atom is common to both a six- and a five-membered ring, since it might be anticipated that an initial substitution reaction would, in this case, be followed by ring

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(4) To whom inquiries should be addressed, University of Oregon, Eugene, Ore.

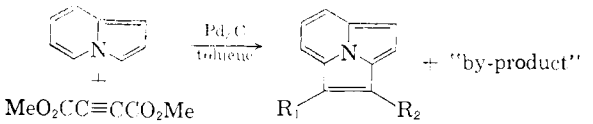
(5) See O. Diels and H. Schrum, *Ann.*, **530**, 68 (1937), for leading references.

(6) (a) R. M. Acheson and G. A. Taylor, *J. Chem. Soc.*, 1691 (1960); (b) for an earlier study by R. B. Woodward and E. C. Kornfeld, see E. C. Kornfeld, Ph.D. Thesis, Harvard University, 1945.

(7) O. Diels, K. Alder, H. Winkler and E. Petersen, *Ann.*, **498**, 1 (1932).

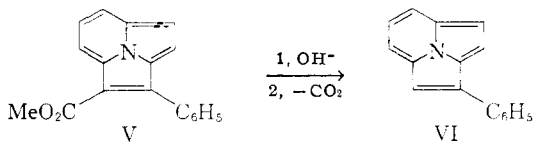
closure. This has now been realized,[8] and the reaction provides a convenient route for the synthesis of cycl(3.2.2)azine and its derivatives.[9]

When a solution of pyrocoline and dimethyl acetylenedicarboxylate in toluene was heated in the presence of a 5% palladium-on-charcoal catalyst, 1,2-dicarbomethoxycycl[3.2.2]azine (I) was formed in 65–75% yield. The structure of the adduct was readily established by its hydrolysis to the corresponding diacid II and the subsequent decarboxylation of II to give the parent ring system, cycl[3.2.2]azine (IV). Since both of these steps proceed in high yields, the sequence is exceptionally useful for synthetic purposes.



I, $R_1 = R_2 = -CO_2Me$
II, $R_1 = R_2 = -CO_2H$
III, R_1 and $R_2 = -COC-$
IV, $R_1 = R_2 =$ -H, $\begin{matrix}\| & \|\\ O & O\end{matrix}$

The generality of this reaction has been explored only in a preliminary fashion, but substituted pyrrocolines may be employed as well.[10] Substitution of methyl phenylpropiolate for dimethyl acetylenedicarboxylate allowed the formation of an adduct V, whose structure was established by its conversion *via* hydrolysis and decarboxylation to the known 2-phenylcycl[3.2.2]azine (VI).[9] However, attempts to effect a reaction between pyrrocoline and certain other dienophiles including diphenylacetylene, diethyl azodicarboxylate and 1,3-cyclohexadiene were unsuccessful.

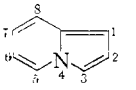


V VI

In an attempt to gain a better understanding of the reaction path, simple molecular orbital calculations were made following the L.C.A.O. procedure[11a,b,c] to determine in the case of pyrrocoline the reactivity of the various positions in terms of atom localization energies. Although some uncertainty may exist with regard to the best choice of parameters for pyrrocoline,[12] it was expected that the results of these calculations would indicate the most favorable types of reactions and the most likely reaction sites.

The atom localization energies for electrophilic, nucleophilic and radical reactions at the various positions in the pyrrocoline molecule are given in Table I. In Table II bond localization energies have been calculated. These are useful for estimating the relative ease of reactions in which a reagent attacks two positions simultaneously. It was assumed that two π-electrons of the aromatic system would be used for this kind of process.

TABLE I



ATOM LOCALIZATION ENERGIES FOR PYRROCOLINE[a]

Position	A_e	A_r	A_n
1	1.815	2.401	2.987
2	2.287	2.546	2.805
3	1.854	2.448	3.043
5	2.155	2.280	2.405
6	2.293	2.470	2.647
7	2.255	2.432	2.609
8	2.152	2.274	2.395

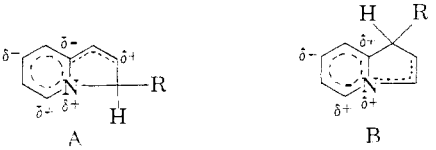
[a] One attempt was made to find out how modification of the parameters would affect the prediction of the relative reactivities of the 1- and 3-positions. The coulomb integral of the hitrogen atom was increased to $\alpha_N = \alpha_C + \beta$ and again the localization energies (1-position, A_e 1.867; 3-position, A_e 1.941) indicate that the 1-position should be the more reactive.

TABLE II

BOND LOCALIZATION ENERGIES

Bond	Localization energy	Bond	Localization energy
1–2	3.479	7–8	3.224
2–3	3.482	1–8	4.329
5–6	3.181	3–5	4.255
6–7	3.773	5–8	3.694

From Table I it is immediately apparent that electrophilic reactions of pyrrocoline would be expected to be very facile. Even the more unreactive positions, 2- and 6-, have about the same localization energies as naphthalene. The values for the 1- and 3-positions are rather close, but the 3-position is indicated to be slightly less reactive than the 1-position. The experimental evidence, however, clearly demonstrates the greater reactivity of the 3-position.[13] It is interesting that in this case, as in naphthalene, the resonance approach is in better agreement with the observed reactivity than the predictions of simple M.O. calculations. In transition state A for attack at the 1-position the charge is distributed over five atoms, whereas in transition



A B

state B the charge is effectively spread over only four atoms.[14]

(8) For preliminary announcements of this observation, see A. Galbraith, T. Small and V. Boekelheide, *J. Org. Chem.*, **24**, 582 (1959), and J. C. Godfrey, *ibid.*, **24**, 581 (1959).

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

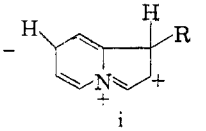
(10) V. Boekelheide and A. Miller, *J. Org. Chem.*, in press.

(11) (a) E. Hückel, *Z. Physik*, **70**, 240 (1931); (b) C. A. Coulson, "Valence," Oxford University Press, London, England, 1952; (c) R. D. Brown, *J. Chem. Soc.*, 272 (1956).

(12) The value for the coulomb integral of the nitrogen atom was taken to be $\alpha_N = \alpha_C + 0.5\beta$ which is the same value used previously for calculations of the cyclazine system[9] and for pyridine and pyridine N-oxide (R. A. Barnes, THIS JOURNAL, **81**, 1935 (1959)).

(13) E. T. Borrows and D. O. Holland, *Chem. Revs.*, **42**, 611 (1948).

(14) The positive charge in transition state B may be located at the 2-position only in less stable contributing structures such as i.

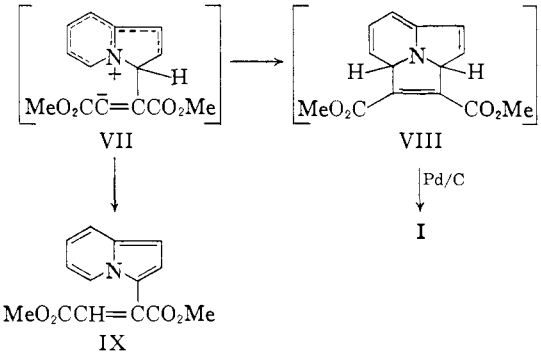


i

It is interesting that for both nucleophilic and radical reactions the six-membered ring is the one predicted to be attacked. The atom localization energies for the 5- and the 8-positions are very close, being nearly the same for both types of reactions.

Bond localization energies have been correlated with such reactions as osmium tetroxide oxidation and the Diels–Alder reaction.[15] The correlation with the latter reaction is surprisingly good especially in view of the recent evidence that it probably occurs in one-electron stages rather than simultaneous reaction at two centers.[16] From Table II it may be seen that reactions such as the osmium tetroxide oxidation and, perhaps, ozonolysis would be expected to occur most readily at the 5–6 bond. Also, a process requiring simultaneous attack at two non-adjacent positions would be predicted to occur at the 5–8-positions. In accord with the correlations of Brown,[15] it would then be expected than an ordinary Diels–Alder addition would occur across the six-membered ring at the 5–8-positions.

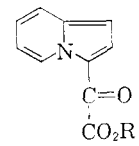
However, it is also apparent from Tables I and II that electrophilic attack is very much favored over localization of two π-electrons. With regard to the reaction of pyrrocoline and dimethyl acetylenedicarboxylate, then, an obvious interpretation would be that the first step involves an electrophilic attack to give VII as a first intermediate. This, on cyclization, would lead to VIII which, on dehydrogenation, would give the observed product I.



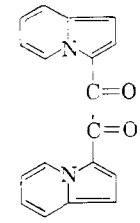
In addition to 1,2-dicarbomethoxycycl[3.2.2]-azine (I), a "by-product" was isolated from the reaction mixture in 10–15% yields and shown to have a composition in accord with the empirical formula $C_{14}H_{13}NO_4$. This corresponds to a dihydro derivative of I and, in view of the above scheme, it might be expected to arise through a tautomerization of VII to give IX. That IX was a likely structure for the "by-product" was also supported by the observation that when pyrrocoline and dimethyl acetylenedicarboxylate were heated in toluene in the absence of a dehydrogenation catalyst, the only compound isolated was the "by-product." Although heating the "by-product" in toluene with palladium-on-charcoal gave 1,2-dicarbomethoxycycl[3.2.2]azine (I), the yield was lower than from the direct reaction of pyrrocoline and dimethyl acetylenedicarboxylate in the presence of palladium-on-charcoal, indicating that the "by-product" is not a true intermediate.

(15) R. D. Brown, *Quart. Revs.*, **6**, 63 (1952).
(16) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

An independent synthesis of IX was undertaken. Treatment of pyrrocoline with oxalyl chloride in benzene gave, after hydrolysis, the corresponding acid X in 80% yield. The diketone XII, resulting from the condensation of two molecules of pyrrocoline with one of oxalyl chloride, also was isolated in 15% yield. After conversion of the acid X to the corresponding ester XI by means of diazomethane, a Reformatski reaction was attempted using methyl bromoacetate in the expectation that this would lead directly to IX. Despite many attempts the Reformatski reaction failed completely, presumably due to the deactivation of the ketone carbonyl by the pyrrocoline ring.

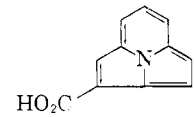


X, R = -H
XI, R = -CH_3



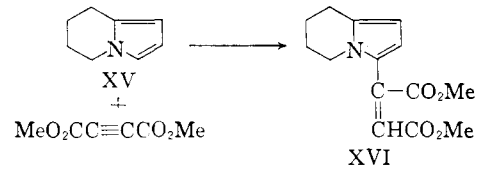
XII

The "by-product" was readily hydrolyzed by base to an acid-ester and this was oxidized in basic solution with aqueous potassium permanganate. On acidification, an acid was isolated which possessed the expected spectral properties and composition for a cycl[3.2.2]azine-monocarboxylic acid (XIII). This structure was confirmed by its ready decarboxylation to cycl[3.2.2]azine, itself.



XIII

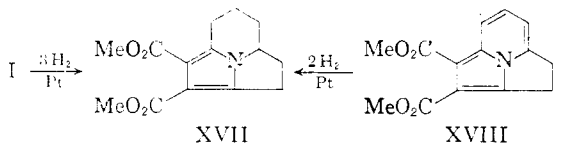
However, on hydrogenation over platinum the "by-product" readily absorbed two molecules of hydrogen to give a crystalline product whose spectral properties were in keeping with those of a substituted pyrrole such as XVI, the expected product from hydrogenation of IX. Therefore, the synthesis of XVI was undertaken. This was readily accomplished by hydrogenating pyrrocoline using Adams catalyst to give 5,6,7,8-tetrahydropyrrocoline (XV), which then readily added dimethyl acetylenedicarboxylate to give XVI. However, the physical properties of the sample of XVI synthesized in this way were clearly different from those of the tetrahydro derivative of the "by-product."



XVI

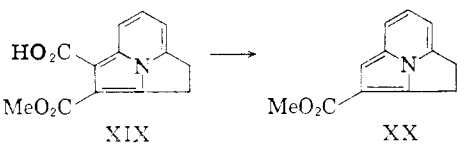
Finally, when 1,2-dicarbomethoxycycl[3.2.2]-azine (I) was subjected to hydrogenation over Adams catalyst, three molecules of hydrogen was absorbed and the resulting hexahydro derivative

was identical to the tetrahydro derivative of the "by-product." Thus, the "by-product" and 1,2-dicarbomethoxycycl[3.2.2]azine must have the same carbon skeleton and their common hydrogenation product must possess structure XVII. Since the "by-product" shows an ultraviolet absorption spectrum typical of a pyrrocoline and very similar to that of 1,2,3-tricarbomethoxypyrrocoline,[17] its correct structure must be XVIII.



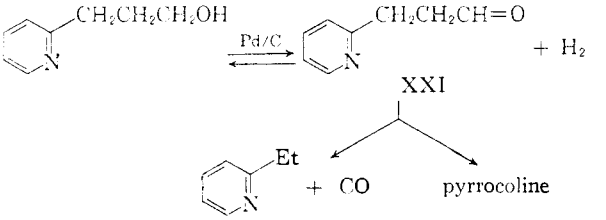
It is apparent that the "by-product" is not an intermediate in the formation of I but most probably arises through tautomerization of VIII which, presumably, is a true intermediate. Although the structural investigations of the "by-product" were undertaken with the hope that they would have an important bearing on the mechanism of the condensation, this hope was not realized and the question of the actual mechanism remains open. The molecular orbital calculations would suggest that the first step in the reaction is one of electrophilic attack to give VII which then cyclizes to VIII. However, the present evidence is accommodated equally as well in terms of a four-center reaction to give VIII directly.

As mentioned earlier, hydrolysis of the "by-product" occurred readily to give an acid-ester to which structure XIX is assigned. Surprisingly, the acid-ester resisted all attempts to effect complete hydrolysis and could not be converted to the corresponding di-acid. Its structural assignment is based on the fact that it underwent decarboxylation to give a monoester XX, the decarboxylation of a 3-carboxypyrrocoline being a more facile process than that for 2-carboxypyrrocolines.[18] Further, the product from permanganate oxidation of XIX must be 2-carboxycycl[3.2.2]azine (XIII) since its infrared spectrum differs from that of an authentic sample of 1-carboxycycl[3.2.2]azine.[19]



The pyrrocoline used in this study was prepared by the cyclization of 3-(2′-pyridyl)-propanol.[20] Because of the quantities required, the reaction has been studied in some detail in an attempt to determine the optimum conditions and to prevent side reactions. That the reaction probably involves dehydrogenation to the aldehyde XXI as a first step is supported from the analysis of the minor products. Carbon monoxide is observed in the effluent gases and 2-ethylpyridine accompanies pyrrocoline in the steam distillate. The use of a palladium-on-charcoal catalyst prepared using formaldehyde rather than by catalytic reduction also favors the formation of pyrrocoline and lessens the side reactions.

A similar cyclization of 2-(γ-hydroxypropyl)-6-methylpyridine gave 5-methylpyrrocoline in 75% yield.



Experimental[21]

1,2-Dicarbomethoxycycl(3.2.2)azine, (I).—To a solution of 16.6 g. of freshly-sublimed pyrrocoline and 27.5 g. of dicarbomethoxy acetylenedicarboxylate in 2.0 l. of toluene there was added 2.0 g. of a 5% palladium-on-charcoal catalyst[22] and the mixture was boiled under reflux in a nitrogen atmosphere for 24 hours. After removal of the catalyst and solvent, the dark, crystalline residue was taken up in benzene and chromatographed over 900 g. of neutral Woelm alumina. From the benzene eluate there was isolated 24.7 g. (68%) of orange-yellow crystals, m.p. 75–88°. Recrystallization of these from benzene or sublimation at 80° and 0.05 mm. gave yellow prisms, m.p. 91–92°, in high yield. Absorption maxima in the ultraviolet were at 410 (log ε 3.97), 309 (3.90), 267 (4.27), 264 (4.38), and 209 mμ (4.30) and in the infrared at 5.76 and 5.85μ (—C=O).

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.45. Found: C, 65.45; H, 4.31; N, 5.57.

When elution of the column from the above experiment was continued, the methanol eluate gave 2.5–3.7 g. (10–15%) of tan crystals. Recrystallization of this "by-product" from methanol gave colorless needles, m.p. 178–180°. The absorption spectrum of these crystals, the **1,2-dicarbomethoxy-3,4-dihydrocycl[3.2.2]azine (XVIII)**, showed absorption maxima in the ultraviolet at 376 (log ε 3.56), 360 (3.81), 345 (3.78), 308 (3.77), 294 (3.78), 250 (4.36), 246 (4.33) and 210 mμ (4.28) and in the infrared at 5.80 and 5.90 μ (—C=O). In contrast to I, XVIII was readily soluble in dilute acid similar to pyrrocoline itself.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.08, 64.48; H, 4.67, 5.07; N, 5.43, 5.50.

1,2-Dicarboxycycl[3.2.2]azine (II).—To a solution of 180 mg. of 1,2-dicarbomethoxycycl(3.2.2)azine in 10 ml. of methanol there was added 10 ml. of a 10% methanolic potassium hydroxide solution and the mixture was allowed to stand at room temperature until the precipitation of crystals was complete. The di-potassium salt of II (300 mg.) was then collected by filtration, washed with methanol, dissolved in water and acidified with 5% hydrochloric acid. The solid, which precipitated, was collected, washed with water and dried to give 160 mg. (100%) of white crystals, m.p. > 310°. No solvent could be found for recrystallization and the crude sample was analyzed directly. Its absorption spectrum showed maxima in the ultraviolet at 438 (log ε 4.00), 417 (3.95), 315 (3.95), 265 (4.25), 250 (4.36) and 215 mμ (4.26) and in the infrared at 5.91 and 6.25 μ (—C=O).

Anal. Calcd. for $C_{12}H_7NO_4$: C, 62.89; H, 3.08; N, 6.11. Found: C, 62.77; H, 3.21; N, 6.17.

The Anhydride of 1,2-dicarboxycycl(3.2.2)azine (III) was prepared by dissolving 90 mg. of II in 10 ml. of acetic anhydride and boiling under reflux for 5 hours. After removal of the solvent *in vacuo*, the residue was sublimed to give 73 mg.

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

(18) V. Boekelheide and K. Fahrenholtz, THIS JOURNAL, **83**, 458 (1961).

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(86%) of yellow crystals, m.p. 267°; absorption maxima in the ultraviolet at 438 (log ε 3.81), 423 (3.84), 310 (3.96), 262 (4.29), 251 (4.34), 235 (4.32) and 209 mμ (4.40) and in the infrared at 5.68 and 5.70 μ.

Anal. Calcd. for $C_{12}H_8NO_3$: C, 68.25; H, 2.39; N, 6.63. Found: C, 68.05; H, 2.67; N, 6.70.

Decarboxylation of 1,2-Dicarboxycycl(3.2.2)azine (II).—A mixture of 70 mg. of II and 100 mg. of copper chromite catalyst in 20 ml. of quinoline was heated at 230° for 5 hours. After removal of the catalyst, the filtrate was acidified with aqueous hydrochloric acid and extracted with ether. Concentration of the ether extract gave a gummy residue which, on sublimation, yielded 31 mg. (72%) of yellow prisms, m.p. 64–65°, undepressed by admixture of an authentic sample of cycl(3.2.2)azine.[9] Also, its infrared spectrum was superimposable with that of the authentic sample.

1-Carbomethoxy-2-phenylcycl(3.2.2)azine (V).—A mixture of 3.4 g. of pyrrocoline, 4.5 g. of methyl phenylpropiolate and 4 g. of a 5% palladium-on-charcoal catalyst in 100 ml. of toluene was boiled under reflux for 20 hours. After removal of the catalyst and solvent, the dark residue was taken up in benzene and chromatographed over alumina. From the benzene–chloroform eluate, there was isolated 90 mg. of a yellow solid which, on sublimation, gave 75 mg. of yellow needles, m.p. 118–120°.

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 77.95; H, 4.89; N, 5.01.

The conversion of 1-carbomethoxy-2-phenylcycl(3.2.2) azine to 2-phenylcyclazine was carried out without isolation or characterization of the intermediate acid and followed the procedure described above. Hydrolysis of 50 mg. of V with methanolic potassium hydroxide gave, after acidification, 30 mg. of the acid as a flocculent, high-melting solid. This was decarboxylated using copper chromite and quinoline to give 15 mg. of a crude solid, m.p. 93–97°. This, on sublimation, gave yellow crystals, m.p. 98–100°. Comparison of these with an authentic sample of 2-phenylcyclazine both in the infrared and by the method of mixture melting points showed the two to be identical.

Hydrolysis of the By-product XVIII.—A solution of 500 mg. of "by-product" XVIII in 10 ml. of concd. hydrochloric acid was allowed to stand until the precipitation of colorless solid no longer occurred. The solid was then collected and, after recrystallization from acetic anhydride, yielded 410 mg. (90%) of white needles, m.p. 292°. Its absorption spectrum in the ultraviolet showed maxima at 376 (log ε 3.91), 358 (4.08), 344 (3.97), 312 (3.78), 299 (3.71), 252 (4.41), 246 (4.33) and 214 mμ (4.36) and in the infrared at 5.90 and 6.25 μ. This product has been assigned structure XIX but, despite repeated attempts with both aqueous acid and base, hydrolysis of the second ester group to give the corresponding dibasic acid could not be accomplished. However, treatment of XIX with diazomethane readily reconverted it to the "by-product" XVIII.

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.75, 63.77; H, 4.45, 4.46; N, 5.75.

Decarboxylation of XIX.—A mixture of 1.53 g. of XIX and 1.2 g. of copper chromite in 35 ml. of quinoline was heated at 230° under a nitrogen atmosphere for 4 hours. After removal of the catalyst and acidification with aqueous hydrochoric acid, the solution was extracted with ether. Concentration of the ether gave a dark solid which was taken up in benzene and chromatographed over Woelm neutral alumina. From the benzene–chloroform eluate there was isolated a pale yellow solid. This, on sublimation, gave 50 mg. of a powdery solid, m.p. 110–111°, to which structure XX has been assigned.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.60; H, 5.50; N, 6.95. Found: C, 71.65; H, 5.60; N, 6.95.

Oxidation of XIX with Permanganate.—To a solution of 1.00 g. of XIX in 25 ml. of a 20% aqueous potassium hydroxide solution there was added dropwise with stirring over a period of 20 minutes a solution of 5 g. of potassium permanganate in 500 ml. of water. When the permanganate color still remained, the mixture was treated with ethanol, filtered, and acidified with sulfuric acid. The precipitate, which separated, was collected, washed with water and sublimed. This gave 135 mg. of a pale yellow solid, m.p. 231–233°. Its absorption spectrum in the ultraviolet showed maxima at 416 (log ε 3.65), 304 (4.07), 250 (4.37) and 206 mμ (4.21) and in the infrared at 5.97 μ (—C=O) and it has been assigned structure XIII.

Anal. Calcd. for $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.31; H, 3.91; N, 7.87.

Decarboxylation of 150 mg. of XIII using copper chromite and quinoline as in the previous cases gave 50 mg. of yellow crystals, m.p. 62–64°. Comparison in the infrared and by mixture melting points with an authentic sample of cycl[3.2.2]azine showed the two samples to be identical.

Reaction of Pyrrocoline and Dimethyl Acetylenedicarboxylate in the Absence of Catalyst.—A solution of 300 mg. of pyrrocoline and 350 mg. of dimethyl acetylenedicarboxylate in 25 ml. of toluene was stored under nitrogen at room temperature for 3 days. The solution was then chromatographed over Woelm neutral alumina. Elution with benzene–chloroform gave a dark solid which, on sublimation, gave almost colorless crystals, m.p. 178–180°. Comparison of these crystals in the infrared and by mixture melting point with an authentic sample of "by-product" XVIII showed the two samples to be identical.

Dehydrogenation of XVIII to Give I.—A mixture of 325 mg. of "by-product" XVIII and 2 g. of a 5% palladium on-charcoal catalyst in 50 ml. of toluene was boiled under reflux for 19 hours. After removal of the catalyst, the solution was chromatographed over Woelm neutral alumina. The chloroform eluate gave 100 mg. of yellow crystals, m.p. 88–91°. Comparison of these with an authentic sample of 1,2-dicarbomethoxy cycl[3.2.2]azine (I) both in the infrared and by mixture melting point showed them to be identical.

Hydrogenation of the "By-product" XVIII.—A mixture of 518 mg. of "by-product" XVIII and 100 mg. of a 5% palladium-on-charcoal catalyst in 50 ml. of ethyl acetate was subjected to hydrogenation at room temperature and atmospheric pressure. Adsorption was complete in 48 hours and corresponded to an uptake of two moles of hydrogen per mole of compound. After removal of the catalyst and solvent, a colorless solid remained which, on crystallization from hexane, gave 500 mg. (95%) of white plates, m.p. 111–112°. Its absorption spectrum in the ultraviolet maxima at 272 (log ε 4.02), 256 (3.94), 220 (4.05) and 207 mμ (4.24) and in the infrared at 5.75 and 5.85 μ.

The crystals were readily soluble in dilute acid and have been assigned structure XVII.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 64.05; H, 6.53; N, 5.20.

Hydrogenation of 1,2-Dicarbomethoxycycl(3.2.2)azine (I).—A mixture of 400 mg. of I and 1 g. of a 5% palladium-on-charcoal catalyst in 50 ml. of ethyl acetate was subjected to hydrogenation at room temperature and atmospheric pressure. Adsorption was complete in 24 hours and corresponded to three moles of hydrogen per mole of compound. After removal of the catalyst and solvent, the residual colorless solid was recrystallized from hexane to give 285 mg. (70%) of white crystals, m.p. 109–111°. Comparison of these crystals with a sample of XVII prepared above both in the infrared and by mixture melting point showed them to be identical.

5,6,7,8-Tetrahydropyrrocoline (XV).—A mixture of 4.5 g. of pyrrocoline and 1.0 g. of a 5% palladium-on-charcoal catalyst in 60 ml. of ethyl acetate was subjected to hydrogenation at room temperature and atmospheric pressure. Hydrogenation was stopped when the uptake corresponded to two moles of hydrogen per mole of compound. Removal of the catalyst and solvent left a colorless liquid which, on distillation, gave 2.0 g. of a clear oil, b.p. 70–74° at 0.2 mm.

Anal. Calcd. for $C_8H_{11}N$: C, 79.25; H, 9.15; N, 11.56. Found: C, 79.75; H, 8.71; N, 11.37.

3-(α,β-Dicarbomethoxyvinyl)-5,6,7,8-tetrahydropyrrocoline (XVI).—A solution of 500 mg. of 5,6,7,8-tetrahydropyrrocoline and 600 mg. of dimethyl acetylenedicarboxylate in 30 ml. of toluene was allowed to stand at room temperature under a nitrogen atmosphere for 6 days. The solution was then chromatographed over Woelm neutral alumina. The benzene–chloroform eluate gave a colorless solid which, after crystallization from hexane, yielded 215 mg. of white rods, m.p. 155–156°. Its absorption spectrum in the ultraviolet showed maxima at 293 (log ε 3.05), 281 (3.63), 235 (4.15) and 207 mμ (4.18) and in the infrared at 5.8 and 6.3μ.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.64; H, 6.52; N, 5.57.

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]

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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

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

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