Syntheses of Fused Aromatic Heterocycles by 1,3-Dipolar Addition Reactions. 3-Azapyrrocolines[1]

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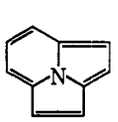
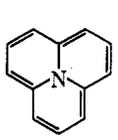
The reaction of pyridin-N-imines with ethyl propiolate is a convenient method for preparing various 3-azapyrrocolines. These can be elaborated further. However, attempts to convert 3,5-trimethylene-3-azapyrrocolinium iodide into 10-azacycl[3.3.2]azine (III) were unsuccessful.

The theoretical interest in studying tricyclic aromatic heterocycles having nitrogen as the central atom common to the three rings has been discussed previously.[3] Although cycl[3.2.2]azine (I) has been prepared[3,4] and its properties have been studied in considerable detail,[4-9] relatively few examples[10-13] of other representatives of this general class are known. Of particular interest is cycl[3.3.3]azine (II) but, despite considerable effort,[14] its synthesis has remained elusive, although Gibson and Leaver have recently reported the synthesis of a tetracyclic structure incorporating the cycl[3.3.3]azine nucleus.[15]



I



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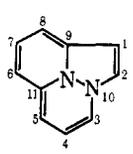
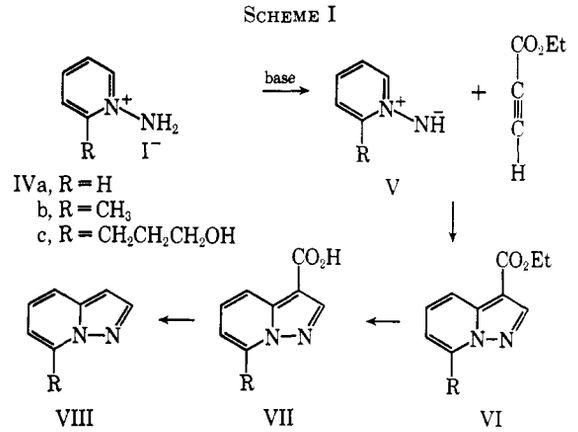


III

In view of the difficulties encountered in attempts to prepare cycl[3.2.2]azine, we were led to consider other structures that were closely related and isoelectronic with cycl[3.3.3]azine. Of these, 10-azacycl[3.3.2]azine (III), was especially attractive because it appeared that the requisite 3-azapyrrocolines needed for its synthesis might readily be made available by a 1,3-dipolar addition of acetylenic esters to the corresponding zwitterionic pyridin-N-imines. Similar 1,3-dipolar addition reactions have been successfully carried out with a variety of heterocyclic zwitterions.[4,5,16]

When a solution of 1-aminopyridinium iodide (IVa) in dimethylformamide was treated with anhydrous potassium carbonate, the mixture developed the deep blue color characteristic of pyridin-N-imine (V) (Scheme I). Addition of ethyl propiolate then resulted in an immediate exothermic reaction giving the desired 1-carbethoxy-3-azapyrrocoline (VIa) in 48% yield.[17] Hydrolysis of the ester occurred readily and in high yield to give the corresponding acid, VIIa. Distillation of VIIa from copper chromite powder gave 3-azapyrrocoline (VIIIa) in 70% yield.[18] Later, it was found that decarboxylation of 3-azapyrrocoline-1-carboxylic acids can be effected smoothly in very high yield on heating with 57% hydriodic acid. Since N-aminopyridine derivatives are readily prepared by the method of Meusen and Gösl,[19] this sequence of reactions makes the conversion of pyridine derivatives into their corresponding 3-azapyrrocoline derivatives a simple and convenient synthetic process.

SCHEME I



For example, 2-picoline was converted in 53% yield into the corresponding N-amino derivative (IVb). This, on treatment with base and ethyl propiolate, gave 1-carbethoxy-5-methyl-3-azapyrrocoline (VIb) in 55% yield. Hydrolysis and decarboxylation of VIb then gave 5-methyl-3-azapyrrocoline (VIIIb) in 75% yield.

For the purpose at hand it was desired to have a substituent at the 5 position which would allow ring closure to provide the tricyclic system present in III. The γ-hydroxypropyl side chain was chosen, particularly because of the ready availability of the required starting material, 3-(2′-pyridyl)propan-1-ol. This was car-

(1) Supported in part by the National Heart Institute of the National Institutes of Health, Grant HE-09813.

(2) Roche Anniversary Fund Fellow. We thank the Roche Fund for partial support of this investigation.

(3) R. J. Windgassen, W. H. Saunders, Jr., and V. Boekelheide, *J. Amer. Chem. Soc.*, **81**, 1459 (1959).

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

(5) F. Gerson, E. Heilbronner, N. Joop, and H. Zimmerman, *Helv. Chim. Acta*, **46**, 1940 (1963).

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(7) F. Gerson and J. D. W. van Voorst, *ibid.*, **46**, 2257 (1963).

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(11) V. Boekelheide and K. Fahrenholtz, *J. Amer. Chem. Soc.*, **83**, 458 (1961).

(12) V. Boekelheide and A. Miller, *J. Org. Chem.*, **26**, 431 (1961).

(13) V. Boekelheide and S. Kertelj, *ibid.*, **28**, 3212 (1963).

(14) V. Boekelheide, H. Fritz, J. M. Ross, and H. X. Kaempfen, *Tetrahedron*, **20**, 33 (1964).

(15) W. K. Gibson and D. Leaver, *Chem. Commun.*, 11 (1965).

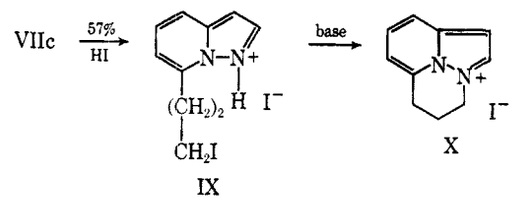
(16) V. Boekelheide and N. A. Fedoruk, *J. Amer. Chem. Soc.*, in press.

(17) While this study was in progress, Huisgen, as a part of his large and elegant investigation of 1,3-dipolar addition reactions, announced the discovery of essentially the same reaction [R. Huisgen, R. Grashey, and R. Krischke, *Tetrahedron Lett.*, 387 (1962)]. However, as yet no details have been provided for their experiments.

(18) The *Chemical Abstracts* name for 3-azapyrrocoline is pyrazolo[1,5-*a*]-pyridine. J. D. Bower and G. R. Ramage, who first prepared this compound, refer to it as 1,7a-diazaindene [*J. Chem. Soc.*, 4506 (1957)]. The properties of our compound and the melting point of its picrate derivative are in full agreement with those reported by Bower and Ramage.

(19) A. Meusen and R. Gösl, *Angew. Chem.*, **69**, 754 (1957); *cf. Org. Syn.*, **43**, 1 (1963).

ried through the same sequence of reactions to give 1-carboxy-5-(γ-hydroxypropyl)-3-azapyrrocoline (VIIc). When VIIc was heated with 57% hydriodic acid, decarboxylation and replacement of the hydroxyl group by iodine occurred in the same operation. Further, neutralization of the resulting hydriodide IX gave the free base which spontaneously cyclized to the desired 3,5-trimethylene-3-azapyrrocolinium iodide (X).



IX X

Although the final step in the preparation of III is simply a dehydrogenation of X, various methods and various catalysts—including palladium on charcoal and sulfur—were tried to no avail. Either the starting material was recovered unchanged or no useful products could be isolated from the reaction.

Experimental Section[20]

1-Carbethoxy-3-azapyrrocoline (VIa).—A solution of 10.2 g (0.046 mol) of 1-aminopyridinium iodide[19] (IVa) in 100 ml of dimethylformamide (distilled from calcium hydride) was stirred at room temperature with 6.9 g of anhydrous potassium carbonate for 30 min. Then, 9.2 g (0.092 mol) of ethyl propiolate was added dropwise with continued stirring to the deep blue solution, causing an immediate exothermic reaction. After addition was complete, the mixture was stirred for 1 hr, diluted with 250 ml of water, and extracted with ether. The ethereal extract was dried, concentrated under reduced pressure, and the residual oil was distilled to give 4.2 g (48%) of a colorless oil: bp 130–135° (2 mm); $\lambda_{max}^{CHCl_3}$ 5.90 and 6.10 μ; λ_{max}^{EtOH} 303 mμ (ε 8370), 246 (8370), 239 (8950), 222 (35,800), and 218 (30,200); nmr (deuteriochloroform) showed a doublet at τ 1.52 (J = 7 cps, 1 H, C-5), a singlet at 1.72 (1 H, C-2), a doublet at 1.90 (J = 7 cps, 1 H, C-8), a split triplet at 2.71 (J = 6.5 cps, 1 H, C-7), a split doublet at 3.12 (J = 6.5 cps, 1 H, C-6), a quartet at 5.69 (J = 7 cps, 2 H), and a triplet at 8.62 (J = 7 cps, 3 H). The fact that the signal for the C-2 proton comes at very low field provides additional evidence that the assigned structure is correct, for, had the 1,3-dipolar addition occurred in reverse fashion to give 2-carbethoxy-3-azapyrrocoline, the singlet proton signal for C-1 should be at much higher field than is observed to be the case.

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.69; H, 5.63; N, 14.45.

1-Carboxy-3-azapyrrocoline VIIa.—A solution of 4.2 g of 1-carbethoxy-3-azapyrrocoline (VIa) in a mixture of 50 ml of methanol and 5 ml of aqueous potassium hydroxide solution was allowed to stand at room temperature for 24 hr. After removal of the methanol under reduced pressure, the aqueous solution was extracted with ether and acidified. The solid, which precipitated, was collected, dried, and recrystallized from benzene to give 3.15 g (89%) of white crystals: mp 223–224°; λ_{max}^{EtOH} 298 mμ (ε 8840), 238 (10,300), 222 (42,700), and 218 (35,900).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.41; H, 3.74; N, 17.33.

3-Azapyrrocoline (VIIIa). A. Decarboxylation of VIIa with Copper Chromite.—A mixture of 425 mg of 1-carboxy-3-azapyrrocoline (VIIa) and 200 mg of powdered copper chromite catalyst was heated to 250° in a molecular still. There collected 213 mg of a pale yellow oil whose spectral properties were identical with those of the product described in method B.

B. Heating VIIa with 57% Hydriodic Acid.—A solution of 3.00 g of 1-carboxy-3-azapyrrocoline (VIIa) in 15 ml of 57% hydriodic acid was boiled under reflux for 3 hr. After neutralization of the cold solution with aqueous potsssium carbonate, the basic organic product was extracted with ether, dried, and concentrated under reduced pressure. Distillation of the residual oil gave 1.86 g (82%) of a colorless oil: bp 93–95° (14 mm); nmr (deuteriochloroform) showed a doublet at τ 1.58 (J = 7 cps, 1 H, C-5), doublet at 2.17 (J = 6 cps, 1 H, C-2), multiplet at 2.55–3.50 (3 H, C-6, 7, and 8), and a doublet at 3.67 (J = 6 cps, 1 H, C-1). The corresponding picrate melted at 150–152° dec.[18]

Anal. Calcd for $C_7H_8N_2$: C 71.17; H, 5.12; N, 23.71. Found: C, 71.40; H, 5.24; N, 23.95.

1-Carbethoxy-5-methyl-3-azapyrrocoline (VIb).—A solution of 2.0 g (0.0085 mol) of 1-amino-2-picolinium iodide[19] in 15 ml of freshly distilled dimethylformamide was stirred for 1 hr at room temperature with 930 mg of solid potassium carbonate. A solution of 2.1 g (0.021 mol) of ethyl propiolate in 5 ml of dimethylformamide was added dropwise with stirring and the resulting mixture was stirred for 1 additional hr at room temperature. After removal of the dimethylformamide under reduced pressure, water was added to the residue and it was extracted with ether. The ether extract was washed with water, dried, concentrated, and the residue distilled to give 850 mg (55%) of a pale yellow oil, bp 138–144° (2 mm). The distillate solidified on standing and, after recrystallization from ether, gave white crystals: mp 71–72°; λ_{max}^{EtOH} 307 mμ (ε 9390), 245 (5300), 240 (5300), 222 (25,300), and 218 (shoulder); nmr (deuteriochloroform) showed a singlet at τ 1.71 (1 H, C-2), a doublet at 1.95 (J = 9 cps, 1 H, C-8), a triplet at 2.75 (1 H, C-7), a doublet at 3.32 (J = 9 cps, 1 H, C-6), a quartet at 5.69 (2 H), a singlet at 7.30 (3 H), and a triplet at 8.62 (3 H).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.96; H, 5.98; N, 13.50.

1-Carboxy-5-methyl-3-azapyrrocoline (VIIb).—A solution of 4.73 g of 1-carbethoxy-5-methyl-3-azapyrrocoline (VIb) in a mixture of 100 ml of methanol and 10 ml of a 10% aqueous potassium hydroxide solution was allowed to stand at room temperature for 35 hr. After removal of the methanol under reduced pressure, water was added and the aqueous solution was extracted with ether to remove neutral material. It was then brought to a pH of 2.0 by addition of 10% aqueous hydrochloric acid and the resulting solid, which precipitated, was collected by filtration. Recrystallization of the precipitate from benzene gave 3.35 g (83%) of white crystals: mp 210–211°; λ_{max}^{EtOH} 304 mμ (ε 11,700), 238 (8600), 221 (36,800), and 218 (shoulder).

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.15; H, 4.72; N, 15.71.

5-Methyl-3-azapyrrocoline (VIIIb).—A solution of 300 mg of 1-carboxy-5-methyl-3-azapyrrocoline (VIIIb) in 15 ml of 57% hydriodic acid was boiled under reflux for 3 hr. It was then made basic and extracted with ether. Concentration of the ether extract followed by distillation of the residue gave 1.6 g (89%) of a colorless oil: bp 100° (14 mm); λ_{max}^{EtOH} 287 mμ (ε 6000), 222 (40,800), and 219 (43,200); nmr (deuteriochloroform) showed a doublet at 2.12 (J = 5 cps, 1 H), a multiplet at 2.6–3.53 (4 H), and a singlet at 7.30 (3 H).

Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.41; H, 6.30; N, 21.13.

1-Carboxy-5-(γ-hydroxypropyl)-3-azapyrrocoline (VIIc).—In this instance because of the nature of the compounds involved and the difficulties of isolating intermediates in a pure state, the conversion of 2-(γ-hydroxypropyl)pyridine to VIIc was carried through directly as follows. A mixture of 41.0 g of 2-(γ-hydroxypropyl)pyridine and 11.3 g of hydroxylamine-O-sulfonic acid in 64 ml of water was heated on a steam bath for 30 min. Then, 13.7 g of solid potassium carbonate was added and the excess 2-(γ-hydroxypropyl)pyridine and water were removed under reduced pressure. After addition of ethanol, the solid potassium sulfate precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The blue oily residue was taken up in 150 ml of dimethylformamide and 13.7 g of powdered potassium carbonate was added. After addition of 15.0 g of ethyl propiolate, the mixture was heated on a steam bath for 1 hr and then allowed to stir at room temperature overnight. After removal of the dimethylformamide under reduced pressure, water was added and the aqueous solution was extracted with chloroform. Concentration of the chloroform extract was followed by chromatography over Florisil using a 10% ether–Skellysolve B mixture for elution. The main fraction was a yellow oil showing ester carbonyl but no hydroxyl or amino absorption. A second chromatogram over Florisil gave 4.06 g

(20) Microanalyses were by Micro-Tech Laboratories and Pascher and Pascher Laboratories. Ultraviolet and visible spectra were determined with a Cary Model 15 spectrometer, infrared spectra with a Beckman IR-5A spectrometer, and nmr spectra were taken with a Varian A-60 spectrometer. We thank the National Science Foundation for funds allowing the purchase of the Varian A-60 as well as the Joy liquid nitrogen apparatus.

of 1-carbethoxy-5-(γ-hydroxypropyl)-3-azapyrrocoline as a pale yellow oil. This was dissolved in a mixture of 150 ml of methanol and 40 ml of a 10% aqueous potassium hydroxide solution and allowed to stand at room temperature for 14 hr. After removal of the methanol, the residue was taken up in water and acidified. The resulting precipitate was collected and recrystallized from benzene to give 2.53 g of white crystals: mp 160–161°; λ_{max}^{Nujol} 2.98 μ (hydroxyl), 6.08 (carboxyl), 12.65 and 13.31 (aromatic CH); λ_{max}^{EtOH} 305 mμ (ε 12,200), 239 (8880), 222 (35,500), and 218 (shoulder).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.74; H, 5.66; N, 12.69.

3,5-Trimethylen-3-azapyrrocolinium Iodide (X).—A solution of 1.0 g of 1-carboxy-5-(γ-hydroxypropyl)-3-azapyrrocoline (VIIIc) in 25 ml of 57% hydriodic acid was boiled under reflux for 3 hr. After neutralization of the cold solution with aqueous potassium carbonate, the solution was extracted with four 70-ml portions of chloroform. When the chloroform extract was dried and concentrated, it yielded an oil soluble in organic solvents and, presumably, mainly the free base derived from IX. However, on standing at room temperature, this oil rapidly crystallized with the solid product having the properties to be expected for the ring-closed, ionic structure X. Recrystallization of this solid from ethanol gave 856 mg of white crystals: mp 320° dec; λ_{max}^{Nujol} 6.18 and 12.61 μ; λ_{max}^{EtOH} 307 mμ (ε 7300), 303 (7300), 292 (7450), 289 (5930), 222 (28,600), and 218 (42,900); nmr [deuterium oxide with 3-(trimethylsilyl)-1-propanesulfonic acid as internal standard] showed complex aromatic absorption between τ 1.52 and 3.46, a triplet (1 H) at 5.20, and the remaining aliphatic protons as a complex between 6.01 and 7.88.

Anal. Calcd for $C_{10}H_{11}N_2I$: C, 41.98; H, 3.86; N, 9.79. Found: C, 42.16; H, 4.16; N, 9.50.

Registry No.—VIa, 16205-44-0; VIb, 16205-45-1; VIIa, 16205-46-2; VIIb, 16205-47-3; VIIc, 16205-48-4; VIIIa, 274-56-6; VIIIb, 16205-50-8; X, 16205-51-9.

The Behavior of 2-Halo- and 2-Trifluoromethyl-1,4-benzoquinones in the Nenitzescu Indole Synthesis

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The 2-halo-1,4-benzoquinones (**1**) usually react with ethyl 3-aminocrotonate (**2a**) to give mixtures of the ethyl 6- and 7-halo-5-hydroxy-2-methylindole-3-carboxylates; however, 2-fluoro-1,4-benzoquinone (**1c**) gives only the 6 isomer. 2-Trifluoromethyl-1,4-benzoquinone (**5**) reacts with **2a** and *t*-butyl 3-aminocrotonate (**2b**) to furnish good yields of the ethyl (**6a**) and *t*-butyl (**6b**) esters of 5-hydroxy-2-methyl-4-trifluoromethylindole-3-carboxylic acid. The reactions of **2a** with 2-chloro-3-trifluoromethyl-1,4-benzoquinone (**9**), 2-chloro-5-trifluoromethyl-1,4-benzoquinone (**12**), and 2-methoxy-5-trifluoromethyl-1,4-benzoquinone (**15**) were also examined. The products isolated in each instance indicate that the inductive effect of the trifluoromethyl substituent largely determines the site of the initial carbon–carbon bond formation and, thus, the orientation of the benzene-ring substituents in the resulting 5-hydroxy-2-methylindole-3-carboxylates. The directive influence of this group in conjunction with its replacement by hydrogen on acid hydrolysis affords a route to difficulty accessible indoles, *e.g.*, the two-stage preparation of 7-chloro-2-methylindol-5-ol (**14**) from **12**. Decarbalkoxylation of *t*-butyl ester **6b** with *p*-toluenesulfonic acid gave 2-methyl-4-trifluoromethylindol-5-ol (**19a**). Lithium aluminum hydride reduction of 5-methoxy-2-methyl-4-trifluoromethylindole (**19b**) furnished 5-methoxy-2,4-dimethylindole (**20**).

The general utility of the Nenitzescu indole synthesis,[1] wherein a *p*-benzoquinone condenses with an alkyl 3-aminocrotonate, for the preparation of 5-hydroxyindole-3-carboxylates is well documented.[2] Although the mechanism[2,3] of this reaction suggests that a monosubstituted quinone could give 4-, 6-, and 7-substituted 5-hydroxyindole-3-carboxylates, the 6 isomer is most generally noted. However, it is apparent that the product distribution will be influenced by the steric nature and electronic character of the quinone substituent.[4] Steric forces may exert their influence in either of two ways. (1) Addition of the enamine to the quinone 5 or 6 position may be preferred over the adjacent 3 position. In fact, the lack of 4 isomer formation with alkylquinones[2,5] can be explained by this effect. (2) When enamine addition occurs at the 6 position, these forces may mitigate against the required subsequent nitrogen–carbon condensation. Thus, the observed quantity of 7 isomer declines precipitously by varying the quinone substituent from methyl to ethyl.[2] The electronic effect of the quinone substituent should influence the isomer distribution in a predictable manner. Thus, with 2-methoxy-1,4-benzoquinone,[2,6] the strong electron-donating methoxy group leads to enamine condensation at the 5 position.[7] On the other hand, substitution of benzoquinone with the electron-withdrawing carbomethoxy group results in condensation at the 3 position, with the subsequent formation of 4-carbomethoxy-5-hydroxyindole.[8] In this paper we describe our studies with quinones having electronegative substituents that might activate the 3 position by inductive effects.

The 2-halo-1,4-benzoquinones were of interest in this respect, inasmuch as the inductive effect of the substituent is opposed by a resonance effect. In fact, as a result of these opposing factors, the formation of a 4-substituted 5-hydroxyindole is not observed. Thus,

(1) C. D. Nenitzescu, *Bull. Soc. Chim. Romania*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 110 (1930).

(2) G. R. Allen, Jr., C. Pidacks, and M. J. Weiss, *J. Amer. Chem. Soc.*, **88**, 2536 (1966).

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(4) H. S. Wilgus, III, E. Frauenglass, E. T. Jones, R. F. Porter, and J. W. Gates, Jr., *J. Org. Chem.* **29**, 594 (1964).

(5) S. A. Monti, *ibid.*, **31**, 2669 (1966).

(6) R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 2029 (1951).

(7) The possibility that steric forces contribute to the exclusive formation of the 6-methoxy isomer (*cf.* 2-ethyl-1,4-benzoquinone) appears unlikely, inasmuch as nucleophilic reactions with 2-methoxy-1,4-benzoquinone lead to high yields of 5-substituted methoxyhydroquinones (see ref 4 for leading references).

(8) G. R. Allen, Jr., and M. J. Weiss, *J. Org. Chem.*, **33**, 198 (1968).