carboline[6] and 0.040 g. of the hydrochloride salt of the above ester were dissolved in 25 ml. of refluxing ethyl alcohol. Ethyleneimine (0.67 g.) dissolved in 10 ml. of ethyl alcohol was added dropwise to the refluxing solution and this heating was continued for 24 hr. On chilling, this solution deposited light yellow crystals which were collected on a Büchner funnel, washed with ethyl alcohol, and then recrystallized from an excess of that solvent. One gram of pure product, m.p. 234–235° dec., was obtained. Infrared absorption shows a strong broad band at 3400 cm.$^{-1}$ (overlap of indole and amide NH) and a strong amide band at 1670 cm.$^{-1}$; $\lambda_{max}^{C_2H_5OH}$ 224 mμ (ε 36,190), 278 (39,340), 289 (6,360).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.26; H, 17.42. Found: C, 69.95; H, 6.29; N, 17.57.

Acknowledgment.—The authors extend their sincere thanks to Dr. E. Schlittler for his continuing interest. We are also indebted to Mr. L. Dorfman and his associates for the microanalytical and spectral data.

(6) F. J. Vejdeiek, V. Treka, and M. Protiva, *J. Med. Pharm. Chem.*, **3**, 427 (1961).

A Synthesis of 6-Methyl-2-phenyl-5-azacycl[3.2.2]azine and Related Compounds[1,2]

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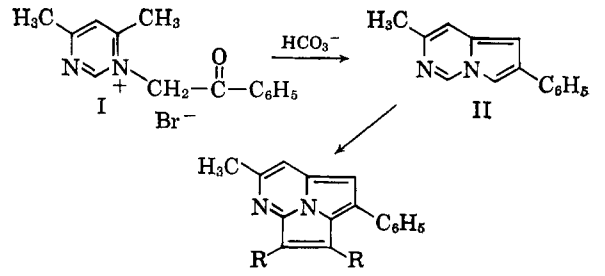
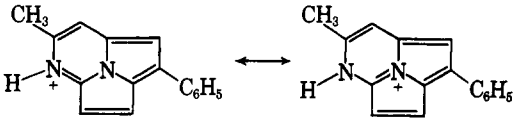
The reaction of pyrrocolines with dimethyl acetylenedicarboxylate,[3–5] an early example of a general procedure now known as the 1,3-dipolar addition reaction,[6] provides convenient access to cycl[3.2.2]azine and its various derivatives. Although the central nitrogen of cycl[3.2.2]azine is not basic, nitrogen atoms placed in the perimeter are basic and allow for the preparaton of the corresponding quaternary salts which are more suitable for physiological testing.[7] It was for this reason that work was initiated on the synthesis of 5-azacycl[3.2.2]azine derivatives. However, since then studies on the correlation of molecular orbital calculations with experimental data on the electronic spectra and basicity of the cyclazines has made it desirable to have additional examples with nitrogen in the periphery as an aid to evaluating the parameter to be assigned to nitrogen.[8,9]

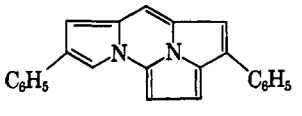
As starting material, 4,6-dimethylpyrimidine was converted in 97% yield to the corresponding quaternary bromide I using phenacyl bromide in benzene at room temperature. Cyclization by the Chichibabin procedure[10] gave 7-methyl-2-phenyl-6-azapyrrocoline(II) in 56% yield. Treatment of II with dimethyl acetylenedicarboxylate in the presence of a palladium-on-charcoal catalyst and toluene then led to the corresponding 5-azacycl[3.2.2]azine III in 28% yield. Hydrolysis of the diester with base proceeded essentially quantitatively to give the diacid IV. Finally, decarboxylation of the diacid using copper powder and aniline occurred smoothly in 78% yield to produce the desired 6-methyl-2-phenyl-5-azacycl[3.2.2]azine (V).



As expected, 6-methyl-2-phenyl-5-azacycl[3.2.2]azine was readily soluble in aqueous acid. However, its ultraviolet and visible absorption spectrum showed an unexpected shift to longer wave lengths in the presence of acid. Thus, in neutral ethanol V showed maxima at 227 (4.26), 264 (4.54), 327 (4.34), and 452 mμ (log ε 3.59), whereas in 0.09 *M* hydrochloric acid maxima were observed at 227 (4.22), 268 (4.55), 366 (4.33), and 473 mμ (log ε 3.31). This shift becomes understandable, however, when it is considered that V, on protonation, is a resonance hybrid with contributing structures such as VI and VII.



In the original plan the presence of the methyl group at the 6-position of V was desired so that a second Chichibabin ring closure could be effected to give the interesting fused bispyrrocoline represented by VIII. Unfortunately, attempts to accomplish this ring closure were unsuccessful.



Experimental[11]

1-Phenacyl-4,6-dimethylpyridinium Bromide (I).—A solution of 11.0 g. of 4,6-dimethylpyrimidine and 21.0 g. of phenacyl bromide in 60 ml. of benzene was allowed to stand at room temperature for 10 days. The orange-yellow precipitate, which separated, was collected by filtration, washed with benzene, and air-dried. This gave 31.4 g. (97%) of product of sufficient purity for use in the next step. Recrystallization of the orange-yellow solid from absolute ethanol gave 23.0 g. (71%) of yellow crystals, m.p. 173° dec.

Anal. Calcd. for $C_{14}H_{15}N_2OBr$: C, 54.73; H, 4.92; N, 9.12; Br, 26.01. Found: C, 54.38; H, 4.95; N, 8.84; Br, 25.94.

7-Methyl-2-phenyl-6-azapyrrocoline (II).—To a stirred solution of 10.5 g. of the crude quaternary bromide I in a mixture of 50 ml. of ethanol and 350 ml. of water there was added a saturated

(1) Abstracted from the M.S. thesis of S. S. Kertelj, University of Oregon, 1963.

(2) Aided in part by the National Science Foundation and by the U. S. Army Research Office (Durham).

(3) J. C. Godfrey, *J. Org. Chem.*, **24**, 581 (1959).

(4) A. Galbraith, T. Small, and V. Boekelheide, *ibid.*, **24**, 582 (1959).

(5) A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.*, **83**, 453 (1961).

(6) R. Huisgen and A. Eckell, *Tetrahedron Letters*, **12**, 5 (1960); *cf.* R. Huisgen, "Theoretische Chemie und Organische Synthese," Festschrift der Zehnjahresfeier des Fond der Chemischen Industrie, Düsseldorf, Germany, 1960.

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

(8) V. Boekelheide, F. Gerson, E. Heilbronner, and D. Meuche, *Helv. Chim. Acta*, in press.

(9) F. Gerson, E. Heilbronner, N. Joop, and H. Zimmermann, *ibid.*, in press.

(10) A. E. Chichibabin, *Ber.*, **59**, 2048 (1926).

(11) Microanalyses by Micro-Tech Laboratories and F. Pascher. Melting points are uncorrected.

aqueous solution prepared from 10 g. of potassium bicarbonate. The resulting orange-brown suspension was heated on a steam bath for 1 hr. and cooled, and the solid which separated was collected. This, after being washed thoroughly with water and then air-dried, was recrystallized from benzene to give 3.8 g. (56%) of yellow crystals, m.p. 180–190° dec. Treatment with charcoal in acetonitrile followed by an additional recrystallization from benzene yielded white crystals, m.p. 180–190° dec. The ultraviolet absorption spectrum of II in ethanol showed a maxima at 254 mμ (log ε 4.74) with a shoulder at 258 mμ (log ε 4.72).

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.67; H, 5.86; N, 13.23.

3,4-Dicarbethoxy-6-methyl-2-phenyl-5-azacycl[3.2.2]azine (III).—To a solution of 9.0 g. of 7-methyl-2-phenyl-6-azapyrrocoline (II) and 9.4 g. of dimethyl acetylenedicarboxylate in 540 ml. of toluene there was added 8.0 g. of a 5% palladium-on-charcoal catalyst, and the mixture was heated under reflux in a nitrogen atmosphere for 21 hr. After removal of the catalyst and solvent, the brown, gummy residue was taken up in benzene and passed over neutral alumina (800 g., grade III, Woelm). Following the initial eluate which contained 0.25 g. of II, the main fraction gave 4.15 g. (28%) of bright yellow crystals, m.p. 152–154°. A further recrystallization from ethyl acetate yielded yellow needles, m.p. 155–156°. The absorption spectrum of III in ethanol showed maxima at 242 (4.53), 266 (4.30), 336 (4.29), and 448 mμ (log ε 3.91).

Anal. Calcd. for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.77; H, 4.75; N, 7.87.

3,4-Dicarboxy-6-methyl-2-phenyl-5-azacycl[3.2.2]azine (IV).—A mixture of 150 mg. of III and 30 ml. of methanol saturated with potassium hydroxide was heated at 50° with stirring until complete solution resulted (30 min.), whereupon precipitation of the dipotassium salt of IV occurred. The mixture was heated for an additional 30 min. before collecting the precipitate by filtration. The solid precipitate was redissolved in a minimum amount of water, and the solution was acidified with concentrated hydrochloric acid. There separated 130 mg. (95%) of yellow crystals, m.p. 230–235°.

Anal. Calcd. for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.20; H, 3.98; N, 8.58.

When the diacid IV was recrystallized from pyridine, the monopyridinium salt of IV separated as long, orange needles, m.p. 170° dec.

Anal. Calcd. for $C_{23}H_{17}N_3O_4$: C, 69.16; H, 4.29; N, 10.52. Found: C, 69.07; H, 4.42; N, 10.55.

6-Methyl-2-phenyl-5-azacycl[3.2.2]azine (V).—A mixture of 900 mg. of the crude diacid IV and 1.0 g. of copper powder in 250 ml. of aniline was boiled under reflux until evolution of carbon dioxide ceased. After removal of the catalyst and concentration under reduced pressure, the gummy residue was taken up in benzene and chromatographed over Florisil (300 g.). From the third fraction of eluate there was obtained 510 mg. (78%) of an orange-yellow solid, m.p. 135–140°. Recrystallization from an ether–pentane mixture (1:1) produced large, yellow-orange crystals, m.p. 145–147°. The n.m.r. spectrum in methylene chloride showed a proton signal for the methyl group at 7.18 τ. In concentrated sulfuric acid this signal was shifted to 6.77 τ with two smaller additional signals at 6.70 and 7.03 τ. The latter two signals are presumably due to protonation on carbon at the 1- and 4-positions.[5]

Anal. Calcd. for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.86; H, 5.28; N, 11.90.

Synthesis and Polymerization of 3-Azabicyclo[4.3.1]decan-4-one and 7,7-Dimethyl-2-azabicyclo[4.1.1]octan-3-one

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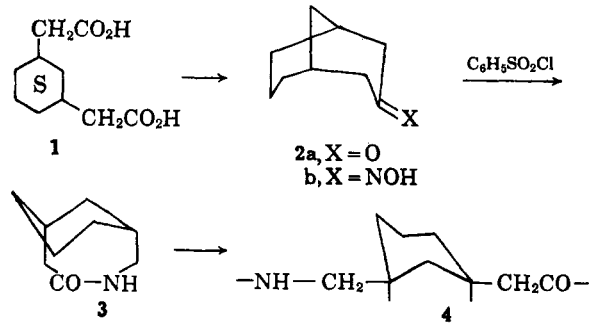
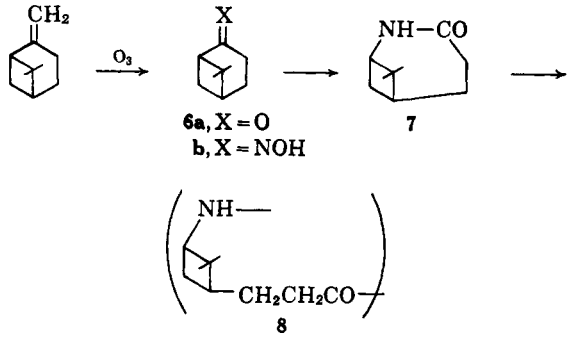
Cyclohexane-1,3-diacetic acid readily cyclized to bicyclo[3.3.1]nonan-3-one (**2a**) when heated with barium oxide. Hydroxylamine converted the ketone to the oxime **2b**, which underwent the Beckmann rearrangement to give the desired lactam, 3-azabicyclo[4.3.1]decan-4-one (**3**). Cyclohexane-1,4-diacetic acid, under conditions which readily cyclized the 1,3-isomer, gave no bicyclo[3.2.2]nonan-3-one (**5**). The ketone **2a** can exist in a stable two-chair conformation, while **5** would possess a strained boat form of the cyclohexane ring. This difference in conformation may account for the difference in ease of formation of the two ketones.



Nopinone (**6a**) recently has been made available[1] by ozonolysis of β-pinene. This preparation was repeated and the ketone was converted to the oxime **6b** and thence by Beckmann rearrangement to a crystalline lactam. The oxime is assigned the configuration with the hydroxyl group *anti* to the cyclobutane ring, since this configuration is sterically less strained than the *syn* form. Because of the *trans* nature of the rearrangement, the lactam is assigned the structure 7,7-dimethyl-2-azabicyclo[4.1.1]octan-3-one (**7**). This type of assignment, applied previously to other atom-bridged oximes and lactams,[2] was shown subsequently to be correct by degradation studies.[3]



Polymerizations.—The lactams were converted to polyamides by heating at 200–223° with 5% of 85% phosphoric acid as catalyst.[2,4] Lactam **3** polymerized much more readily than lactam **7**. Hydrogen crowding within the bridged rings is considered to be the destabilizing factor in these molecules which causes them to polymerize. Like many other polyamides possessing alicyclic rings in the polymer chain,[2,4] these polymers displayed quite high melting points; **4** melted at 297° and **8** at 358°.

Experimental

Cyclohexane-1,3- and 1,4-diacetic Acids.—Pure *m*-phenylenediacetic acid was not available but an approximately 1:1 mixture

(1) J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 5445 (1960).
(2) H. K. Hall, Jr., *ibid.*, **82**, 1209 (1960).
(3) R. C. Elderfield and E. T. Losin, *J. Org. Chem.*, **26**, 1703 (1961).
(4) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **80**, 6412 (1958).