[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Synthesis of 2-Phenyl-1-azacycl[3.2.2]azine[1]

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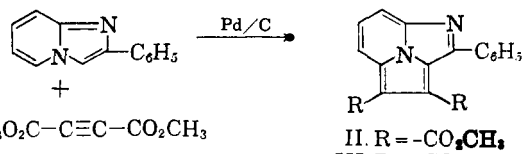
The addition of dimethyl acetylenedicarboxylate to 2-phenyl-1-azapyrrocoline yields the corresponding 1-azacyclazine. Hydrolysis and decarboxylation of the adduct gives 2-phenyl-1-azacycl[3.2.2]azine.

The discovery that dimethyl acetylenedicarboxylate reacts with pyrrocoline in the presence of a dehydrogenating agent to give cycl[3.2.2]azine derivatives provides a particularly convenient route for the synthesis of members of this class of compounds.[3] One characteristic of the cycl[3.2.2]-azines is the fact that the central nitrogen atom is nonbasic, indicating its pi-electrons are completely involved in the aromatic π-electron system and thus not readily available for bonding. For this reason it was of interest to prepare examples of this class which would contain a periphery nitrogen and thus be capable of forming both acid and quaternary salts, compounds whose solubility would be more favorable for physiological testing. In the present paper the synthesis of 2-phenyl-1-azacycl-[3.2.2]azine is described.

The 2-phenyl-1-azapyrrocoline (I), needed as starting material, was prepared from 2-aminopyridine following the procedure of Chichibabin.[4,5] When this was allowed to react with dimethyl acetylenedicarboxylate in boiling toluene in the presence of a palladium-on-charcoal dehydrogenation catalyst, there was formed in about 29% yield a product having the correct composition for 3,4-dicarbomethoxy-2-phenyl-1-azacycl[3.2.2]-azine (II). Hydrolysis of II using methanolic potassium hydroxide followed by acidification gave the corresponding diacid III in 88% yield. Decarboxylation of III was accomplished using copper chromite in boiling diphenyl ether and led to 2-phenyl-1-azacycl[3.2.2]azine (IV) in quantitative yield.



II. R = $-CO_2CH_3$
III. R = $-CO_2H$
IV. R = $-H$

The infrared and ultraviolet absorption spectra of 2-phenyl-1-azacycl[3.2.2]azine were very similar to those of 2-phenylcycl[3.2.2]azine.[6] As expected, 2-phenyl-1-azacycl[3.2.2]azine was readily soluble in dilute acid and its ultraviolet absorption spectrum in acidic ethanol was only altered slightly from that in neutral ethanol.

It was hoped that 1-azacycl[3.2.2]azine, itself, could be prepared in a similar fashion. Unfortunately, the general methods worked out for the synthesis of pyrrocolines unsubstituted in the five-membered ring[7] failed when it was attempted to apply them to the case of 1-azapyrrocoline.

EXPERIMENTAL[8]

3,4-Dicarbomethoxy-2-phenyl-1-azacycl[3.2.2]azine (II). To a solution of 1.5 g. of 2-phenyl-1-azapyrrocoline[4,5] (I, m.p. 136–137°) and 2.3 g. of dimethyl acetylenedicarboxylate in 225 ml. of toluene there was added 3.2 g. of a 5% palladium-on-charcoal catalyst and the mixture was boiled under reflux in a nitrogen atmosphere for 25 hr. After removal of the catalyst, concentration of the filtrate gave a tarry residue. This was taken up in benzene and passed over alumina (activity II). From the benzene eluates there was recovered 419 mg. of 2-phenyl-1-azapyrrocoline and 540 mg. (29%, based on unrecovered 2-phenyl-1-azapyrrocoline) of yellow crystals, m.p. 156–162°. These, on sublimation, gave yellow needles; m.p. 163–164°; ultraviolet absorption (log ϵ) in ethanol: 393 (4.19), 326 (4.16), 257 (4.44), and 208 mμ (4.50); and infrared absorption: peaks at 5.78 and 5.88 (ester carbonyls), 12.60 and 14.57 μ.

Anal. Calcd. for $C_{19}H_{14}N_2O_4$: C, 68.25; H, 4.21; N, 8.38. Found: C, 68.18; H, 4.42; N, 8.39.

Hydrochloride of 3,4-dicarboxy-2-phenyl-1-azacycl[3.2.2]-azine (III). When 125 mg. of the diester II was dissolved in a warm solution prepared from 13 ml. of methanol and 5.2 g. of potassium hydroxide, the potassium salt of the diacid III began precipitating immediately and hydrolysis was complete in 5 min. The potassium salt (100% yield) was collected by filtration and then dissolved in 6*N* hydrochloric acid. This caused the precipitation of 100 mg. (88%) of III as a yellow powder. Since III did not melt below 300° and was insoluble in the common organic solvents, it could

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(3) A. Galbraith, T. Small, and V. Boekelheide, *J. Org. Chem.*, **24**, 582 (1959).

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

(5) C. Djerassi and G. R. Pettit, *J. Am. Chem. Soc.*, **76**, 4470 (1954) have questioned the structure of Chichibabin's product, suggesting by analogy with their observations on the reaction of 2-pyridinethiol and phenacyl bromide that the correct structure was probably 3-phenyl-1-azapyrrocoline. The addition reaction employed in our synthetic scheme requires that the 3-position be unsubstituted and thus establishes the product as 2-phenyl-1-azapyrrocoline in agreement with Chichibabin's original assignment.

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

(7) V. Boekelheide and R. J. Windgassen, Jr., *J. Am. Chem. Soc.*, **81**, 1456 (1959).

(8) All melting points are corrected. Analyses by the Micro-Tech Laboratories.

not readily be purified further and was used as such in the next experiment. For analytical purposes, the hydrochloride of III was prepared by dissolving 30 mg. of the pure diester II in 5 ml. of boiling 6*N* hydrochloric acid and concentrating the solution to dryness. The crystalline residue melted at 288–290°.

Anal. Calcd. for $C_{17}H_{11}N_2O_4Cl$: C, 59.57; H, 3.24; N, 8.17. Found: C, 59.88; H, 3.51; N, 8.39.

2-Phenyl-1-azacycl[3.2.2]azine (IV). A mixture of 150 mg. of III and 115 mg. of copper chromite catalyst in 30 ml. of diphenyl ether was boiled under reflux for 8 hr. The solution was then diluted with benzene and the catalyst was removed by filtration. The filtrate was extracted several times with 6*N* hydrochloric acid. After neutralization, the aqueous acid extract was extracted in turn with an ether-benzene mixture. Concentration of the organic layer gave 107 mg. (100%) of yellow-orange crystals, m.p. 73–79°. These, on sublimation gave 77 mg. (72%) of pale yellow crystals; m.p. 83–84°; ultraviolet absorption (log ϵ) in neutral ethanol: 395 (4.32), 380 (4.18), 312 (4.24), 251 (4.48), 232 (4.28) and 209 mμ (4.30); ultraviolet absorption (log ϵ) in acidic ethanol (saturated with gaseous hydrogen chloride): 388 (4.32), 370 (4.39), 301 (3.99), 255 (4.45), 235 (4.19) and 212 mμ (4.48).

Anal. Calcd. for $C_{15}H_{10}N_2$: C, 82.54; H, 4.62; N, 12.84. Found: C, 82.90; H, 4.87; N, 12.86.

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[CONTRIBUTION FROM THE RESEARCH DIVISION, CIBA PHARMACEUTICAL PRODUCTS INC.]

3-Aminomethylindoles and 2-(3-Indolyl)oxazolidines from Indole-3-aldimines. Some Observations on the Acetylation of Schiff Bases

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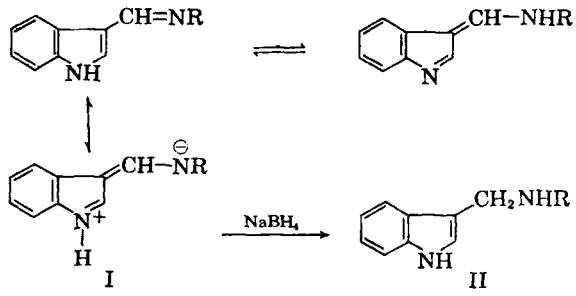
Sodium borohydride reduction of imines prepared from indole-3-carboxaldehyde and primary amines affords a practical synthesis of 3-alkylaminomethylindoles. Imines derived from the same aldehyde and ethanolamines undergo simultaneous acetylation and ring closure with acetic anhydride, giving 1-acetyl-2-(1-acetyl-3-indolyl)oxazolidines. This ring closure is contrasted with acetylation of certain other β-hydroxyimines in which similar oxazolidine formation does not occur, and the implications of the reaction in the special case of 3-acylindole derivatives are discussed briefly.

The appearance of several recent reports[2,3] concerning the chemistry of 3- acylindoles and corresponding indole-3-carbinols, derived from them by sodium borohydride reduction, prompts us to describe some work along similar lines which has been carried out in this laboratory during the past two years.

We became interested in aminomethylindoles for several reasons. It appeared to us that while the preparation of compounds basically related to tryptamine currently is undergoing exhaustive development in the hands of numerous investigators, little or no attention has been focused recently upon compounds related to gramine, which, pharmacologically, is interesting in its own right. Although some tertiary amines closely related to gramine have been prepared,[4] few, if any, secondary amines of the same type have been reported. Gramine and its quaternary salts have been employed frequently as synthetic intermediates ever since their now well known utility in alkylation reactions was demonstrated by Snyder[5] and his colleagues, but the field comprised of analogs of gramine has remained little exploited. Therefore we set about synthesizing a series of N_b-substituted 3-aminomethylindoles, hoping to find some representatives of this class of compounds which would have useful pharmacological properties.

It is now known that Schiff bases derived from aromatic aldehydes are reduced to secondary amines with sodium borohydride.[6] We have investigated the use of this procedure with a variety of aldimines, and we find that it is almost universally applicable whenever the products obtained are stable under alkaline conditions. Furthermore, with methanol as the solvent as directed,[6] even those secondary amines which are very sensitive to hydrogenolysis under the conditions of catalytic hydrogenation undergo a minimum of this undesirable cleavage. In the particular case at hand, the most practical approach at present to synthesis of compounds of general structure II is found to



I II

(1) Mrs. Edwin L. Klett.

(2) E. Leete, *J. Am. Chem. Soc.*, 81, 6023 (1959).

(3) J. Szmuszkowicz, *J. Am. Chem. Soc.*, 82, 1180 (1960).

(4) See P. L. Julian, "The Chemistry of Indoles," Chap. 1, in Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, 1952, Vol. 3, p. 54, for a summary of some gramine analogs prepared by the usual Mannich condensation.

(5) H. R. Snyder, *et al.*, *J. Am. Chem. Soc.*, 66, 200 (1944); 70, 1857, 3770 (1948); 71, 663 (1949). See also Ref. 4.

(6) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, 22, 1068 (1957).