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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO.]

Reductive Alkylation of Indole with Pyridinecarboxaldehydes

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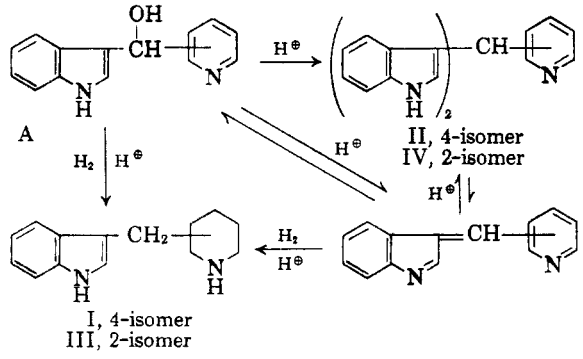
Reductive alkylation of indole has been effected with both 2- and 4-pyridinecarboxaldehyde. Modest yields of the corresponding skatylpiperidines were obtained, accompanied in each case by the unreduced 3,3′-diindolylmethylpyridine. The course of these reactions is discussed.

A recent report[1] from these laboratories described the reaction of indoles with pyridinecarboxaldehydes in glacial acetic acid. The available evidence supported the formulation of the products as 3,3′-diindolylmethylpyridines, impurities resulting from dissociation equilibria and oxidation reactions being considered responsible for coloration[2a] (particularly marked in acid solution).

In this connection it appeared of interest to attempt the reductive alkylation of indole with 2- and 4-pyridinecarboxaldehyde.[2b] When equimolar quantities of indole and 4-pyridinecarboxaldehyde were dissolved in glacial acetic acid and hydrogenated at room temperature over Adams catalyst, there were obtained 29% of 4-skatylpiperidine (I) and 20% of the unreduced 4-(3,3′-diindolylmethyl)pyridine (II). Under the same conditions, 2-pyridinecarboxaldehyde afforded appreciably less 2-skatylpiperidine (III) and correspondingly more of the diindolyl product (IV). The following equilibria would appear to be involved:



Thus, this constitutes a one-step synthesis of the skatylpiperidines, albeit by no means in spectacular yield. (No doubt yields could have been improved considerably by using more than one molar equivalent of aldehyde. Since present interest was focused on the course of the reaction, this was not done.) Although I has not previously been reported, III has been prepared by Akkerman and Veldstra,[3] and, more conveniently, by Bader and Oroshnik.[4] These latter authors condensed 2-pyridyllithium with 3-indolecarboxaldehyde and hydrogenated the resulting, isolated pyridylcarbinol (A) over Adams catalyst in a mixture of acetic acid and ethanol. In addition to 2-skatylpiperidine they obtained 3.5% of what was apparently 3-indolyl-2-piperidinemethanol and 30% of a substance the structure of which was not established, but which, rather implausibly, they considered to be the symmetric ether of the hydroxy compound. Since similar equilibria would be expected to be involved, the apparent absence, here, of products containing oxygen might be attributable to the greater acidity of the medium used.

Bader and Oroshnik's comments,[4] suggesting that hydrogenation of an indolyl-substituted pyridine in glacial acetic acid (in place of the acetic acid in ethanol which they used) will result in reduction of the benzenoid ring of the indole nucleus rather than in saturation of the pyridine ring, require answer. The structures assigned to I and III are in accord with the fact that the compounds absorb as typical indoles in the ultraviolet region (see Table I). Further, the physical properties of III correspond well with those of the 2-skatylpiperidine previously obtained.[3,4] In fact, in our experience[5] the hydrogenation in glacial acetic acid of indolyl substituted pyridine bases [particularly 2- and 4-(3-

(1) A. P. Gray and W. L. Archer, *J. Am. Chem. Soc.*, **79**, 3554 (1957).

(2a) See also M. Strell, A. Zocher and E. Kopp, *Chem. Ber.*, **90**, 1798 (1957).

(2b) In a mechanistic sense, this was expected to parallel the base catalyzed 3-alkylation of indoles by alcohols [see E. F. Pratt and L. W. Botimer, *J. Am. Chem. Soc.*, **79**, 5248 (1957) for leading references].

(3) A. M. Akkerman and H. Veldstra, *Rec. trav. chim.*, **73**, 629 (1954).

(4) H. Bader and W. Oroshnik, *J. Am. Chem. Soc.*, **79**, 5686 (1957).

(5) Unpublished work from these laboratories.

indolylethyl)pyridines], in which the indole nucleus is *not conjugated* with the pyridine ring, has invariably led to reduction of the pyridine and not the indole nucleus. Under conditions essentially as described here, reductions are slow but yields of the corresponding piperidines are good (*ca.* 70%). It might be well to point out that the only possibly valid example cited by Bader and Oroshnik as evidence for the reverse behavior is that of 1-skatylisoquinoline.[6] The course of the catalytic hydrogenation of this has not been unequivocally clarified, but, if it proceeds as postulated, it would appear to be an exceptional case which requires other explanation than one based on the inherent relative ease of hydrogenation of the two ring systems. The other examples cited, *i.e.*, tetrabyrine and, more obviously, yobyrine, are compounds in which the indole nucleus *is conjugated* with the pyridine system. Their behavior cannot be expected to be indicative of the behavior of compounds in which the two nuclei act essentially as isolated entities.[7]

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA[a]

Compound	Position of Maxima, Mμ (Log E)
I. HCl	280 (3.77); 223 (4.22)
III. HCl	280 (3.72); 220 (4.32)
II	280 (4.08); 450 (2.66)
IV	280 (4.12); —
Composite Spectrum[b]	280 (4.12); —

[a] Determined in 95% ethanol using a Beckman model DU spectrophotometer. [b] Calculated on the basis of the absorptions of 2 moles of 4-(3-indolylethyl)-1-methylpiperidine[1] and 1 mole of pyridine.

The diindolylmethylpyridines II and IV, obtained in the present experiments, were identical with the materials previously prepared in air.[1] Further support for the formulation of these compounds was adduced from the fact that their ultraviolet absorption spectra corresponded well with a calculated composite spectrum based on the absorptions of 2 moles of a 3-substituted indole and 1 mole of pyridine (see Table I). The spectrum of II did reveal an additional weak maximum in the long wavelength region, but that of IV showed no such maximum, only a weak trailing off of absorption above 300 mμ. Absorption in the long wave-length region can presumably be ascribed to the colored impurities.[2] It is of interest that the pyridine ring in both II and IV was unaffected under the acidic hydrogenation conditions. Explanation would seem to lie in steric requirements for approach of the pyridine ring to the surface of the catalyst.

(6) V. Boekelheide and Chu-tsin Liu, *J. Am. Chem. Soc.*, **74**, 4920 (1952).

(7) It has already been amply demonstrated that, in sharp contrast to the behavior of β-carboline quaternary salts, the isolated pyridinium cation is catalytically hydrogenated rapidly under conditions that leave the indole system unaffected. See A. P. Gray, E. E. Spinner, and C. J. Cavallito, *J. Am. Chem. Soc.*, **76**, 2792 (1954) and references cited therein; J. Finkelstein and J. Lee, U. S. Patent **2,773,875** (1956); A. P. Gray and W. L. Archer[1]; R. C. Elderfield, B. Fischer, and J. M. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957).

EXPERIMENTAL[8]

Reaction with 4-pyridinecarboxaldehyde. To an ice-cold solution of 12.3 g. (0.11 mole) of 4-pyridinecarboxaldehyde in 100 ml. of glacial acetic acid was added 11.7 g. (0.1 mole) of indole. The resultant orange-red solution was hydrogenated over 0.4 g. Adams platinum oxide catalyst at room temperature and 45 p.s.i. Hydrogen absorption was slow, and after 40 hr. an additional 0.3 g. catalyst was introduced and shaking was continued for 30 more hours. Approximately 85% of the calculated amount of hydrogen was absorbed in all. The filtered solution was diluted with 500 ml. of water (slightly cloudy) and extracted with two portions of ether. The red ether solution was dried over sodium sulfate and concentrated *in vacuo* under nitrogen to a purple-red resin, weight 5.9 g. This was crystallized from aqueous ethanol with the addition of a few drops of concentrated ammonia to give 3.4 g. (20% yield based on indole) of *4-(3,3'-diindolylmethyl)pyridine* (II), m.p. 155–156° (gas evolution), no m.p. depression on admixture with the material previously prepared.[1]

The aqueous layer remaining after the ether extraction was brought to *p*H 8–9 with solid potassium carbonate and exhaustively extracted with chloroform. The dried chloroform extract was concentrated to a red glass, weight 15 g. This was charcoaled in isopropyl alcohol and the solution diluted with Skellysolve B. Crystallization of the resulting precipitate from isopropyl alcohol-Skellysolve B yielded 6.3 g. (29%) of *4-skatylpiperidine* (I) as creamy white crystals, m.p. 169–173°.

Anal. Calcd. for $C_{14}H_{18}N_2$: N (basic), 6.54. Found: N (basic), 617.

The *hydrochloride* of I formed lustrous platelets from ethanol-ether and did not melt below 260°.

Anal. Calcd. for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64; Cl, 14.14. Found: C, 67.19; H, 7.91; Cl, 14.11.

Reaction with 2-pyridinecarboxaldehyde. Similarly, a solution of 21.4 g. (0.2 mole) of 2-pyridinecarboxaldehyde and 23.4 g. (0.2 mole) of indole in 150 ml. of glacial acetic acid was shaken with a total of 1.9 g. of Adams catalyst under 45 p.s.i. of hydrogen at room temperature. Approximately 65% of the calculated amount of hydrogen was absorbed in 45 hr. The reaction solution was worked up essentially as before, although considerably more tar was encountered. There was obtained 12.1 g. (37% based on indole) of *2-(3,3'-diindolylmethyl)-pyridine* (IV) as gray crystals, m.p. 210–212° (dec.), m.p. of a mixture with the material previously prepared[1] undepressed.

Further work up as before afforded 5.2 g. (12%) of *2-skatylpiperidine* (III), m.p. 147–151°. Recrystallization of this from benzene gave colorless crystals, m.p. 156–157° (lit.[3,4] m.p. 156–157°; 156–156.5°, respectively).

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47. Found: C, 78.23; H, 8.33.

Acknowledgment. Determinations of ionic halogen, basic nitrogen and ultraviolet spectra were made by Mr. D. F. Cortright.

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(8) Melting points were corrected for stem exposure. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill.