[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Synthesis of β-(2-Piperidyl)-indoles

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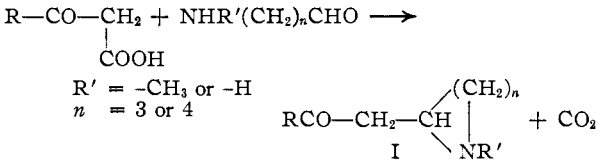
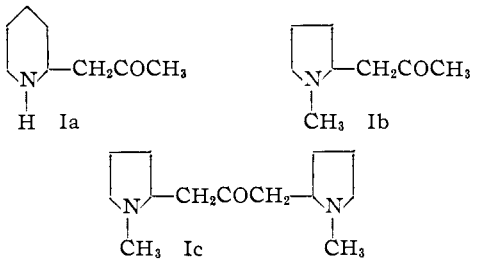
Indole has been condensed with Δ^1-piperideine and with N-methyl-2-hydroxypiperidine to yield, respectively, β-(2-piperidyl)-indole and β-(2-N-methylpiperidyl)-indole. Similarly, α-methylindole was transformed to α-methyl-β-(2-piperidyl)-indole, the structure of which was proved by alternate synthesis: ring closure of 2-pyridylacetone phenylhydrazone to α-methyl-β-(2-pyridyl)-indole followed by saturation of the pyridine ring.

During recent years several groups of workers[2-4] have studied the reaction of selected nucleophilic reagents with δ-aminovaleraldehyde and γ-aminobutyraldehyde (or the N-methyl derivatives thereof), a process which in all successful cases results in attachment of a 2-piperidyl or 2-pyrrolidyl residue to the nucleophilic center. Active methylene components which have been utilized are benzoylacetic acid[2] and acetonedicarboxylic acid,[2-4] both of which suffer decarboxylation during the reaction sequence, producing β-(2-piperidyl)- or β-(2-pyrrolidyl) ketones (I). Of considerable impor-

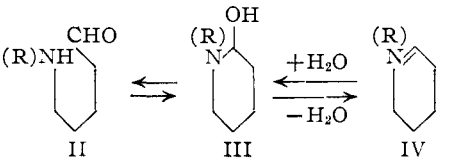


tance is the observation that this condensation can be made to proceed under so-called *physiological conditions, i.e.*, at room temperature in aqueous medium of *p*H at or near 7. By this means such alkaloids as methylisopelletierine (Ia), hygrine (Ib)

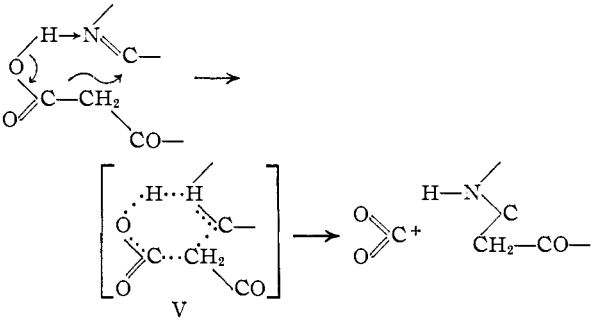


and cuscohygrine (Ic) have been constructed in the laboratory, thereby lending additional credence to the Robinson[5] theory of alkaloid biogenesis.

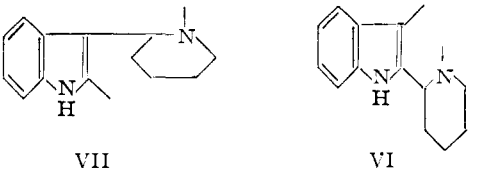
In practice, δ-aminovaleraldehydes have been generated from several sources: (a) Δ^1-piperideine trimer, best obtained by the dehydrohalogenation of N-chloropiperidine,[4c] (b) an acetal of the aminoaldehyde, by the action of aqueous acid,[3,4a] and (c) N-methylpiperidone, by reduction with controlled amounts of lithium aluminum hydride.[2] It seems probable that, at least in the aqueous medium which is ordinarily used for reaction, the aminoaldehyde II is equilibrated with two other species, the cyclic aldehyde-ammonia III and the piperideine (IV).



Because of the nature of the starting components, the reaction may be classified as belonging to the Mannich type, and considerations[6] which have been applied in that area may well be appropriate here. Particularly tempting is the surmise that, of the three available species II, III and IV, the piperideine is the reactive one; the mechanism operative then would appear to conform to the type requiring a hydrogen contributor and an electrophilic center, *i.e.*, in this case the imino group, equivalent to the more familiar carbonyl group. The attractive possibility that condensation with a β-keto acid may occur by means of a concerted, cyclic mechanism (V) in which carbon dioxide is extruded simultaneously, has not been investigated experimentally.



It is of some interest to note that the introduction of an indole as an active hydrogen component implies three possibilities for the structure of the product: an α-(2-piperidyl)-(VI), β-(2-piperidyl)-(VII)



or N-(2-piperidyl)-indole (VIII); VI constitutes the ABD ring system of the alkaloid yohimbine, whereas VII incorporates rings I, II and VI of the strychnine skeleton. In connection with the development of synthetic approaches involving reac-

(1) Wisconsin Alumni Research Foundation Unassigned Research Assistant 1952–1954.

(2) (a) F. Galinovsky, A. Wagner and R. Weiser, *Monatsh.*, **82**, 551 (1951); (b) F. Galinovsky, O. Vogl and R. Weiser, *ibid.*, **83**, 114 (1952).

(3) E. Anet, G. K. Hughes and E. Ritchie, *Nature*, **163**, 289 (1949).

(4) (a) C. Schopf and F. Oechler, *Ann.*, **523**, 1 (1936); (b) C. Schopf and H. Steuer, *ibid.*, **558**, 124 (1947); (c) C. Schopf, A. Komzak, F. Braun and E. Jacobi, *ibid.*, **559**, 1 (1948).

(5) R. Robinson, *J. Chem. Soc.*, **111**, 876 (1917).

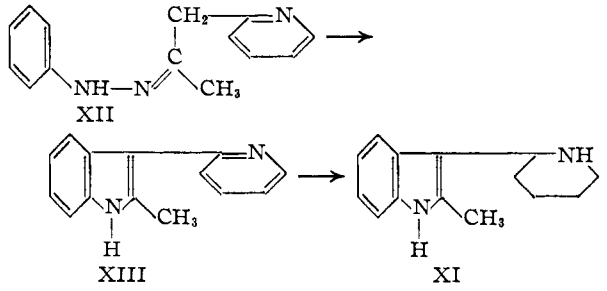
(6) E. R. Alexander and E. J. Underhill, THIS JOURNAL, **71**, 4014 (1949).

tions similar to those described above, we considered it instructive to study this simple case of indole itself; the previously reported utilization of this aromatic in the Mannich reaction[7] made it seem likely that condensation along these lines very probably would occur.

Repetition of Galinovsky's procedure[2] for the reduction of N-methylpiperidone followed by introduction of indole into a solution of the product at a suitable *p*H gave at best only a few per cent. of the expected β-(2-N-methylpiperidyl)-indole (IX), the structural evidence for which will be presented in the sequel. Many modifications, including variations in *p*H and in the mode of piperidone reduction, were not effective in raising the yields above this level. We turned, therefore, to the use of Δ^1-piperideine and found this base to react smoothly with indole at room temperature in a citrate buffer, affording a 40–55% yield of β-(2-piperidyl)-indole (X), melting point 121.5–122°. Monomethylation of this base through the use of methyl iodide yielded the previously obtained N-methyl product IX thereby confirming the relation between these two substances.

In an effort to extend the reaction pattern, we attempted condensation of Δ^1-piperideine with α-methylindole, skatole, indole-β-acetic acid and 2-(β-indolyl)-ethyl bromide. All of these trials failed except that with α-methylindole, which afforded a small yield of α-methyl-β-(2-piperidyl)-indole (XI). This base could not be induced to solidify but did form a nicely crystalline, orange picrate which, in the hydrated state, exhibited a widely variable melting point, but in the anhydrous form melted reproducibly at 180–181°.

Two features relating to the general structure VII required confirmation: (a) attachment of a piperidyl group through its 2-position, and (b) juncture of the moieties through the β-position of the indole ring. Proof of (a) in the case of product XI was realized by independent preparation: Fischer indole synthesis starting with 2-pyridylacetone phenylhydrazone (XII) followed by saturation of the pyridyl ring in the resulting indole. The ring closure of the phenylhydrazone was accomplished by refluxing in aqueous hydrochloric acid,



XII

XIII XI

after which crystalline α-methyl-β-(2-pyridyl)-indole (XIII) was obtained by ether extraction of the basified reaction product. Catalytic hydrogenation over Adams catalyst afforded non-crystalline material which formed, however, a picrate exhibiting all the characteristics of, and apparently identical with, the picrate of XI; the infrared spectra of the regenerated bases were indistinguishable. We assume that condensation of indole itself with Δ^1-piperideine occurs in a like fashion, the only point of uncertainty being that described in (b) above. Evidence bearing on this question arises from several quarters. Initially, it may be pointed out that the nitrogen–hydrogen absorption (2.86 μ) of the (N-methylpiperidyl)-indole in the infrared precludes attachment of the piperidyl substituent to the nitrogen of the indole ring. Beyond that, the preferred reactivity of indole at the β-position in more orthodox Mannich reactions (*e.g.*, the preparation of gramine[7]) suggests similar behavior in the present case. Similarly, reaction of α-methylindole and non-reaction of skatole with Δ^1-piperideine indicates a preference for β-attachment. Third, the piperidylindole X gave a distinct, positive Erhlich test, indicative of an open α-position. Last, comparison of the ultraviolet spectra of IX with spectra of authentic α- and β-substituted indoles demonstrates the validity of assignment to the β-category. Table I shows that α-methylindole absorbs at 272, 277, 280 and 288 mμ, whereas skatole and gramine, as well as X, possess essentially identical curves, incorporating peaks at, roughly, 280 and 290 mμ with distinctly lower extinction coefficients. Thus the structures assigned initially to IX and X are confirmed satisfactorily.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA[a]

	λ_{max}, mμ	ε	λ_{max}, mμ	ε
2-Methylindole	272	7340	277	7250
	280	7110	288	5660
3-Methylindole	282	5680	290	4770
Gramine	280	6330	289	5110
(2-Piperidyl)-indole	280	5940	288	4830

[a] Measured in ethanol with a Cary ultraviolet spectrophotometer.

Experimental[8]

β-(2-N-Methylpiperidyl)-indole (IX).—N-Methyl-2-piperidone (2.26 g., 0.02 mole) was reduced with lithium aluminum hydride (0.23 g., 0.02 mole) according to the directions of Galinovsky. The reduction mixture was added to a solution of 4 ml. of acetic acid in 60 ml. of water, and the *p*H was subsequently adjusted to 4–5. After removal of the supernatant ether layer by evaporation, the solution was filtered and mixed with 2.3 g. (0.02 mole) of finely divided indole. During the next 40 hours the mixture was shaken occasionally. Unreacted indole was removed by extraction with ether and the remaining aqueous portion was made distinctly basic with dilute sodium hydroxide. The resulting precipitate was taken up in hot, aqueous acetone and crystallization allowed to take place. Three hundred and fifty milligrams (8%) of (2-N-methylpiperidyl)-indole, m.p. 154–156°, was obtained. Two additional crystallizations raised the melting point to 157.5–158.0°.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.08. Found: C, 78.71; H, 8.20; N, 13.17.

β-(2-Piperidyl)-indole (X).—To 1.20 g. (10.2 mmoles) of indole, suspended in 640 ml. of citrate buffer (*p*H 4.6–4.8) at room temperature, was added a solution of 0.83 g. (3.33 mmoles) of Δ^1-piperideine trimer in 10 ml. of 1 *N* hydrochloric acid. After standing for 24 hours, the indole had gone essentially completely into solution. The filtered solution was then made basic by adding solid sodium hydroxide. Extraction of the resulting oil with two 100-ml. portions of ether followed by crystallization from hot ligroin (b.p. 100–140°) of the material obtained by vaporization of the ether, yielded 0.81–1.09 g. (40–55%) of β-(2-piperidyl)-indole as a colorless, crystalline solid, m.p.

(7) H. Kuhn and O. Stein, *Ber.*, **70**, 567 (1937).

(8) All melting points are corrected.

113–115°. One crystallization from ethyl acetate afforded analytically pure material, m.p. 121.5–122.0°.

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05. Found: C, 77.72; H, 8.13.

The N-*p*-nitrobenzoyl derivative of X melted at 188.0–188.5° after recrystallization from ethanol.

Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48. Found: C, 68.82; H, 5.66.

Methylation of X.—To 0.40 g. of X in refluxing methanol was added slowly an equivalent amount of methyl iodide as a 2 millimolar solution in methanol. After the addition was complete, refluxing was continued for 0.25 hour. The oil remaining on evaporation of the methanol was taken up in 9 ml. of boiling acetone and then diluted with 15 ml. of water. On standing overnight in the cold, the solution deposited 130 mg. of crystalline IX, m.p. 145–148°. Recrystallization from aqueous acetone gave 80 mg. of material with m.p. 154–155°, which was not lowered on admixture with IX obtained as previously described.

α-Methyl-β-(2-piperidyl)-indole (XI).—2-Methylindole (0.63 g.) and 0.83 g. of Δ^1-piperideine trimer (dissolved in 10 ml. of 1 *N* hydrochloric acid) were allowed to condense in a fashion similar to that described for indole itself, except that 640 ml. of *p*H 7 phosphate buffer was used and the reaction was allowed to proceed for 60 hours. The brown, oily product obtained after basification and ether extraction was converted to the picrate, which was crystallized from 60% ethanol. Material thus obtained (0.4 g., 20%) gave an analysis which corresponded to the monohydrate; the m.p. of the picrate, although sharp, varied randomly between 135 and 175° on subsequent recrystallizations.

Anal. Calcd. for $C_{20}H_{21}N_5O_7 \cdot H_2O$: C, 52.06; H, 5.03. Found: C, 52.08; H, 5.18.

After being dried *in vacuo* (0.1 mm.) for 24 hours at 60°, the once-recrystallized picrate melted reliably at 175–177°. Through recrystallization and final vacuum drying, the melting point could be raised to 180–181°.

Anal. Calcd. for $C_{20}H_{21}N_5O_7$: C, 54.17; H, 4.77. Found: C, 54.15; H, 4.89.

α-Methyl-β-(2-pyridyl)-indole (XIII).—2-Pyridylacetone[9] (4.05 g.) was converted to its phenylhydrazone, which, after two recrystallizations from ligroin (b.p. 100–140°), melted at 121.5–123° and weighed 2.5 g. The rather unstable derivative (8.0 g.) was cyclized by refluxing in 100 ml. of concentrated hydrochloric acid for three hours. The reaction mixture was concentrated *in vacuo* to an oil, which, when treated with 20 ml. of 15% ammonium hydroxide, solidified. Extraction with ether and recrystallization of the recovered product from ligroin (100–140°)–ethyl acetate yielded 3.73 g. (50%) of α-methyl-β-(2-pyridyl)-indole, m.p. 134–136°. Two more recrystallizations raised the melting point to 137–138°.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81. Found: C, 80.56; H, 5.93.

Attempted cyclization of XII using gaseous hydrogen chloride and 95% ethanol resulted only in cleavage—phenylhydrazine was obtained as the hydrochloride.

Hydrogenation of XIII.—Sixty-two milligrams of XIII was hydrogenated over platinum in 95% ethanol to which had been added one equivalent of hydrogen chloride (calculated hydrogen uptake at room temperature and atmospheric pressure, 22.5 ml.; found 26.4 ml.). After removal of the catalyst by filtration and concentration of the filtrate *in vacuo*, aqueous alkali was added. Extraction with ether and subsequent evaporation left a reddish-brown oil which was dissolved in ether and converted to the picrate. One hundred and six milligrams (81%) of material which, after vacuum drying, melted at 175–177°, was obtained; recrystallization from 60% ethanol raised the melting point to 180°. A mixed melting point using picrate obtained by condensation of indole and Δ^1-piperideine was the same, and the infrared spectra of the bases regenerated from the picrates by alkali basification and chloroform extraction, were identical, as were the ultraviolet spectra of the same two substances.

(9) J. P. Wibaut and M. G. J. Beets, *Rec. trav. chim.*, **59**, 553 (1940).

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

The Synthesis of DL-*cis*-3,5-*cis*-3′,5′-Tetramethyl-1,1′-spirobipiperidinium Bromide

BY C. R. NOLLER AND C. E. PANNELL

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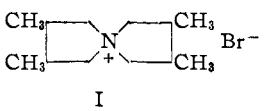
DL-*cis*-3,5-*cis*-3′,5′-Tetramethyl-1,1′-spirobipiperidinium bromide has been synthesized to provide an example of a compound having two like pair of enantiomorphic groups attached to a central atom.

Recently McCasland and Proskow[1] reported the preparation of *meso*-2,3-dimethyl-1,4-butanediol and the corresponding dibromide, and the condensation of the latter with pyrrolidine to give the spiro quaternary bromide. They stated that this work was done "to facilitate the solution of a more fundamental problem." We have learned by private communication with Dr. McCasland that their principal effort has been to synthesize the various stereoisomers of 3,3′,4,4′-tetramethyl-1,1′-spirobipyrrolidinium bromide (I).



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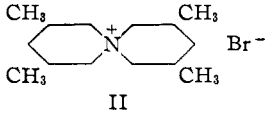
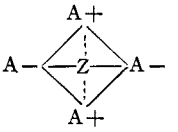


II

Inasmuch as we have synthesized the DL-*cis*-*cis* isomer of the analogous spirobipiperidinium compound II and have used procedures similar to those used by McCasland and Proskow, it seems desirable to report our results to date.

The particular isomer which we have synthesized is that in which the members of the pair of asymmetric carbon atoms in each ring are enantiomorphic and in which the pair in one ring is identical with the pair in the other. The molecule is an example of two like pair of enantiomorphic groups attached to a single atom Z. If no bond links the members of the enantiomorphic pair as in III, the molecule has a fourfold alternating (or mirror) axis of symmetry and is identical with its mirror image. If, however, the enantiomorphic groups are linked together to give a spiro structure, a pair of non-identical mirror images is



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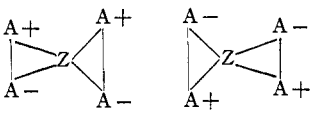

IV

(1) G. E. McCasland and S. Proskow, THIS JOURNAL, **76**, 3486 (1954).