Five grams of 2-amino-5-nitrothiazole (VI) (m.p. 200–201°) was added to sufficient acetic anhydride (about 300 ml.) to effect solution. Approximately 0.5 g. of Raney nickel[10] was added, and the mixture was shaken at 40 p.s.i. of hydrogen for 3 hr. with no observed pressure drop. Additional portions of catalyst were added periodically until the theoretical pressure drop was recorded. (A total of four portions was added over a period of 2 days). The slurry was filtered and the solids were extracted with hot acetic acid. A 65% yield of 2,5-diacetamidothiazole V (4.46 g.) m.p. > 300° (lit., m.p.[7] > 285°) was obtained by evaporation of the acetic acid extracts. This product can be recrystallized from acetic acid–water mixtures.

Anal. Calcd. for $C_7H_9N_3O_2S$: C, 42.20; H, 4.53; N, 21.05. Found: C, 42.47; H, 4.28; N, 21.16.

Reductive Acetylation of 2,4-Dinitrothiazole.—The procedure followed here was that described in the previous example, but the isolation procedure was slightly different because of the solubility of the product in acetic anhydride. After reduction was complete, the catalyst was filtered, the acetic anhydride removed under vacuum, and the residue was recrystallized from hot water. From 5 g. of dinitrothiazole, 4.95 g. (87% yield) of product (m.p. 244.5–245.5° corr.) (lit.,[9] m.p. 240–241°) were obtained.

Anal. Calcd. for $C_7H_9N_3O_2S$: C, 42.20; H, 4.53; N, 21.05. Found: C, 42.42; H, 4.60; N, 20.75.

Acknowledgment.—The author is indebted to J. J. Kobliska and his associates for the microanalyses and to Miss J. L. Gove for the infrared spectra.

(10) Prepared according to L. Covert and H. Adkins, *J. Am. Chem. Soc.*, **54**, 4116 (1932).

A Flavopereirine Synthesis[1]

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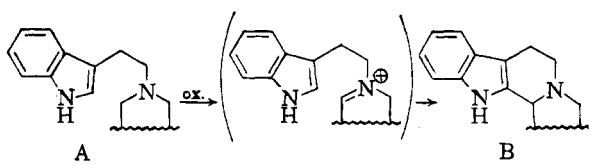
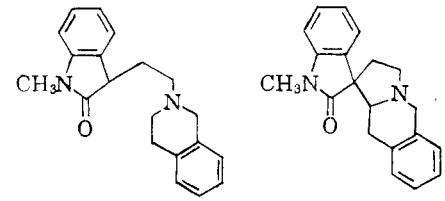
As part of a general search for new methods of synthesis of indole alkaloids the scheme outlined below (A→B) came under consideration. While two procedures were developed, one using mercuric acetate as the oxidizing agent[1] and the other palladium, the latter is the subject of this communication.



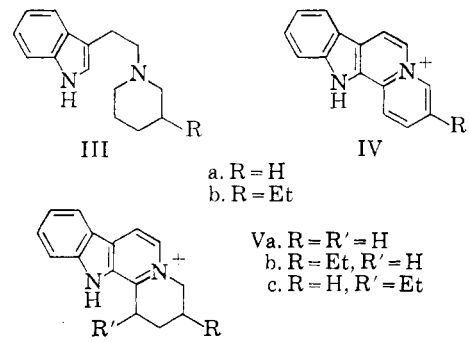
A B

It was decided to model our oxidative cyclization after the strikingly elegant and simple, but unapplied example of a palladium-induced conversion of the oxindole derivative I into II.[3] However, since substances of general type B are known to undergo palladium-catalyzed dehydrogenation,[4] the final products were expected to be anhydronium compounds, tetradehydro and octadehydro derivatives of B.



I II

Exposure of the hydrochloride of *N*-[β-(3-indolyl)ethyl]piperidine (IIIa)[5] to palladium-charcoal at 300° for twenty minutes and conversion of the products to salts led to the anhydronium in compounds IVa and Va. A similar treatment of 1[β-(3-indolyl)-ethyl]-3-ethylpiperidine (IIIb)[6] yielded the salts of flavopereirine (IVb), tetrahydroflavopereirine (Vb), and tetrahydroisoflavopereirine (Vc).



III IV

a. R = H
b. R = Et

Va. R = R′ = H
b. R = Et, R′ = H
c. R = H, R′ = Et

The last reaction constitutes a novel and short synthesis of flavopereirine, one of the alkaloids of the bark of *Geissospermum vellosii* and *laeve*.[7]

Experimental

Dehydrogenations.—A solution of 500 mg. of the piperidinoindole in a minimum amount of methanol was saturated

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(3) P. L. Julian, A. Magnani, J. Pikl, and W. J. Karpel, *J. Am. Chem. Soc.*, **70**, 174 (1948); B. Belleau, *Chem. and Ind.*, 229 (1955); K. T. Potts and R. Robinson, *J. Chem. Soc.*, 2675 (1955).

(4) *Cf.* E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958).

(5) R. C. Elderfield, B. Fischer, and J. M. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957).

(6) Compounds IIIb and Vc were prepared previously by Dr. B. Wickberg[1] in connection with another study.

(7) (a) M.-M. Janot, R. Goutarel, A. LeHir, and L. O. Bejar, *Ann. pharm. France*, **16**, 38 (1958). (b) H. Rapoport, T. P. Onak, N. A. Hughes, and M. G. Reinecke, *J. Am. Chem. Soc.*, **80**, 1601 (1958). (c) N. A. Hughes and H. Rapoport, *ibid.*, **80**, 1604 (1958). (d) A. Bertho, M. Koll, and M. I. Ferosie, *Chem. Ber.*, **91**, 2581 (1958). For previous syntheses see (e) A. LeHir, M.-M. Janot, and D. van Stolk, *Bull. soc. chim. France*, 551 (1958). (f) K. B. Prasad and G. A. Swan, *J. Chem. Soc.*, 2024 (1958). (g) J. Thesing and W. Festag, *Experientia*, **15**, 127 (1959). (h) H. Kaneko, *J. Pharm. Soc. Japan*, **80**, 1374 (1960). (*i*) Y. Ban and M. Seo, *Tetrahedron*, **16**, 5 (1961).

with anhydrous hydrogen chloride gas. Palladium-charcoal, 1 g., was added *cautiously* (to prevent spontaneous ignition!) and the mixture evaporated under vacuum. While maintaining a constant pressure of nitrogen over the mixture of solids, it was heated at 295–305° for 20 min. The cooled mixture was extracted continuously for 18 hr. with anhydrous methanol, to which a few milliliters of glacial acetic acid had been added. The yellow fluorescing solution was evaporated under vacuum and the residue partitioned between 10% sodium hydroxide solution and chloroform. The aqueous solution was extracted repeatedly with chloroform until no more color transferred. The combined chloroform extracts were washed once with water, dried over anhydrous sodium sulfate, and filtered. After addition of enough glacial acetic acid to discharge the bright orange color, the solution was evaporated under vacuum on the steam bath. The residual yellow mixture of gum and crystals was dissolved in a minimum quantity of chloroform and transferred onto a chromatography column whose contents had been prepared from 33 g. of cellulose and 11 ml. of 1% (by volume) of aqueous acetic acid mixed intimately in dry chloroform. Fifty milliliter eluates were collected and treated with a few milliliters of dilute aqueous hydrochloric acid to prevent possible air oxidation of the desired products.

Desethylflavopereirine (IVa) and Its Tetrahydro Product (Va).—Elution of the chromatogram of the reaction mixture from the dehydrogenation of compound IIIa with wet chloroform removed all tars. Elution with 2.5:1 wet chloroform–*n*-butyl alcohol gave solid products. The first three fractions were combined and the solvent evaporated. Dissolution of the residue in a minimum amount of water and addition of a few drops of glacial acetic acid and 10% aqueous sodium perchlorate solution yielded a precipitate. Crystallization of the latter from aqueous ethanol gave 48 mg. of cream-colored crystals of Va perchlorate, m.p. 242–246°, mixed m.p. 241–246°. Its ultraviolet and infrared spectra were identical with those of an authentic sample, m.p. 242–247°, prepared by dissolving crystalline Va hydrobromide, m.p. 278–281° (lit.,[8] m.p. 280° dec.), in 10% sodium hydroxide solution extracting exhaustively with chloroform, adding glacial acetic acid to the organic extract, evaporating the solvent, and converting the residue to a perchlorate in the above manner.

Anal. Calcd. for $C_{15}H_{14}N_2 \cdot HClO_4$: C, 55.82; H, 4.69; N, 8.68. Found: C, 55.74; H, 4.78; N, 8.75.

The last twenty chromatographic fractions from the chloroform–butanol elution were combined, concentrated to a small volume, and divided into two parts. One was treated with a saturated methanol solution of picric acid. Crystallization of the resulting solid from absolute ethanol yielded 21 mg. of crystalline IVa picrate, m.p. and mixed m.p. 250–252° (lit.,[7f] m.p. 252–253°). The other part was concentrated and ether added. This led to 11 mg. of long needles of IVa chloride, m.p. 291–296° dec. (lit.,[7f] m.p. 295° dec.) infrared spectrum identical with that recorded in the literature.[7f]

Flavopereirine (IVb) and the Tetrahydro Products Vb and Vc.—Elution of the chromatogram of the reaction mixture from the dehydrogenation of compound IIIb,[6] m.p. 112–113.5°, with wet chloroform removed all tars, while elution with 5:1 wet chloroform–*n*-butyl alcohol yielded solid products. The first three fractions were combined and evaporated and the residue dissolved in a minimum amount of hot water and a trace of acetic acid. Dropwise addition of 10% sodium perchlorate led to a precipitate which on crystallization from absolute ethanol yielded 31 mg. of tetrahydroflavopereirine (Vb), m.p. and mixed m.p. 219–222°. Its infrared and ultraviolet spectra were identical with those of an authentic sample.[7c,9]

Since the later fractions of the chromatogram yielded a mixture of products, all eluates were combined, the salts reconverted to their organic bases, the latter transformed to acetic acid salts and chromatographed on cellulose as above. Elution with 9:1 wet chloroform–*n*-butyl alcohol yielded at first a solid which on crystallization from isopropyl alcohol-isopropyl ether afforded 9 mg. of Vc perchlorate, m.p. and mixed m.p. 246–252°. Its infrared and ultraviolet spectra were identical with those of an authentic sample.[6] The later chromatographic fractions were combined and concentrated. Crystallization of the precipitate from isopropyl alcohol and from water gave crystals, m.p. 320–325°. Recrystallization of this substance, 3 mg., from water and drying at 80° and 1 mm. pressure for 18 hr., and a similar treatment of an authentic sample[9] of IVb perchlorate yielded crystalline flavopereirine perchlorate, m.p. and mixed m.p. 323–327°. The ultraviolet and infrared spectra of the two specimens were identical.

(8) L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 650 (1952).

(9) The authors are indebted to Professor Henry Rapoport for a gift of a sample of this compound.

Synthesis of Toluene-α-D_3-1-C^{14}; Exchange during an Attempted Catalytic Deuteration

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Toluene-α-D_3-1-C^{14} was needed as a precursor of radioactive *p,p'*-ditrideuteromethylhydrazobenzene. The nondeuterated hydrazotoluene had previously been synthesized from radioactive toluene. In order to comparet he yields of the products from the rearrangement of the two compounds, it was desired to have the compounds with equal specific activity. Accordingly toluene-1-C^{14} was used as the initial precursor of toluene-α-D_3-1-C^{14}.

It was reasoned that the most economical method of synthesis would be to reduce methyl benzoate with deuterium gas in the presence of copper chromite

$$C_6H_5{-}CH_3 \xrightarrow{KMnO_4} C_6H_5CO_2H \xrightarrow{CH_2N_2} C_6H_5CO_2Me \xrightarrow[CuCrO_2]{D_2} C_6H_5CD_3$$

Practice hydrogenations were carried out under different conditions. The experimental data are listed in Table I.

Optimum conditions appeared to involve use of ethanol as a solvent. However, the toluene that was obtained by the reaction of deuterium with radioactive methyl benzoate was shown by infrared analysis to have very little deuterium in the methyl group. Apparently there was a rapid equilibration of the deuterium gas with the hydrogen present in the ethanol, or the ethanol itself was directly responsible for the reduction.

(1) National Institutes of Health Predoctoral Fellow, 1961–1962.