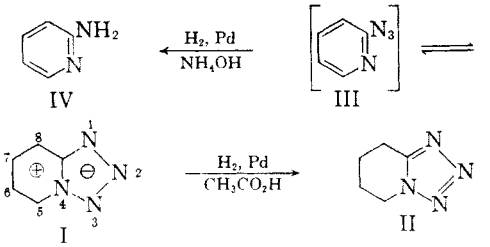
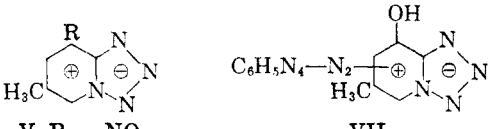
trast, reduction in the presence of ammonium hydroxide gives 2-aminopyridine (IV) inm oderate yield with no tetramethylenetetrazole and a similar reduction in ethanol gives lower yields of both II and IV.



Stannous chloride in hydrochloric acid transforms 6-methyl-8-nitropyridotetrazole (V) into 6-methyl-8-aminopyridotetrazole (VI). Apparently tetrazole destabilization as a result of the presence of the electron attracting nitro group is ineffective in the presence of an opposing electromeric shift demanded by the acid environment.

A derivative tentatively assigned the structure of an azo compound (VII) is obtained upon treatment of diazotized VI with boiling water.



V, R = NO_2
VI, R = NH_2

VII

EXPERIMENTAL[8]

Tetramethylenetetrazole. A solution of 10.65 g. (0.09 mol.) of pyridotetrazole in 5.40 g. (0.09 mol.) of glacial acetic acid and 200 ml. of 95% ethanol was treated with hydrogen (initial pressure of 2 atm.) over 1.25 g. of 10% palladium on charcoal. Hydrogen pressure decreased to a constant value after about 4 hr. The solution, separated from catalyst, was evaporated to dryness *in vacuo*. Addition of *n*-hexane to dried and decolorized chloroform extracts of the residue precipitated 8.6 g. (85%) of tetramethylenetetrazole as colorless needles, m.p. 117–118° after recrystallization from a mixture of chloroform and *n*-hexane (lit.[9] m.p. 115–116°).

Anal. Calcd. for $C_5H_8N_4$: C, 48.38; H, 6.49; N, 45.14. Found: C, 48.65; H, 6.54; N, 45.39.

A trace of 2-aminopyridine in the filtrate was detected as the picrate, melting point and mixture melting point 215–216° (lit.[9] m.p. 216–217°).

The reduction was repeated with the substitution of 0.09 mol. of ammonium hydroxide for 0.09 mol. of glacial acetic acid. Addition of hexane to a chloroform solution of the product did not precipitate tetramethylenetetrazole. Addition of a saturated ethanolic solution of picric acid gave 7.81 g. of *2-aminopyridine* picrate, melting point and mixture melting point 216–217° after recrystallization. Based upon quantitative picrate formation this represents a 29.4% yield of 2-aminopyridine.

In another reduction, neither acid nor base was added to the ethanol solvent. A 15.8% yield of 2-aminopyridine was isolated as its picrate derivative and a 35.0% yield of tetramethylenetetrazole was obtained.

Preparation of 6-methyl-8-aminopyridotetrazole. A solution of 11.3 g. (0.05 mol.) of stannous chloride dihydrate and 15 ml. of concentrated hydrochloric acid was cooled to 5°. The temperature rose to about 60° with the addition of 1.69 g. (0.01 mol.) of 6-methyl-8-nitropyridotetrazole[10] in one portion. The solution was vigorously stirred for about 5 min. until a clear solution resulted and was then stirred in an ice bath for 1 hr. and filtered. The filtrate was treated dropwise with a solution of 40% sodium hydroxide to precipitate the amine as a fine solid, 0.92 g. (61%), m.p. 214–215° (dec.) after recrystallization from boiling water and drying *in vacuo* overnight at 80°.

Anal. Calcd. for $C_6H_7N_5$: C, 48.31; H, 4.73; N, 46.95. Found: C, 48.43; H, 4.90; N, 46.86.

Preparation of 6-methyl-8-acetamidopyridotetrazole. A solution of 0.3 g. (0.002 mol.) of 6-methyl-8-aminopyridotetrazole and 2 g. of acetic anhydride was heated for a few minutes, and cooled. The precipitate, 0.32 g. (84%), m.p. 238–239°, was recrystallized from ethanol.

Anal. Calcd. for $C_8H_9N_5O$: C, 50.25; H, 4.74; N, 36.63; O, 8.37. Found: C, 50.45; H, 4.72; N, 36.83; O, 8.53.

Preparation of 6-methyl-8-hydroxy 5(or 7)-(8′-azo-6′-methyl-pyridotetrazolo)-pyridotetrazole. A solution of 0.3 g. (0.002 mol.) of 6-methyl-8-aminopyridotetrazole, 3 g. of water and 3.6 g. (0.36 mol.) of concentrated sulfuric acid was chilled to 0–5° in an ice-salt bath with stirring. Dropwise addition of a solution of 0.15 g. (0.0022 mol.) of sodium nitrite was accompanied by an evolution of gas. After stirring for 5 to 10 min. the diazotization mixture was added slowly to 10–20 ml. of boiling water. A crude red solid after recrystallization from *N,N*-dimethylformamide gave 0.05 g. (48.4%) of 6-methyl-8-hydroxy 5(or 7)-8′-azo-6′-methyl-pyridotetrazole)-pyridotetrazole, m.p. 230° (explosive dec.) and 0.20 g. of starting material, m.p. 214–215°.

Anal. Calcd. for $C_{12}H_{10}N_{10}O$: C, 46.49; H, 3.25; N, 45.18; O, 5.16. Found: C, 46.70; H, 3.29; N, 44.61; O, 5.87.

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(8) Semimicro analyses by Alfred Bernhardt, Max Planck Institut Mülheim (Ruhr), Germany. Melting points are not corrected.

(9) W. Marckwald, *Ber.*, **27**, 1317 (1894).

(10) J. H. Boyer and W. Schoen, *J. Am. Chem. Soc.*, **78**, 423 (1956).

Hofmann Degradation of 3a-(3,4-Methylenedioxyphenyl)-1-methyloctahydroindole

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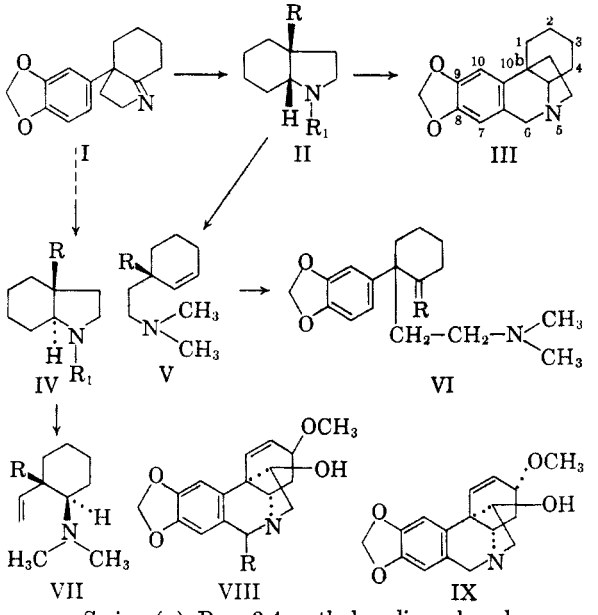
The synthesis of (±)-crinane (III) demonstrated that several Amaryllidaceae alkaloids are derivatives of 5,10b-ethanophenanthridine.[1,2] A key intermediate in this synthesis was the hexahydroindole (I) which was reduced by catalytic methods to an octahydroindole of unknown stereochemistry. It was reasoned[3] that catalytic hydrogenation of I should proceed by the addition of hydrogen to the enamine from the side opposite that occupied

(1) W. C. Wildman, *Chem. & Ind. (London)*, 1090 (1956).
(2) W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958).
(3) N. Sugimoto and H. Kugita, *Pharm. Bull.*, **5**, 378 (1957).

by the methylenedioxyphenyl group. Such a process would lead to a *trans*-octahydroindole (IVa, R_1 = H). Sodium borohydride reduction of I gave the same octahydroindole as was obtained by catalytic reduction. Since this type of reduction would be expected to lead to the more stable *cis*



Series: (a). R = 3,4-methylenedioxyphenyl
(b). R = H

isomer (IIa, R_1 = H), independent evidence for the stereochemistry of the C:D ring junction was sought. Although structural studies on the alkaloids haemanthamine (VIII, R = H),[4] haemanthidine (VIII, R=OH)[5] and crinamine (IX)[4] provided degradative evidence that rings C and D of these bases were *cis* fused, independent proof based on the synthesis of III was sought for the nature of this ring fusion.

The recent studies by Booth and King[6] prompted us to examine the stereochemistry of the hydrogenation product of I by the Hofmann degradation. Hofmann degradation of *cis*-octahydro-1-methylindole (IIb, R_1 = CH_3) leads to 3-(β-dimethylaminoethyl)-cyclohexene (Vb)[7-9] while the corresponding *trans* compound (IVb, R_1 = CH_3) affords *trans*-1-dimethylamino-2-vinylcyclohexane (VIIb).[6] It seemed likely that the mode of elimination found for these simple indoles should prevail in the analogous precursor of crinane (IIa or IVa, R_1 = CH_3). By this reasoning, if the octahydroindole formed by the reduction of I were *cis* fused (IIa, R_1 = H), Va would result from the Hofmann degradation of IIa (R_1 = CH_3), while a *trans* fusion (IVa, R_1 = H) would give rise to VIIa under similar conditions.

Preliminary attempts to prepare the requisite starting material by methylation of the octahydroindole with formaldehyde and formic acid were unsuccessful. The only product isolated by this method was (±)-crinane (III), formed by a Pictet-Spengler type of cyclization to the activated aromatic nucleus. The desired *N*-methyl derivative was prepared successfully by reductive methylation of the secondary amine in the presence of formaldehyde, palladium-on-charcoal, and hydrogen. Quaternization of the product with methyl iodide and pyrolysis of the derived methohydroxide gave a product which was proved to be Va by spectral evidence and by the synthesis of the dihydro derivative (VI, R = H_2).

The methine (Va) showed no bands in the infrared spectrum attributable to a terminal methylene group but showed absorption at 3015 and 702 $cm.^{-1}$ characteristic of an unsubstituted cyclohexene. Catalytic hydrogenation of Va afforded a dihydro derivative (VI, R = H_2) which showed neither of these bands. Finally, VI (R = H_2) was synthesized in an unambiguous manner. Alkylation of 2-(3,4-methylenedioxyphenyl)-cyclohexanone[2] with β-dimethylaminoethyl chloride in the presence of sodamide gave an aminoketone (VI, R = O). Wolff-Kishner reduction of this gave a product identical with that obtained from catalytic reduction of Va.

These data support the assignment of a *cis* C:D ring fusion in (±)-crinane and the Amaryllidaceae alkaloids based on this nucleus. It is evident that the catalytic and chemical reduction product of I is IIa (R_1 = H) and that the course of the Hofmann degradation of IIa (R_1 = CH_3) parallels that of the simpler analog IIb (R_1 = CH_3). Conformational considerations consistent with the observed reaction path have been discussed earlier.[10]

EXPERIMENTAL[11]

Attempted methylation of IIa (R_1 = H) *with formic acid and formalin.* A solution of 654 mg. of IIa (R_1 = H) in 5 ml. of formic acid and 3 ml. of formalin was refluxed for 23 hr. The mixture was made basic with concentrated sodium hydroxide and extracted four times with ether. The ethereal solution was washed twice with water and twice with brine.

(4) H. M. Fales and W. C. Wildman, *Chem. & Ind.* (London), 561 (1958); *J. Am. Chem. Soc.*, **82**, 197 (1960).
(5) S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2590 (1958).
(6) H. Booth and F. E. King, *J. Chem. Soc.*, 2688 (1958).
(7) J. McKenna, *Chem. & Ind. (London)*, 406 (1954).
(8) B. Bailey, R. D. Haworth, and J. McKenna, *J. Chem. Soc.*, 967 (1954).
(9) F. E. King, J. A. Barltrop, and R. J. Walley, *J. Chem. Soc.*, 277 (1945).
(10) F. E. King and H. Booth, *J. Chem. Soc.*, 3798 (1954).
(11) All melting points were observed on a Köfler microscope hot stage and are corrected. Infrared spectra were determined with either a Perkin-Elmer model 21 or a Beckman model IR-7 spectrophotometer. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J.

The solvent was removed under reduced pressure to give 678 mg. of an oil whose infrared spectrum resembled that of crinane. Two recrystallizations from ether gave 323 mg. of material melting at 108–111°; mixture melting point with (±)-crinane, 106–110°.[2,12]

Cis-3a-(3,4-methylenedioxyphenyl)-1-methyloctahydroindole (IIa, R_1 = CH_3). An ethanolic solution of 234 mg. of IIa (R_1 = H) was stirred under hydrogen at room temperature and atmospheric pressure in the presence of 230 mg. of 10% palladium-on-charcoal and 5 ml. of formalin. In 45 min. the mixture absorbed 20.3 ml. of hydrogen (85%). The product was filtered, concentrated and chromatographed on Merck alumina. Elution with chloroform gave 231 mg. of oil which was dissolved in acetone and treated with methyl iodide. Addition of ether precipitated 258 mg. of material, m.p. 169–175°. Four recrystallizations of the *methiodide* from chloroform–ethyl acetate gave colorless prisms, m.p. 198.5–199.5°.

Anal. Calcd. for $C_{17}H_{24}NO_2I$: C, 50.88; H, 6.03; N, 3.49. Found: C, 50.91; H, 6.04; N, 3.53.

The *picrate* was prepared in ethanol and recrystallized from acetone-ethanol and from acetone-ether to give prisms, m.p. 196–198°.

Anal. Calcd. for $C_{16}H_{21}NO_2 \cdot C_6H_3N_3O_7$: C, 54.09; H, 4.95; N, 11.47. Found: C, 53.99; H, 4.88; N, 11.57.

Hofmann degradation of IIa (R_1 = CH_3). A solution of 194 mg. of the methiodide of IIa (R_1 = CH_3) in 1:1 ethanol-water was treated with silver oxide that had been freshly prepared from 93 mg. of silver nitrate. The mixture was scratched and stirred for a few minutes, then centrifuged. The solid material was washed twice with water and once with methanol. The combined supernatant liquid was evaporated to dryness at 40–50° under reduced pressure, then heated for 25 min. at a temperature gradually increasing from 125 to 165°. The resulting residue, 130 mg., was partitioned between 0.1*N* hydrochloric acid and ether. The aqueous layers were made basic with ammonium hydroxide and extracted four times with ether. The ether extracts were washed with water and brine and concentrated under reduced pressure to give 97 mg. of oil. This was chromatographed on 10 g. of Merck alumina. Benzene elution produced 8 mg. of fore run, followed by 38 mg. of Va, then 20 mg. of material whose infrared spectrum suggested it to be slightly impure Va. Elution with 1–5% ethyl acetate gave 20 mg. of material trailing in many fractions.

The infrared spectrum (carbon tetrachloride) of Va purified in this manner showed absorption at 3012 and 702 cm.$^{-1}$. The ultraviolet absorption spectrum (ethanol) showed maxima at 234 (ϵ 4240) and 287 mμ (ϵ 4240).

1-(β-Dimethylaminoethyl)-1-(3,4-methylenedioxyphenyl)-cyclohexane (VI, R = H_2). A solution of 38 mg. of Va in ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 40 mg. of pre-equilibrated 10% palladium-on-charcoal. Absorption of hydrogen ceased after the uptake of 3.55 ml. (theor. 3.2 ml.) in 29 min. The mixture was filtered, and the solvent was removed under reduced pressure to give 40 mg. of a clear oil. The infrared spectrum (carbon tetrachloride) showed no absorption at 3012 or 702 cm.$^{-1}$. The ultraviolet absorption spectrum (ethanol) showed maxima at 235 (ϵ 4120) and 288 mμ (ϵ 3980).

The *picrate* was prepared in ethanol to yield 48 mg. of material, m.p. 108–131°. Three recrystallizations from ethanol gave 27 mg. of short prisms, m.p. 133.5–135°. On standing in a vial for 3 months, the melting point was found to be 174–176°. The infrared spectrum (chloroform) of this material was identical with that obtained by synthesis from VI (R = O), (*vide infra*).

Anal. Calcd. for $C_{17}H_{25}NO_2 \cdot C_6H_3N_3O_7$: C, 54.75; H, 5.59; N, 11.11. Found: C, 55.10; H, 5.54; N, 11.16.

2-(β-Dimethylaminoethyl)-2-(3,4-methylenedioxyphenyl)-cyclohexanone (VI, R = O). To a stirred suspension of sodamide (prepared from 690 mg. of sodium) and 20 ml. of benzene was added dropwise a solution of 2.22 g. of 2-(3,4-methylenedioxyphenyl)-cyclohexanone[2] in dry benzene. A dark brown color appeared. The mixture was refluxed for 3 hr. At the end of this time a solution of β-chloroethyldimethylamine (prepared from 10.9 g. of the amine hydrochloride) was added. The reaction mixture was refluxed for 16 hr., chilled, and treated first with ethanol, then with water. The layers were separated, and the aqueous portion was extracted twice with benzene. The benzene solution was extracted once with dilute hydrochloric acid and twice with water, then concentrated under reduced pressure to give 0.917 g. of neutral material with an infrared spectrum identical with that of the starting ketone.

The acidic solution was made basic with sodium hydroxide and extracted four times with benzene to give 1.966 g. of an oil which was chromatographed on 100 g. of alumina. Elution with 10–50% ethyl acetate in benzene and finally with ethyl acetate gave 770 mg. of a clear oil. Infrared spectra of the various chromatographic fractions showed only minor differences.

The *hydrochloride* was formed by saturating an ethanolic solution of the amine with gaseous hydrogen chloride. Three recrystallizations from ethanol–ethyl acetate gave fine white needles, m.p. 245–249° (dec.).

Anal. Calcd. for $C_{17}H_{24}NO_2Cl$: C, 62.66; H, 7.42; N, 4.30. Found: C, 62.70; H, 7.38; N, 4.37.

1-(β-Dimethylaminoethyl)-1-(3,4-methylenedioxyphenyl)-cyclohexane (VI, R = H_2). A solution of 488 mg. of VI (R = O), 2.9 g. of potassium hydroxide and 5 ml. of hydrazine hydrate in 17 ml. of diethylene glycol was refluxed for 6.5 hr. at 150–160°. The mixture was diluted with water, acidified with hydrochloric acid and extracted twice with benzene. The aqueous layer was filtered, made basic with sodium hydroxide and extracted four times with chloroform. The chloroform was evaporated under reduced pressure to leave 256 mg. of oil. The infrared spectrum of this oil showed that reduction was not complete.[13] Chromatography of the oil on 20 g. of alumina and elution with 10% ethyl acetate gave 77 mg. of a clear oil which showed no carbonyl absorption.

The *picrate* was prepared in ethanol and recrystallized three times from ethanol to give elongated prisms, m.p. 173–174°. A mixture melting point with the higher melting polymorphic picrate of VI (R = H_2) which had been obtained from the reduction of Va was 173.5–174.5°.

Anal. Calcd. for $C_{17}H_{25}NO_2 \cdot C_6H_3N_3O_7$: C, 54.75; H, 5.59; N, 11.11. Found: C, 54.97; H, 5.51; N, 11.25.

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(12) (±)-Crinane was reported[2] to melt at 97–99°. A re-examination of this material showed that it is a low melting polymorph of the (±)-crinane reported above. The higher melting form may be isolated either by sublimation of the material melting at 97–99° or by seeding a melt with the higher melting polymorph at 105°. The infrared spectra ($CHCl_3$) of the two forms are identical.

(13) More forcing conditions for the Wolff-Kishner reduction of compounds similar to VI (R = O) have led to ill-defined products lacking the methylenedioxy group, so this method of attempting to improve the yield of VI (R = H_2) was not used. However, it was established that lengthening the reaction time caused no improvement in yield.