l. min.$^{-1}$ was obtained in the present study. Since concentrations of nitromethane anion were one thousand times greater in the present study, the agreement is excellent.

Since deuterium exchange at the 1-position is faster than *syn–anti* equilibration the exchange cannot involve loss of configuration about the oxime double bond. Methazonate ion, produced from nitromethane anion in deuterium oxide as solvent, does not contain any deuterium. Therefore, the dimerization of nitromethane anion to methazonate ion occurs more rapidly than hydrogen exchange between water and nitromethane anion.

## Experimental

The proton resonance spectra were obtained as described previously.[9] Two molar solutions were prepared by dissolving the appropriate amount of solid in 0.25 ml. of solvent. Despite care to introduce the salts of nitromethane slowly into solution excessive reaction sometimes occurred.[10] Methazonic acid was prepared by an established method.[11]

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# Syntheses Based on 2-Methyl-5-nitrogramine. Preparation of 2-Methyl-5-nitroindole-3-acetic Acid

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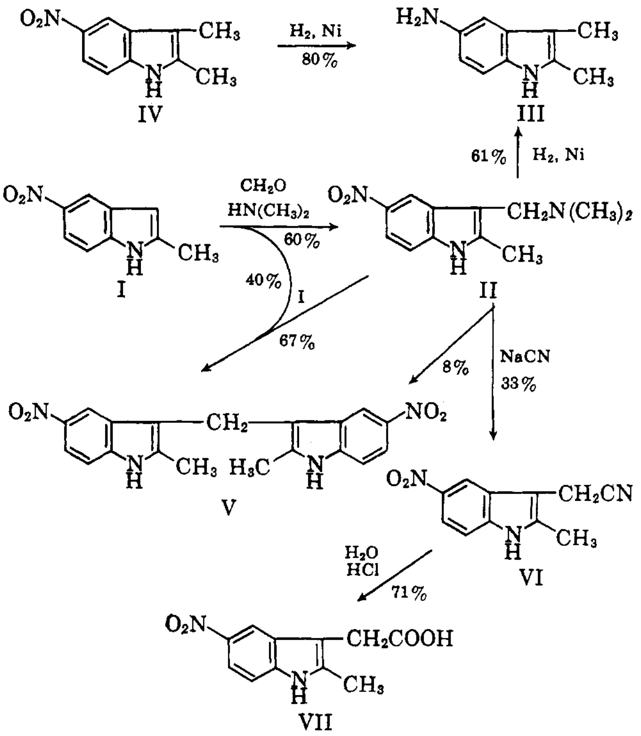
Nitration of 2-methylgramine with nitric acid in acetic acid has been reported to yield 2-methyl-5-nitrogramine, m.p. 158–160°.[2] The product was subsequently proved, however, to be 2-methyl-6-nitrogramine.[3] In a recent paper from this laboratory[4] the preparation of authentic 2-methyl-5-nitrogramine, m.p. 173–175°, has been described, by a Mannich reaction with 2-methyl-5-nitroindole (I), the nitration product of 2-methylindole in concentrated sulfuric acid. Absence of a well defined NH band in the Nujol infrared spectrum of the gramine derivative suggested the possibility that the Mannich reaction might have occurred at the 1-position. Equilibration with deuterium oxide, however, produced a series of weak ND bands,[5] thus showing that the NH group is still present in the gramine derivative.[4]

The structure of 2-methyl-5-nitrogramine (II) has now been proved by chemical means. Catalytic hydrogenolysis of II, with concomitant hydrogenation of the nitro group, gave the known 5-amino-2,3-dimethylindole (III),[6-9] identical with a sample prepared by catalytic hydrogenation of 2,3-dimethyl-5-nitroindole (IV),[6,9-11] the nitration product of 2,3-dimethylindole in concentrated sulfuric acid. Other evidence that II is 3-substituted is provided by its reaction with I in acetic acid, which gave 3,3′-methylenebis(2-methyl-5-nitroindole) (V). This nucleophilic replacement of the dimethylamino group of II by I is analogous to the formation[4] of V as a coproduct with II during the Mannich reaction. The presence of an NH band in the infrared spectrum of V is consistent with the formulation of V and of its precursor II as 3-substituted indole derivatives. Nucleophilic replacement of the dimethylamino group of II with cyanide ion gave 2-methyl-5-nitroindole-3-acetonitrile (VI) as well as a small amount of V. The presence of a well defined NH band in VI provides additional evidence that its precursor II is not a 1-substituted indole derivative.



Acid hydrolysis of VI provides a convenient synthesis of 2-methyl-5-nitroindole-3-acetic acid (VII).

## Experimental

Melting points were determined on a calibrated Fisher-Johns hot stage.

**2-Methyl-5-nitrogramine (3-Dimethylaminomethyl-2-methyl-5-nitroindole[12]) (II).**—By increasing the mole ratio of formaldehyde and dimethylamine relative to 2-methyl-5-nitroindole the yield of 2-methyl-5-nitrogramine has been increased to 60% from the 18% previously reported.[4]

A solution of 2-methyl-5-nitroindole[4] (4.20 g., 0.0238 mole) in acetic acid (500 ml.) was added dropwise, with stirring, to a solution of formalin (2.50 g. of 37% formaldehyde, 0.031 mole) and dimethylamine (6.00 g. of aqueous 25% solution, 0.033 mole) in acetic acid (150 ml.) at 5°. Stirring was continued at 5° for an additional 1.5 hr., at room temperature for 1 hr., and at steam

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bath temperature for 0.5 hr. After cooling, the mixture, which contained a precipitate, was neutralized to pH 6 with sodium hydroxide solution, and the precipitate was filtered off and dried. Recrystallization of the precipitate from acetone gave **3,3′-methylenebis(2-methyl-5-nitroindole)** (V) as bright orange-yellow needles (1.74 g., 40%), m.p. > 350°; reported 51%, m.p. 348–354° dec.[4]

The filtrate was made basic pH 10, giving a light yellow precipitate, which was filtered and dried. Recrystallization from methylene chloride–light petroleum (b.p. 60–68°) yielded **2-methyl-5-nitrogramine** as pale yellow needles (3.5 g., 60%), m.p. 173–175°; lit.[4] m.p. 173–175°.

**2,3-Dimethyl-5-nitroindole** (IV).—The preparation was carried out by nitration in concentrated sulfuric acid at 5° essentially according to the literature procedure,[6,10,11] except that no urea was used and sodium nitrate was substituted for the more expensive potassium nitrate. The yield was 66%, m.p. 189–190°; reported 60–65%,[9] m.p. 188–189°,[10] 190°[11]; $\lambda_{max}$ m$\mu$ (log $\epsilon$) in 95% ethanol[13]: 214 (4.29), 277 (4.30), 337 (3.95); $\nu_{NH}$ 3250 s, $\nu_{NO_2}$ 1518 mw or 1498 mw, 1312 vs cm.$^{-1}$ in Nujol.

**5-Amino-2,3-dimethylindole** (III). **A. From 2,3-Dimethyl-5-nitroindole**.—The reduction has been carried out previously with alkaline sodium hydrosulfite[6] in 52[7]–55[9]% yield and by Raney nickel-catalyzed hydrogen transfer from hydrazine in 91% yield.[8]

2,3-Dimethyl-5-nitroindole (1.15 g., 0.00605 mole) was dissolved in absolute ethanol (100 cc.) and hydrogenated over Raney nickel (1 g.) at 2 atm. and room temperature for 1 hr. The catalyst was filtered off and the ethanol evaporated under reduced pressure, leaving a pale yellow solid. Crystallization, with charcoal, from methylene chloride–light petroleum (b.p. 60–68°) yielded white flakes (0.78 g., 80%), m.p. 178.5–183°; lit.[6,8,9] m.p. 177–178°; $\lambda_{max}$ m$\mu$ (log $\epsilon$) in 95% ethanol: 234 (4.41), 285 (3.84), 304 diffuse infl. (3.69); $\nu_{NH}$ 3340 s, 3190 w cm.$^{-1}$ in Nujol.

**B. From 2-Methyl-5-nitrogramine**.—2-Methyl-5-nitrogramine (0.57 g., 0.00245 mole) was dissolved in absolute ethanol (100 cc.) and hydrogenated over Raney nickel (1 g.) at 2 atm. and 60° for 5.5 hr. Treatment as in part A gave a gray solid, which was sublimed at 160° (1 mm.), yielding white flakes (0.24 g., 61%), m.p. 178.5–183°. The mixture melting point with the sample described in part A was undepressed, and the infrared spectra of the two samples in Nujol were identical.

**3,3′-Methylenebis(2-methyl-5-nitroindole)** (V) **from 2-Methyl-5-nitrogramine and 2-Methyl-5-nitroindole**.—A solution of 2-methyl-5-nitrogramine (0.24 g., 0.00103 mole) and 2-methyl-5-nitroindole[4] (0.18 g., 0.00102 mole) in acetic acid (40 ml.) was stirred at room temperature for 1.5 hr. and then refluxed for 2 hr. The resulting mixture was cooled and the precipitate filtered and crystallized from acetone, yielding bright orange-yellow needles (0.25 g., 67%), m.p. > 350°; lit.[4] m.p. 348–354° dec. The mixture melting point with an authentic sample[4] did not depress below 350°, and the infrared spectra of the two samples in Nujol were identical.

**2-Methyl-5-nitroindole-3-acetonitrile** (VI).—A solution of 2-methyl-5-nitrogramine (0.50 g., 0.00214 mole) and sodium cyanide (0.50 g., 0.0102 mole) in aqueous 60% ethanol (80 ml.) was refluxed for 7.5 hr. The solid which had formed was filtered, dried, and crystallized from acetone, giving **3,3′-methylenebis(2-methyl-5-nitroindole)** (V) as bright orange-yellow needles (0.03 g., 8%), m.p. >350°. The mixture melting point with an authentic sample[4] did not depress below 350°, and the infrared spectra of the two samples in Nujol were identical.

The filtrate was diluted with water and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and evaporated. The residual yellow solid was crystallized with charcoal from methylene chloride–light petroleum (b.p. 60–68°), yielding, after concentration, **2-methyl-5-nitroindole-3-acetonitrile** as light yellow needles (0.15 g., 33%), m.p. 185–186°; $\lambda_{max}$ m$\mu$ (log $\epsilon$) in 95% ethanol: 205 (4.36), 266 (4.33), 326 (3.92); $\nu_{NH}$ 3280 m; $\nu_{C\equiv N}$ 2240 mw; $\nu_{NO_2}$ 1517 ms, 1335 s cm.$^{-1}$ in Nujol.

*Anal.* Calcd. for $C_{11}H_9N_3O_2$ (215.21): C, 61.39; H, 4.22; N, 19.53. Found: C, 61.24; H, 4.26; N, 19.83.

**2-Methyl-5-nitroindole-3-acetic Acid** (VII).—A solution of 2-methyl-5-nitroindole-3-acetonitrile (0.40 g., 0.00186 mole) in concentrated hydrochloric acid (37.9%, 200 cc.) and ethanol (100 cc.) was refluxed for 60 hr. The resulting black solution was cooled and extracted with ether. The ether extract was then extracted with sodium bicarbonate solution until carbon dioxide was no longer evolved. The ether was dried over anhydrous magnesium sulfate and evaporated; there was no residue.

The sodium bicarbonate extract was acidified to pH 2 with hydrochloric acid, and the resulting mixture of precipitate and solution was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and evaporated. The residual yellow solid was crystallized with charcoal from hot water, yielding bright yellow needles (0.31 g., 71%), m.p. 240–241° dec., with gas evolution; $\lambda_{max}$ m$\mu$ (log $\epsilon$) in 95% ethanol: 211 (4.33), 273 (4.31), 333 (3.96); $\nu_{NH}$ 3250 m; $\nu_{OH}$ 2700 w; $\nu_{C=O}$ 1704 s; $\nu_{NO_2}$ 1506 m, 1333 s cm.$^{-1}$ in Nujol.

*Anal.* Calcd. for $C_{11}H_{10}N_2O_4$ (234.21): C, 55.41; H, 4.30; N, 11.96. Found: C, 56.64; H, 4.49; N, 11.95.

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## The Selective Hydrolysis of Steroidal Acetates on Alumina

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The importance of the selective reaction of a functional group in the presence of a similar moiety has been well demonstrated in steroid chemistry.[1] Among such reactions one that is not readily achieved is the selective hydrolysis of the ester of a primary alcohol in preference to the same ester of an unhindered secondary alcohol.[2] We wish to report a facile procedure that specifically effects this hydrolysis, offering a potentially superior alternative to selective esterification[3] and providing in good yield a group of compounds otherwise difficult to synthesize. This hydrolysis occurs readily on untreated alumina by the use of a modified chromatographic technique, incidentally affording ready separation of the pure monoester. Ester hydrolysis, a normal occurrence on alumina,[4] is demonstrated to proceed at a rate that allows clear distinction between the hydrolysis of primary and secondary acetates, thus affording a synthetically useful tool.

The chromatographic purification of pseudodiosgenin diacetate (**1a**) on alumina afforded the first example of selective acetate hydrolysis. A compound isolated in small amounts after elution of the pure diacetate was tentatively identified as the C-26 monohydroxy compound (**1b**) by inspection of the n.m.r. spectrum. Only a single acetate band (three protons) was seen; the C-3 $\alpha$-proton signal at 275 c.p.s. ($\Delta\nu$ from tetramethylsilane at 60 Mc.) was unchanged; and, also, the doublet for the C-26 protons, found at 233 and 238 c.p.s. in the starting material, had been shifted to 205 and 210 c.p.s. Chemical evidence to support this structural assignment was obtained by acetylation of the new compound to the starting diacetate and also

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