A Synthesis of 1,3,4,5-Tetrahydropyrrolo[4,3,2-*de*]quinoline

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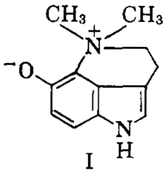
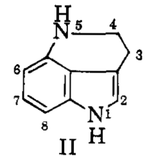
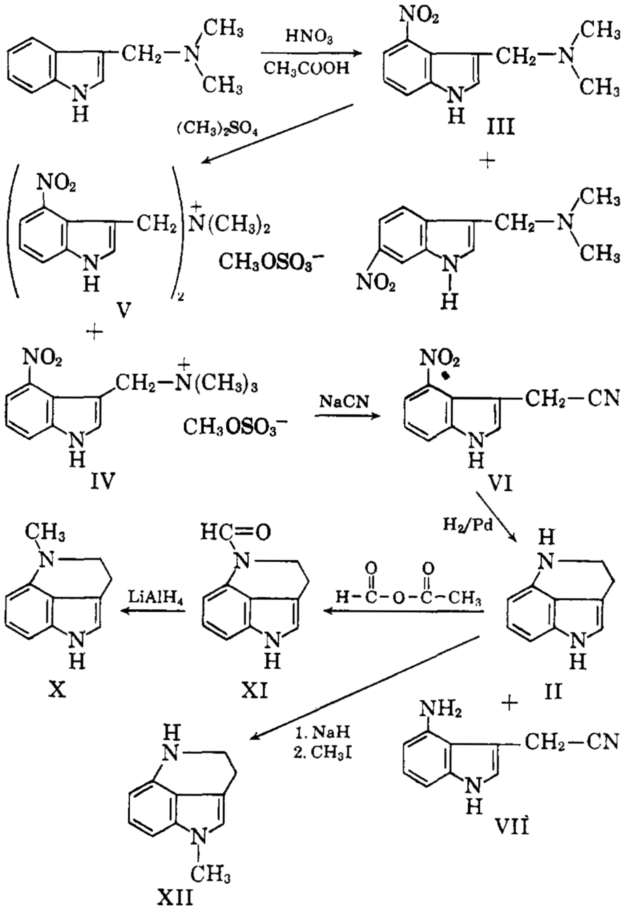
1,3,4,5-Tetrahydropyrrolo[4,3,2-*de*]quinoline (II) has been prepared by catalytic reduction of 4-nitroindol-3-ylacetonitrile. Methods for selectively alkylating both nitrogens of II have been developed.

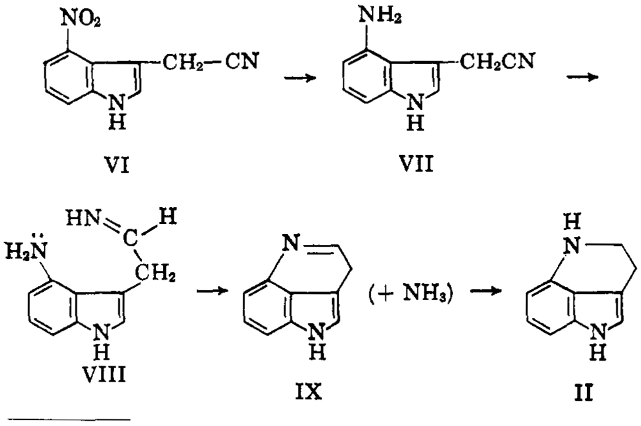
The recent revision of the dehydrobufotenin[1,2] structure (I) prompted us to prepare II, the simplest member of the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system for biological evaluation.


I


II

4-Nitrogramine (III), the starting material for this synthesis, was obtained by direct nitration of gramine.[3] The mixture of nitrogramines thus obtained was separated by fractional precipitation. 6-Nitrogramine, the major product, is a weaker base than the 4-nitro isomer and was precipitated selectively from an aqueous solution of the acetic acid or nitrate salts with ammonium hydroxide. When the filtrate from this precipitation was made strongly alkaline with sodium hydroxide, practically pure 4-nitrogramine was obtained. To facilitate nitrile formation, 4-nitrogramine was converted to a mixture of crystalline methosulfates (IV, V). Although no experimental conditions could be found that would preclude V, its formation was minimized by the dropwise addition of a tetrahydrofuran solution of the gramine to a large excess of dimethyl sulfate in ice-cold tetrahydrofuran.[4] (The reaction of gramine with methyl iodide to form a bis adduct, analogous to V, and trimethylamine has been discussed by Geissman and Armen.[5]) Fractional crystallization of the methosulfate mixture from methanol afforded a separation of the slightly soluble bis adduct (V) from IV. Displacement of trimethylamine from IV to yield the nitrile (VI) was best effected in a pH 4.7 acetate buffer with sodium cyanide by a modified procedure of Brown and Garrison.[6] Under these conditions, the bis adduct V reacted with sodium cyanide to yield the nitrile (VI) and 4-nitrogramine which could be recovered. For this reason it was unnecessary to fractionate the crude methosulfate mixture before carrying out the nitrile displacement. Catalytic hydrogenation of 4-nitroindol-3-ylacetonitrile (VI) with a palladium catalyst at about 70° yielded the expected product, 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (II), a cyclization reminiscent of two published approaches to indoles.[7-9] This reaction probably proceeds in four steps. Initial, facile reduction of the nitro group yields an aminonitrile (VII) which has been isolated as a by-product from the reaction mixture. As is characteristic of nitriles under these conditions,[10] reduction of VII yields an imine (VIII) which condenses with the primary amine at C-4, to form the cyclic imine (IX) and ammonia. Reduction of this imine results in II which was isolated in moderate yield by silica gel chromatography. The n.m.r. spec-





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trum of II shows two well-defined triplets centered at 177.0 and 203.5 c.p.s. (apparent $J = 5.5$ c.p.s.), downfield from tetramethylsilane, which have been assigned to the methylene protons on C-3 and C-4, respectively.[1,2] A singlet at 231 c.p.s. was assigned to the proton at N-5. When this nitrogen was methylated, the 231-c.p.s. peak was replaced by a strong singlet at 175 c.p.s. which was assigned to the N-methyl protons of X (*vide infra*). Structure II was supported also by its ultraviolet spectrum which was similar to that reported for 4-amino-2,3-dimethylindole.[11]

When II was allowed to react with formic acetic anhydride,[12] the expected N-formyl derivative (XI) was obtained. Reduction of XI with lithium aluminum hydride resulted in the N-methyl derivative (X). Methylation of the indole nitrogen to yield XII was accomplished by treatment of a dimethylformamide solution of the sodium salt of II (prepared *in situ* with sodium hydride) with methyl iodide.

Experimental[13]

4-Nitrogramine and 6-Nitrogramine.—A stirred mixture of 207.4 g. (1.19 moles) of gramine and 1040 ml. of acetic acid was cooled to 10° and treated dropwise with a solution of 178.5 ml. of nitric acid (*d* 1.37) in 415 ml. of acetic acid during 40 min. The mixture was allowed to warm to 20° and stand for 8.5 hr. The nitrate salt which had crystallized from the mixture was collected by filtration, washed with absolute ethanol, and dried at 40° *in vacuo* (yield 185.6 g.). The filtrate was concentrated to a small volume, diluted with ethanol, and allowed to crystallize. The combined product was dissolved in warm water and decolorized with activated carbon; the resulting solution was made strongly ammoniacal. The precipitate, a mixture of 4-nitrogramine and 6-nitrogramine, was washed with water and dissolved in dilute acetic acid.

This stirred solution was treated dropwise with dilute ammonium hydroxide until the mixture was strongly ammoniacal (pH 8). The precipitate was collected by filtration, washed with water, and redissolved in dilute acetic acid. Reprecipitation of 6-nitrogramine with ammonium hydroxide yielded a further separation of the two isomers; an additional quantity of the 4-nitrogramine remained in solution. The precipitate was collected by filtration, washed with water, and dried *in vacuo* at 40° to yield 131.9 g. (50.5%) of 6-nitrogramine, m.p. 172–175°. Final purification was effected by recrystallizing this material from methanol, m.p. 176–179° (lit.[3] m.p. 176–178°). The ultraviolet spectrum (ethanol) had end absorption and λ_{max} 251, 325, and 366 mμ (ϵ 10,500, 8410, and 7300, respectively) with an inflection at 262 mμ (ϵ 9750). The infrared spectrum (Nujol) showed NO_2, 1515 and 1330 cm.$^{-1}$.

Each of the filtrates from the three ammonium hydroxide precipitations was made strongly basic with concentrated sodium hydroxide. The resulting crystalline precipitate was collected by filtration, washed with water, and dried *in vacuo* at 40° to yield 41.15 g. (18.8%) of 4-nitrogramine, m.p. 120–123°. Purification of this material was effected by methanol–water crystallization, m.p. 126–128.5° (lit.[3] m.p. 120–122°). The infrared spectrum (Nujol) showed NO_2, 1510 and 1320 cm.$^{-1}$. The ultraviolet spectrum (ethanol) had end absorption and λ_{max} 350 and 379 mμ (ϵ 4020 and 4190, respectively) with an inflection at 234 mμ (ϵ 9180).

Reaction of 4-Nitrogramine with Dimethyl Sulfate.—A solution of 500 mg. (2.28 mmoles) of 4-nitrogramine and 0.03 ml. of acetic acid in 10 ml. of dry tetrahydrofuran was added slowly, at room temperature under nitrogen, to a stirred solution of 1.07 ml. of dimethyl sulfate and 0.03 ml. of acetic acid in 5 ml. of dry tetrahydrofuran. After 3 hr., the product had separated from the reaction mixture as a gummy precipitate. The solvent was removed by decantation, and the product was washed with ether and treated with methanol. Crystallization of the methanol-soluble material from methanol–ether yielded 264 mg., m.p. 160° dec., of 4-nitrogramine methosulfate (IV). An analytical sample, m.p. 157–159°, was prepared by recrystallizing this material from methanol–ether. The ultraviolet spectrum (ethanol) had λ_{max} 223 and 368 mμ (ϵ 8600 and 4880, respectively) with an inflection at 328 mμ (ϵ 3880). The infrared spectrum (Nujol) showed NH, 5290 cm.$^{-1}$; and NO_2, 1525 and 1325 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55; N, 12.16; S, 9.29. Found: C, 45.66; H, 5.49; N, 12.05; S, 9.24.

The methanol-insoluble product (V) from this reaction, which was collected by filtration and washed with methanol, amounted to 251 mg., m.p. 182° dec. It was recrystallized from hot methanol for analysis, m.p. 182–183°. The infrared spectrum (Nujol) showed NH, 3200 cm.$^{-1}$; and NO_2, 1515 and 1315 cm.$^{-1}$. The ultraviolet spectrum (ethanol) had end absorption and λ_{max} 234 and 370 mμ (ϵ 17,630 and 9250, respectively) with an inflection at 328 mμ (ϵ 7170).

Anal. Calcd. for $C_{21}H_{23}N_5O_8S$: C, 49.89; H, 4.59; N, 13.86; S, 6.34. Found: C, 50.13; H, 4.45; N, 13.48; S, 6.03.

4-Nitroindol-3-ylacetonitrile (VI). A.—A mixture of 4.58 g. (13.3 mmoles) of methosulfate (IV), 140 ml. of a sodium acetate–acetic acid buffer (3.0 g. of acetic acid + 4.1 g. of sodium acetate dissolved in 500 ml. of water), and 300 ml. of ether, contained in a 500-ml. hydrogenation bottle, was treated with 4.58 g. of sodium cyanide. The bottle was sealed and allowed to shake at room temperature for 11.25 hr. The reaction mixture was extracted with a mixture of ethyl acetate and ether; the extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. Crystallization of the residue from ethyl acetate yielded 1.73 g. (64.7%) of 4-nitroindol-3-ylacetonitrile, m.p. 196–199°. The analytical sample, m.p. 199–200°, was prepared by recrystallizing this material from ethyl acetate. The ultraviolet spectrum (ethanol) had λ_{max} 234 and 374 mμ (ϵ 9600 and 4800) with an inflection at 332 mμ (ϵ 3700). The infrared spectrum (Nujol) showed NH, 3400 cm.$^{-1}$; C═N, 2160 cm.$^{-1}$; and NO_2, 1520 and 1320 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.48; H, 3.42; N, 20.84.

B.—A solution of 20.0 g. (91.3 mmoles) of 4-nitrogramine and 1.2 ml. of acetic acid in 500 ml. of dry tetrahydrofuran was added, under nitrogen, dropwise to an ice-cold, stirred solution of 60 ml. of dimethyl sulfate and 1.2 ml. of acetic acid in 300 ml. of dry tetrahydrofuran during 1.5 hr. The resulting mixture was allowed to warm slowly to room temperature and stand for 5.33 hr. The product then was collected by filtration, washed with anhydrous ether, and dried *in vacuo* over potassium hydroxide to yield 31.3 g. of the methosulfate, m.p. 141–155°. This material was divided into four equal parts. Each part (7.83 g.) was mixed with 240 ml. of the sodium acetate buffer (3.0 g. of acetic acid + 4.1 g. of sodium acetate dissolved in 500 ml. of water), a small amount of ether, and 7.83 g. of sodium cyanide in a 500-ml. hydrogenation bottle. The bottle was sealed and allowed to shake at room temperature for 12.5 hr. It was then allowed to stand without shaking for an additional 11 hr. The combined reaction mixtures were extracted with a mixture of ethyl acetate and ether. The extract was washed successively with water, dilute acetic acid, saturated sodium chloride solution, dilute ammonium hydroxide, and saturated sodium chloride solution; dried over anhydrous sodium sulfate; and concentrated at room temperature to yield 9.03 g. of the crystalline nitrile, m.p. 196–199°. Concentration of the mother liquors yielded an additional 2.83 g. of the product, m.p. 190–196°.

The acetic acid extracts were filtered and made alkaline with sodium hydroxide. 4-Nitrogramine recovered in this manner was recrystallized from methanol–water to yield 3.67 g., m.p. 126–128°. The total yield of 4-nitroindol-3-ylacetonitrile based on the recovered starting material was 79%.

1,3,4,5-Tetrahydropyrrolo[4,3,2-*de*]quinoline (II) and 4-Aminoindol-3-ylacetonitrile (VII).—A mixture of 4.0 g. (19.9 mmoles) of the nitrile (VI), 2.0 g. of 10% palladium on carbon, and 300 ml. of pure ethyl acetate was hydrogenated for 2.6 hr. in a Parr shaker at an initial pressure of 45 p.s.i. The temperature was

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[11] E. Shaw and D. W. Woolley, *J. Am. Chem. Soc.*, **75**, 1877 (1953).

[12] E. Shaw, *ibid.*, **76**, 1384 (1954).

[13] Melting points were taken in a capillary tube and are corrected. Ultraviolet spectra were determined in 95% ethanol with a Cary spectrophotometer, Model 14. Infrared spectra were determined in Nujol with a Perkin-Elmer recording infrared spectrophotometer, Model 421. N.m.r. spectra were determined in deuteriochloroform with a 60-Mc. instrument. Skellysolve B is a commercial hexane, b.p. 60–70°, made by Skelly Oil Co., Kansas City, Mo.

raised by external heating from 25° at the start of the reaction to about 70° at the end. Filtration of the mixture through Celite yielded a colorless filtrate which was concentrated *in vacuo*, under nitrogen to yield a colorless gum. A benzene solution of this material was adsorbed on 100 g. of silica gel in a chromatographic column. Elution of the column with a 10% solution of ether in benzene yielded 1.31 g. (41.4%), m.p. 131–134°, of 1,3,-4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline. The analytical sample, m.p. 132.5–133.5°, was prepared by recrystallizing some of this material from methanol–water. This material could also be crystallized from ether, ether–Skellysolve B, and benzene–Skellysolve B. The white, crystalline compound turned dark when exposed to air and light for several days. The ultraviolet spectrum (ethanol) had λ_{max} 227, 277, 290, and 299 mμ (ϵ 33,650, 6600, 5950, and 6050, respectively).

Anal. Calcd, for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.11; H, 6.18; N, 17.32.

Further elution of the silica gel column with ether yielded 0.386 g. (11.3%), m.p. 134–136°, of 4-aminoindol-3-ylacetonitrile. The analytical sample, m.p. 135–136°, was prepared by recrystallizing a portion of this material from ethyl acetate–Skellysolve B. The ultraviolet spectrum (ethanol) had λ_{max} 225, 273, and 295 mμ (ϵ 45,300, 7100, and 5000, respectively) with an inflection at 288 mμ (ϵ 5300). The infrared spectrum (Nujol) showed NH, 3400, 3350, 3330, and 3240 cm.$^{-1}$; and –C≡N, 2250 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70.39; H, 5.45; N, 24.24.

5-Formyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (XI).—Formic acetic anhydride was prepared by mixing 9.45 ml. of acetic anhydride with 3.98 ml. of 98% formic acid. To 3 ml. (21.4 mmoles) of this solution, cooled in an ice bath, was added slowly 1.54 g. (9.73 mmoles) of the amine (II). The resulting solution was allowed to stand at room temperature for 5 hr. Ether was added and the solution was allowed to stand for 18 hr. It then was washed successively with water, dilute ammonium hydroxide, and brine. The resulting ether solution was dried over anhydrous sodium sulfate and concentrated *in vacuo* under nitrogen. Crystallization of the residue from ethyl acetate–Skellysolve B yielded 1.55 g., m.p. 138–139°, and 0.173 g., m.p. 128–132° (95.1%), of the N-formyl derivative. The analytical sample, m.p. 131–134°, was prepared by recrystallizing this material from ethyl acetate–Skellysolve B. The ultraviolet spectrum (ethanol) had λ_{max} 225 and 294 mμ (ϵ 31,750 and 9300, respectively) with an inflection at 288 mμ (ϵ 9500). The infrared spectrum (Nujol) showed NH, 3250 cm.$^{-1}$; and C=O, 1663 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41. Found: C, 70.83; H, 5.04.

5-Methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (X).—To an ice-cold mixture of 1.5 g. of powdered lithium aluminum hydride in 200 ml. of dry tetrahydrofuran was added 1.69 g. (9.08 mmoles) of the amide (XI). The resulting mixture was allowed to stir at room temperature under nitrogen for 20 hr. After the mixture had been allowed to reflux for 1 hr., it was cooled in an ice bath and treated successively with 1.5 ml. of water, 1.5 ml. of 15% sodium hydroxide, and 4.5 ml. of water. The inorganic salts were collected by vacuum filtration through Celite and washed with ether. Concentration of the combined filtrates under nitrogen and reduced pressure yielded an oil which was dissolved in benzene and chromatographed on silica gel with 2% ether–benzene to yield 1.39 g. (89.3%) of 5-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline, m.p. 119–121°. The analytical sample, m.p. 121–123°, was prepared by recrystallizing this material from benzene–Skellysolve B. The ultraviolet spectrum (ethanol) had λ_{max} 227, 282, and 299 mμ (ϵ 33,850, 7250, and 7900, respectively). The infrared and n.m.r. spectra supported the proposed structure.

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.74; H, 7.39; N, 15.96.

1-Methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline Hydrochloride (XII).—To a stirred solution of 2.00 g. (12.7 mmoles) of the amine (II) in 150 ml. of dry dimethylformamide was added, under nitrogen, 600 mg. (13.3 mmoles) of a 53.2% mineral oil suspension of sodium hydride. After 1.5 hr., methyl iodide (0.828 ml., 13.3 mmoles) was added to the mixture; the resulting solution was allowed to stand at room temperature for 2 hr. It then was poured into about 1 l. of water, and the resulting mixture was saturated with sodium chloride and extracted with ether. The ether extract was washed with brine, dried over anhydrous potassium carbonate, and concentrated to yield, after preliminary silica gel chromatography, 2.06 g. of a mixture of product and starting material. Careful chromatography of this material on silica gel with 0.5% ether–benzene resulted in a pure product which was converted to the hydrochloride and crystallized from methanol–ethyl acetate to yield 1.05 g. (39.7%), m.p. >200° dec., of 1-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]-quinoline hydrochloride. A sample of this material was recrystallized three times from methanol–ethyl acetate for analysis and had m.p. 220–235° (sublimation and decomposition in a sealed capillary). The ultraviolet spectrum (ethanol) had λ_{max} 228, 284, and 310 mμ (ϵ 32,900, 5700, and 7050, respectively) with an inflection at 303 mμ (ϵ 6500). The infrared spectrum supported the proposed structure.

Anal. Calcd. for $C_{11}H_{13}ClN_2$: C, 63.31; H, 6.28; Cl, 16.99; N, 13.43. Found: C, 63.46; H, 6.39; Cl, 17.08; N, 13.42.

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A Search for the Sulfonium Radical Intermediate

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The existence of a sulfonium and sulfonium-type radical intermediate in some free-radical reactions of phenyl sulfide has been studied. It has been found that the *t*-butoxy radical with phenyl sulfide gives phenyl sulfoxide and the *t*-butyl radical; these could form *via* a sulfonium-type radical intermediate. The cumyloxy radical and benzophenone triplet were apparently not reactive enough to give the intermediate, and alkyl radicals gave indefinite products.

Recent work by Walling and Rabinowitz[2] has offered substantial evidence that the phosphorus atom undergoes an expansion of its valence shell to accommodate nine electrons under certain free-radical reaction conditions. This state was described as an intermediate consisting of four groups bonded to and a free electron associated with the central phosphorus atom.

Research both by Price and Zomlefer[3] on free-radical additions to vinyl sulfides and Martin and Bentrude[4] on the rates of decomposition of *o*-methylthiophenyl peresters indicates that a d-orbital of a sulfur atom might also be capable of accepting an unpaired electron, thus elevating its octet to a nonet. The resulting transient intermediate, with three alkyl or aryl groups and an un-

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[1] (a) IBM Research Laboratory, San Jose 14, Calif.; to whom inquiries should be sent; (b) from the M.S. thesis of D. J. C., June, 1963.

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