m.p. 91–92°; λ_{max}^{KBr} 6.39 μ (C=C): λ_{max}^{MeOH} 282 mμ (ϵ 13,100), 277 (13,100), and 229 (25,900); no shift was observed after addition of a drop of 5 *N* HCl; n.m.r. (CCl_4) indicated nine aromatic protons at 6.8–7.7, six protons [$N(CH_3)_2$] at 3.06, and three protons (CCH_3) at 2.4 p.p.m.

Anal. Calcd. for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.77; H, 7.33; N, 11.23.

1-(Dimethylamino)-3-methyl-2-methylene-3-phenylindoline (IX).—A solution of 53.2 g. (0.2 mole) of Vb in 200 ml. of absolute ether was added to a Grignard solution prepared from 14.4 g. (0.6 g.-atom) of magnesium turnings and 85 g. (0.6 mole) of methyl iodide in 600 ml. of ether. The reaction mixture was heated at reflux temperature for 2 hr. With cooling, 300 ml. of a saturated ammonium chloride solution was added. The organic layer was washed with water, dried (K_2CO_3), and evaporated to give a pale yellow solid. Recrystallization from 2-propanol gave yellow crystals: 40.2 g. (76%); m.p. 68–69°; λ_{max}^{MeOH} 6.03 μ (C=C); λ_{max}^{MeOH} 273 mμ (ϵ 15,800); n.m.r. showed nine aromatic protons at 6.4–7.3, two protons at 3.8 and 4.2 (=CH_2), six protons at 2.9 [$N(CH_3)_2$], and three protons at 1.65 p.p.m. (CH_3).

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.62; N, 10.59. Found: C, 81.60; H, 7.50; N, 10.48.

3-Benzyl-1-(dimethylamino)-3-phenylindoline Hydrochloride (X).—The reduction of 14.5 g. of Vc was carried out with 8 g. of lithium aluminum hydride in 500 ml. of absolute ether at reflux temperature for 16 hr. It was worked up as in the preparation of VI. The crude product, m.p. 40–45°, was very soluble in every organic solvent. It was dissolved in 100 ml. of cyclohexane and an excess of HCl gas was introduced. The hydrochloride was recrystallized from acetone to give 11.3 g. (73%) of a white crystalline product, m.p. 196–198°. There was no absorption in the carbonyl region of the infrared spectrum.

Anal. Calcd. for $C_{23}H_{25}ClN_2$: C, 75.61; H, 6.90; N, 7.67. Found: C, 75.53; H, 6.83; N, 7.69.

Acknowledgment.—The author wishes to thank Mrs. B. L. Cummings and Miss M. J. Weaver for technical assistance, Mr. C. E. Childs and staff for microanalytical data, and Dr. J. M. Vandenbelt, Mr. R. B. Scott, and Mr. E. J. Schoeb for spectral data.

4,7-Diazaindole Derivatives

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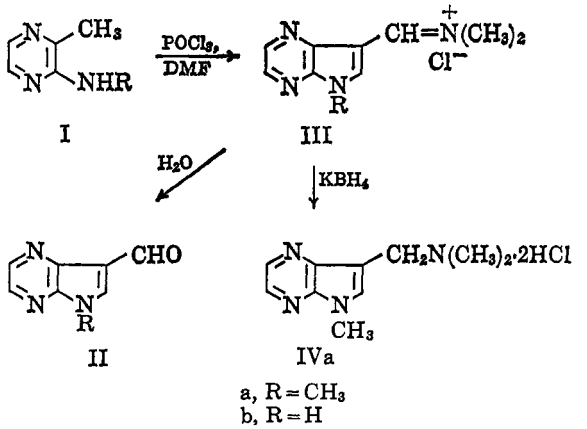
Received May 18, 1965

Condensation of 2-amino-3-methylpyrazine or its N-methyl analog with the Vilsmeier reagent furnished the corresponding 4,7-diazaindole-3-carboxaldehydes. Various transformations of these compounds, including the elaboration of 4,7-diaza analogs of gramine, tryptophane, and tryptamine, are reported.

While numerous examples of indole analogs containing one or more nitrogen atoms in the benzenoid ring have been recorded in the literature, the 4,7-diazaindole ring system has not been previously reported. In connection with our interest in certain phases of pyrazine chemistry,[1] we discovered a convenient synthetic route to aldehyde derivatives of this new heterocyclic nucleus. The reaction involves treatment of 2-amino-3-methylpyrazines with the Vilsmeier reagent.

Recently, Arnold[2] reported the reaction of 4-picoline with the Vilsmeier reagent to give either 2-(4-pyridyl)-malonaldehyde or 3-dimethylamino-2-(4-pyridyl)acrolein, depending on work-up conditions. Subsequently, Bredereck and Simchen[3] described the preparation of 2-(4-pyrimidyl)malonaldehyde from 4-methylpyrimidine under similar conditions.

Treatment of 2-methylamino-3-methylpyrazine (Ia) with the preformed phosphorus oxychloride–dimethylformamide complex furnished an immonium salt, IIIa, which, after hydrolysis, afforded a new crystalline compound with empirical formula, $C_8H_7N_3O$, indicating the incorporation of two additional carbon atoms. This was assigned the structure, 1-methyl-4,7-diazaindole-3-carboxaldehyde[4] (IIa), on the basis of the following evidence. Spectral data indicated the formation of a new chromophoric system, including a carbonyl function generated from the immonium salt; this could be confirmed by the formation of aldehyde derivatives. Further verification of the assigned structure was provided by the n.m.r. spectrum which showed, in addition to the three N-methyl protons (4.02 p.p.m.) and protons on positions 5 and 6 (quartet centered at 8.50 p.p.m.), two one-proton singlets at 10.23 and 8.28 p.p.m., ascribed to the aldehyde and C-2 protons, respectively.



It was also found that 2-amino-3-methylpyrazine[5] (Ib) condensed with the Vilsmeier reagent to furnish the high-melting 4,7-diazaindole-3-carboxaldehyde (IIb), although no immonium derivative, analogous to IIIa, could be isolated in this case. The N-unsubstituted aldehyde (IIb) was converted to IIa on treatment with dimethyl sulfate.

While the formation of the aldehydes (II) might be rationalized in terms of an intermediate such as V,

(1) W. B. Lutz, S. Lazarus, S. Klutchko, and R. I. Meltzer, *J. Org. Chem.*, **29**, 1645 (1964).

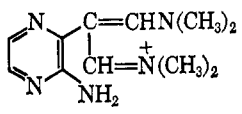
(2) Z. Arnold, *Collection Czech. Chem. Commun.*, **28**, 863 (1963).

(3) H. Bredereck and G. Simchen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 738 (1963).

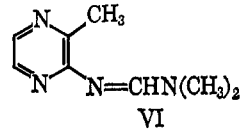
(4) According to the systematic *Chemical Abstracts* nomenclature, compound IIa is 5-methyl-5H-pyrrolo[2,3-*b*]pyrazine-7-carboxaldehyde. Because of greater clarity and conciseness, the designation of these compounds as diazaindoles is preferred by the authors.

(5) H. Gainer, M. Kokorudz, and W. K. Langdon, *J. Org. Chem.*, **26**, 2360 (1961).

by analogy to the formation of malonaldehyde derivatives from similar methyl heterocycles,[2,3] the presence of the amino group introduces a complicating factor. Thus, reaction of 2-amino-3-methylpyrazine (Ib) with a limited amount of phosphorus oxychloride in dimethylformamide furnished N,N-dimethyl-N′-(3-methyl-2-pyrazinyl)formamidine (VI). Whether or not VI is an intermediate in the formation of IIb, several alternative pathways for ultimate conversion to IIb appear to be reasonable. It has not been possible to distinguish between these paths.

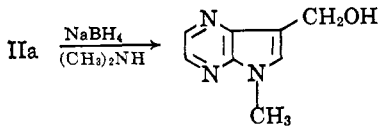


V

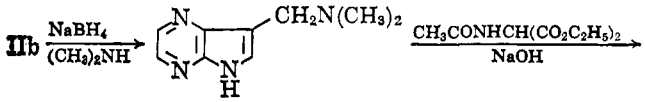


VI

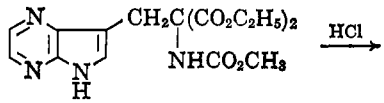
When the immonium salt IIIa was subjected to borohydride reduction, rather than hydrolysis, 1-methyl-4,7-diazagramine (IVa) was obtained and characterized as the dihydrochloride. While the corresponding immonium salt IIIb could not be isolated, 4,7-diazagramine (IVb) was obtained in excellent yield by borohydride reduction of the aldehyde IIb in the presence of a large excess of aqueous dimethylamine. While similar reductive alkylations using borohydride in neutral solution have been reported,[6] the ability of IIb to act as an efficient alkylating agent under these conditions appears to be due to formation of the corresponding anion in the highly basic reaction medium, since reduction of the related N-methylaldehyde IIa under these conditions gave only the corresponding alcohol (VII) which was also obtained by reduction in methanol.



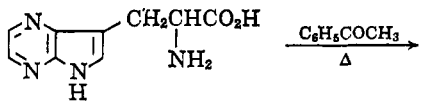
VII



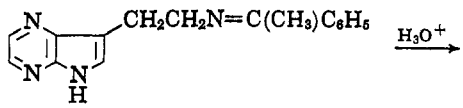
IVb



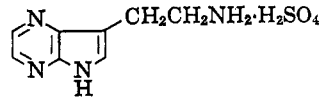
VIII



IX



X



XI

In spite of the electron-withdrawing properties of the pyrazine nucleus, IVb reacted smoothly with acetamidomalonic ester, as do gramine[7] and 7-azagramine,[8] to give the amino acid precursor VIII. Acid hydrolysis and decarboxylation then furnished 4,7-diazatryptophane (IX). Thermal decarboxylation of this amino acid in acetophenone[9] gave the Schiff base (X), which was then converted by aqueous acid to 4,7-diazatryptamine (XI), characterized as the sulfate.

The shift in ultraviolet absorption maxima to longer wave length in going from the aldehydes (II) to compounds bearing saturated substituents at position 3 in this series is presumably due to more effective conjugation of the pyrrole ring with the electron-deficient pyrazine ring in the absence of additional electron-withdrawing groups attached to the pyrrole moiety. This is in contrast to the situation in the indole series where the benzene ring is not electron deficient; here the 3-carboxaldehyde[10] absorbs at longer wave lengths than other indoles such as gramine.[11]

Experimental Section

Dimethyl[(1-methyl-4,7-diazaindol-3-yl)methylene]ammonium Chloride (III).—To a solution of 326 g. (2.1 moles) of phosphorus oxychloride in 700 ml. of dimethylformamide was added a solution of 87 g. (0.71 moles) of 2-methylamino-3-methylpyrazine (Ia) in 100 ml. of dimethylformamide. After the initial mildly exothermic reaction had moderated, the mixture was heated on a steam bath for 3 hr. Filtration of the cooled reaction mixture furnished 75.5 g. of the crude dimethylimmonium derivative III. A small portion of this salt was recrystallized twice from methanol, giving tan crystals: m.p. 273–275° dec.; $\nu_{C=N}^{Nujol}$ 1580, 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{13}ClN_4$: C, 53.45; H, 5.83; Cl, 15.78; N, 24.94. Found: C, 53.35; H, 6.05; Cl, 16.04; N, 24.25.

1-Methyl-4,7-diazaindole-3-carboxaldehyde (IIa). A. From 2-Methylamino-3-methylpyrazine.—The crude immonium salt (70 g. of III) was heated briefly in 350 ml. of water; the resulting solution was treated with charcoal and extracted with a total of 1 l. of methylene chloride after the addition of solid potassium carbonate. The organic extracts were dried and evaporated, leaving 46 g. (41%) of the 1-methylaldehyde II, m.p. 148–150°. Recrystallization from ethyl acetate furnished pale yellow crystals: m.p. 149–150°; $\nu_{C=O}^{CHCl_3}$ 1680 cm.$^{-1}$; λ_{max}^{EtOH} 259 mμ (ε 13,180), 292 mμ (ε 11,200).

Anal. Calcd. for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.55; H, 4.54; N, 25.80.

The thiosemicarbazone (m.p. 238–240° dec.) was obtained by brief heating of a solution of the aldehyde IIa and thiosemicarbazide in 0.05 *N* aqueous acetic acid.

Anal. Calcd. for $C_9H_{10}N_6S$: C, 46.14; H, 4.30; N, 35.87. Found: C, 45.91; H, 4.26; N, 35.81.

B. From 4,7-Diazaindole-3-carboxaldehyde.—To a stirred solution of 200 g. (1.36 moles) of the unsubstituted aldehyde IIb in 3 l. of 50% aqueous methanol containing 700 g. of potassium carbonate, 189 g. (1.5 mole) of dimethyl sulfate was added rapidly, causing the temperature to rise to 75°. During the next 2 hr., a total of 90 g. (0.71 mole) of dimethyl sulfate was added in two portions. After having been stirred for an additional 1 hr., the methanol was evaporated and solid potassium carbonate was added. The resulting crude 1-methylaldehyde IIa was extracted into methylene chloride. The dried organic extracts were treated with charcoal and evaporated to dryness. This left 100 g. of crude IIa, m.p. 138–142°. Recrystallization

(6) K. A. Schellenberg, *J. Org. Chem.*, **28**, 3259 (1963).

(7) E. E. Howe, J. A. Zambito, H. R. Snyder, and M. Tishler, *J. Am. Chem. Soc.*, **67**, 38 (1945).

(8) M. M. Robison and B. L. Robison, *ibid.*, **77**, 457 (1955).

(9) G. Chatelus, *Compt. rend.*, **248**, 690 (1959).

(10) R. A. Morton and N. I. Fahmy, *Nature*, **182**, 939 (1958).

(11) T. A. Geissman and A. Armen, *J. Am. Chem. Soc.*, **74**, 3916 (1952).

from methanol gave 57 g. (26%) of IIa, m.p. 148–150°, identical in all respects with material prepared by route A.

4,7-Diazaindole-3-carboxaldehyde (IIb).—To a solution of 460 g. (3 moles) of phosphorus oxychloride in 1 l. of dimethylformamide at 55°, 109 g. (1 mole) of 2-amino-3-methylpyrazine (Ib) was rapidly added. The temperature of the resulting dark solution was held at 110° by ice-bath cooling until the initial exothermic reaction had moderated. After 2 hr., when the temperature had dropped to 70°, the viscous reaction mixture was slowly poured into water. Periodic addition of ice maintained the temperature at 55°. The pH of the resulting solution (3 l.) was raised to *ca.* 2 by addition of 10 *M* potassium hydroxide solution, whereupon the aldehyde IIb separated as a tan solid. The cooled mixture was filtered and the solid was washed in turn with water, 2-propanol, and petroleum ether (b.p. 30–60°). The crude aldehyde, m.p. 313–315°, weighed 84 g. (56%) and was suitable for further reactions.

For purification, 20 g. of the above product was dissolved in 300 ml. of dilute sodium hydroxide, and the solution was clarified and neutralized with acetic acid. The resulting light tan solid was filtered and washed with water, giving 18.7 g. of pure IIb: m.p. 315–317°; $\nu_{C=O}^{Nujol}$ 1674 cm.$^{-1}$; λ_{max}^{EtOH} 257 mμ (ε 10,830), 292 mμ (ε 12,300); $\lambda_{max}^{0.1\ N\ NaOH}$ 282 mμ (ε 76,000).

Anal. Calcd. for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.57. Found: C, 57.00; H, 3.30; N, 28.58.

Because of its low solubility in useful solvents, the n.m.r. spectrum of this compound was not obtained.

N,N-Dimethyl-N′-(3-methyl-2-pyrazinyl)formamidine (VI).—To a cooled solution of 38 g. (0.25 mole) of phosphorus oxychloride in 110 ml. of dimethylformamide, 27.3 g. (0.25 mole) of 2-amino-3-methylpyrazine (Ib) was added, keeping the temperature below 50°. The resulting solution was allowed to stand overnight at room temperature. After removal of most of the dimethylformamide *in vacuo*, the dark, viscous residue was added, with cooling, to 600 ml. of 10 *N* potassium hydroxide. The resulting mixture was warmed 1 hr., cooled, and extracted with ether. Some 2-amino-3-methylpyrazine was removed by filtration and the ethereal filtrate was dried and evaporated, leaving 15 g. of viscous oil. Distillation of 10 g. of this oil furnished 6.5 g. (24%) of the formamidine VI as a pale yellow oil, b.p. 105° (0.3 mm.). A small amount of unchanged Ib was also obtained as a lower boiling fraction. A center cut of the formamidine was used for analysis: $n^{22}D$ 1.6067, $\nu_{C=N}^{film}$ 1620 cm.$^{-1}$; $\lambda_{max}^{95\%\ EtOH}$ 218 mμ (ε 3340), 266 (18,700), 333 (12,850).

Anal. Calcd. for $C_8H_{12}N_4$: C, 58.51; H, 7.31; N, 34.12. Found: C, 58.27; H, 7.40; N, 34.06.

Acid hydrolysis of this formamidine furnished 2-amino-3-methylpyrazine (Ib), identical in all respects with authentic material.

1-Methyl-4,7-diazagramine (IVa).—Potassium borohydride (1 g., 0.02 mole) was added to a stirred solution of 2.2 g. (0.01 mole) of purified immonium salt III in 75 ml. of methanol. After 1 hr. the solvent was removed and the residue was taken up in water. After saturation with potassium carbonate, the aqueous mixture was extracted with ether. Hydrogen chloride was added to the dried ether solution, precipitating a hygroscopic yellow salt, 2.3 g., m.p. 235–237° dec. Two recrystallizations from methanol–ether gave the pure dihydrochloride of IV: 2.0 g.; m.p. 237–239° dec.; ν_{NH}^{Nujol} 2000, 2100, 2400 cm.$^{-1}$; $\lambda_{max}^{95\%\ EtOH}$ 220 mμ (ε 17,200), 294 (8700), 300–308 (8600).

Anal. Calcd. for $C_{10}H_{14}N_4 \cdot 2HCl$: C, 45.64; H, 6.13; N, 21.29; Cl, 26.94. Found: C, 45.89; H, 6.21; N, 21.34; Cl, 26.81.

4,7-Diazagramine (IVb).—To a cooled solution of 42 g. (0.28 mole) of 4,7-diazaindole-3-carboxaldehyde (IIb) in 140 ml. of 40% aqueous dimethylamine and 400 ml. of water, 24 g. (0.63 mole) of solid sodium borohydride was added during 15 min. The mixture was stirred for 2 hr. at room temperature; it was then cooled and saturated with solid potassium carbonate and extracted with methylene chloride. The organic extracts were dried over potassium carbonate and evaporated, leaving 41 g. (82%) of the gramine analog IVb as a yellow, amorphous solid, m.p. 150–153°. This material was pure enough for use in further reactions. Recrystallization from ethyl acetate gave white crystals: m.p. 155–157°; $\lambda_{max}^{H_2O}$ 215 mμ (ε 15,100), 307 mμ (ε 9350).

Anal. Calcd. for $C_9H_{12}N_4$: C, 61.34; H, 6.86; N, 31.71. Found: C, 61.57; H, 7.00; N, 31.63.

3-Hydroxymethyl-1-methyl-4,7-diazaindole (VII).—Potassium borohydride (2.69 g., 0.05 mole) was added to a cooled solution of 8 g. (0.05 mole) of 1-methyl-4,7-diazaindole-3-carboxaldehyde (IIa) in 200 ml. of methanol. After stirring for 3 hr. at room temperature, the solvent was removed and the residue was taken up in 100 ml. of water. The resulting solution was saturated with solid potassium carbonate and extracted with methylene chloride. Evaporation of the organic solvent, after drying, left 7.6 g. (95%) of the light yellow alcohol, m.p. 128–130°. Recrystallization from ethyl acetate furnished 5.3 g. (65%) of the pure alcohol VII as pale yellow needles: m.p. 129–131°; ν_{OH}^{Nujol} 3350 cm.$^{-1}$; $\lambda_{max}^{95\%\ EtOH}$ 227 mμ (ε 17,250), 307 mμ (ε 8451).

Anal. Calcd. for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.72; H, 5.72; N, 25.83.

This alcohol was also obtained by the reduction of 1 g. of the aldehyde IIa in 16 ml. of 20% aqueous dimethylamine with 1 g. of potassium borohydride.

Diethyl α-Acetamido-α-[3-(4,7-diazaindolyl)methyl]malonate (VIII).—To a hot, azeotropically dried mixture of 6 g. (0.15 mole) of sodium hydroxide in *ca.* 1500 ml. of xylene was added 75.6 g. (0.43 mole) of 4,7-diazagramine (IVb) and 94.5 g. (0.435 mole) of diethyl acetamidomalonate. The mixture was refluxed for 6 hr. and then filtered while hot to remove sodium hydroxide. On cooling, 68.5 g. (46%) of the product (VIII) was obtained as yellow crystals, m.p. 163–165°. A further 6.0 g. of less pure material was obtained from the mother liquors after standing for several days. Extending the heating period to 18 hr. did not increase the yield.

Two recrystallizations from ethyl acetate furnished the analytically pure diester VIII as white crystals: m.p. 165–167°; ν_{NH}^{Nujol} 3100, 3150 cm.$^{-1}$; $\nu_{C=O}^{Nujol}$ 1680, 1735 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{20}N_4O_5$: C, 55.17; H, 5.79; N, 16.08. Found: C, 55.38; H, 6.00; N, 16.30.

4,7-Diazatryptophane (IX).—A solution of 17.4 g. (0.05 mole) of the aminomalonic ester derivative VIII in 250 ml. of concentrated hydrochloric acid was heated on the steam bath for 8 hr. The solution was evaporated to dryness; the residue was dissolved in 400 ml. of water and filtered from traces of insoluble material. The pH of the filtrate was then adjusted to 7.5–8.0 with concentrated ammonium hydroxide. The solution, after standing overnight, was filtered to give 9.5 g. (92%) of the free amino acid IX, m.p. 313–316° dec. For purification this was dissolved in dilute hydrochloric acid and reprecipitated by the addition of ammonium hydroxide solution to pH 7.5; two such isoelectric precipitations furnished 8.0 g. (77%) of 4,7-diazatryptophane (IX): m.p. 314–316° dec.; ν_{NH}^{Nujol} 2500–3100 cm.$^{-1}$; $\nu_{C=O}^{Nujol}$ 1560, 1675 cm.$^{-1}$; $\lambda_{max}^{0.1\ N\ HCl}$ 224 mμ (ε 12,950), 307 mμ (ε 9250).

Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.30; H, 5.12; N, 27.17.

4,7-Diazatryptamine–Acetophenone Schiff Base (X).—In an open beaker a slurry of 12.5 g. (0.06 mole) of pulverized 4,7-diazatryptophane (IX) and 300 ml. of acetophenone was stirred and heated to 180–185°, when decarboxylation occurred. After 15 min., when all the solid had dissolved, the mixture was cooled and filtered, and the resulting solid was washed with 2-propanol, giving 8 g. (50%) of the Schiff base X, m.p. 203–205°. Additional crude material could be recovered from the filtrate by the addition of petroleum ether. Reaction conditions were found to be rather critical; thus higher temperatures, longer heating periods, and retention of the water formed in the reaction all affected the yield and quality of the product adversely. For analysis, material from the first fraction obtained above was recrystallized twice from 2-propanol giving X as a light tan solid: m.p. 213–215°; $\nu_{C=N}^{Nujol}$ 1580, 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.63; H, 6.34; N, 21.04.

4,7-Diazatryptamine Sulfate (XI).—A solution of 8 g. (0.03 mole) of the Schiff base X in a mixture of 100 ml. of 3 *N* hydrochloric acid and 200 ml. of benzene was heated on the steam bath for 30 min. The mixture was cooled and separated. The aqueous layer was washed twice with ether to remove acetophenone. The solution was made basic and saturated with potassium carbonate, then extracted with ethyl acetate. The resulting ethyl acetate solution was dried (potassium carbonate), decolorized with charcoal, and acidified with hydrogen chloride, giving 4.5 g. (63%) of 4,7-diazatryptamine dihydrochloride, m.p. 255–258° dec. After recrystallization from methanol–isopropyl alcohol, the yellow salt had m.p. 258–260° dec., but satisfactory analytical data could not be obtained.

For conversion to the sulfate XI, the purified dihydrochloride (5 g.) was dissolved in 8 ml. of water and treated with 12 ml. of 9 *N* sulfuric acid. Addition of 160 ml. of 2-propanol gave the sulfate XI as an oil which crystallized on standing and, after trituration with methanol, had m.p. 222–224° dec. Recrystallization, by the addition of absolute ethanol to a concentrated aqueous solution, did not change the melting point. This pure salt (XI) showed $\nu_{NH_3}^{Nujol}$ 2120, 2500–3200 cm.$^{-1}$; $\lambda_{max}^{H_2O}$ 222 mμ (ε 15,600), 308 mμ (ε 8950).

Anal. Calcd. for $C_8H_{12}N_4O_4S$: C, 36.92; H, 4.65; N, 21.55. Found: C, 36.96; H, 4.85; N, 21.47.

Acknowledgment.—The authors are indebted to Mrs. U. Zeek for the elemental analyses, to Mr. R. Puchalski for spectral data, and to Mr. George Conrad for the preparation of substantial quantities of some of the intermediates described herein.

Nitration of Indoles. III. Polynitration of 2-Alkylindoles[1]

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Received February 15, 1965

Nitration in concentrated nitric acid of 2-methylindole and 1,2-dimethylindole gives the corresponding 3,6-dinitroindoles **5** and **16**; **5** was also obtained from 2-methylindole-3-carboxaldehyde and 2-methyl-6-nitroindole (**3**). 2-Methyl-3-nitroindole (**1**) and 2-methyl-3H-indol-3-one oxime (**2**) gives both **5** and 3,4-dinitro-2-methylindole (**6**); **6** was also obtained from 2-methyl-4-nitroindole (**4**). Further nitration of **5** and **16** or their precursors gives the 3,4,6-trinitroindoles **7** and **17**; 3-acetyl-2-methyl-4-nitroindole (**9**) and **4** also gave **7**. Nitration in concentrated nitric acid of 2-methyl-5-nitroindole (**20**) and 1,2-dimethyl-5-nitroindole (**27**) gives the corresponding 3,5-dinitroindoles **22** and **28**. Further nitration of **22** and **28** (or **27**) gives the 3,5,6-trinitroindoles **24** and **31**; **24** was also obtained from the 1-acetyl derivative (**21**) or **20**. Dimethylation of **22** gave 3,5-dinitro-2-*ethyl*-1-methylindole (**36**), as proved by preparation from 2-ethylindole *via* the 5-nitro (**34**) and 3,5-dinitro (**35**) derivatives and methylation to **36**. Nitration in concentrated sulfuric acid of 1,2,3-trimethylindole and 2,3,3-trimethyl-3H-indole gives the corresponding 5-nitro derivatives **41** and **43**. The differing mechanisms of nitration of indoles in sulfuric acid and in nitric or acetic acids are discussed, and a set of orientation rules for nitration of 2-alkylindoles is presented.

In this paper the nitration in concentrated nitric acid of 2-methylindole and its derivatives (including the 1-methyl, 3-acetyl, 3-formyl, and 3-, 4-, 5-, and 6-mononitro derivatives), which leads to dinitro and ultimately to trinitroindoles, is described. The structures of all the nitration products are rigorously proved, and the results are correlated with plausible interpretations of the differing mechanisms of nitration of indoles in concentrated sulfuric acid and in nitric or acetic acids. A set of generalizations concerning the orientation of nitration of 2-alkylindoles is then presented.

2-Methyl-3,4,6-trinitroindole Series.—Nitration of 2-methylindole with cold fuming nitric acid (*d* 1.50),[3] or by warming to about 50° with a large excess of concentrated nitric acid (*d* 1.38–1.42) until a vigorous reaction begins (accompanied by evolution of NO_2 fumes),[4,5] gives a dinitro derivative (**5**). Nitration of 2-methylindole or of **5** past the dinitro stage by heating with nitric acid on a steam bath for 30 min. gives a trinitro derivative[5] (**7**). Nitration of 2-methyl-3-nitroindole (**1**) and of 2-methyl-3H-indol-3-one oxime (**2**, accompanied by oxidation) is also reported[6] to give **5**, although no details of the comparison were reported. Nitration of 2-methylindole-3-carboxaldehyde in acetic acid has recently been reported[7] to give 2-methyl-6-nitroindole-3-carboxaldehyde (47%), the deformylated by-products 3,6-dinitro-2-methylindole and **1**, and a small amount of an unidentified compound, m.p. 268–271°.

We have confirmed the isolation of **5**[8] from nitration with nitric acid of 2-methylindole, of **1**, and of **2** (Chart I), and have also isolated it (as a product of deformylation) from a similar nitration of 2-methylindole-3-carboxaldehyde. In the nitrations of **1** and **2** we have also isolated an isomeric dinitro-2-methylindole (**6**).[9] Chromic acid oxidation of **5** gave N-acetyl-4-nitroanthranilic acid[10] (**10**). Since **5** has been derived from **1** and **2**, this proves that **5** is 3,6-dinitro-2-methylindole.

Nitration of 3-acetyl-2-methylindole in acetic acid at 0° gave **1** (a product of deacetylation[11]) and two mononitro-3-acetyl-2-methylindoles **8** and **9**. Chromic

(1) Paper II: W. E. Noland, L. R. Smith, and D. C. Johnson, *J. Org. Chem.*, **28**, 2262 (1963).

(2) Taken in part from (a) L. R. Smith, Ph.D. Thesis, University of Minnesota, May 1960; *Dissertation Abstr.*, **21**, 1766 (1961) [it is a pleasure to acknowledge support of this portion of the work through a Frederick Gardner Cottrell Grant from the Research Corporation (1958–1959), to the Upjohn Co. for a summer fellowship (1959), and to the Dow Chemical Co. for an academic year fellowship (1959–1960)]; and (b) K. R. Rush, Ph.D. Thesis, University of Minnesota, Sept. 1963; *Dissertation Abstr.*, **25**, 2241 (1964); National Science Foundation Graduate Fellow, June 1961–Sept. 1963.

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(8) Compound **5** sublimed on the hot stage at about 260°, darkened at 290°, and melted at 305° with decomposition. When the melting point was taken in a capillary tube, a wide range of melting points was observed between 250 and 305°, depending upon the rate of heating, as the compound sublimes. Hence, it is not surprising that a wide range of melting points has been reported: dec. upon heating,[3] m.p. 260° dec.,[6b] 265–267°,[5] 268°,[4] 300–302°.[7]

(9) It seems possible to us that the unidentified compound, m.p. 268–271°,[7] isolated from nitration of 2-methylindole-3-carboxaldehyde in acetic acid may be an impure sample of **6** (3,4-dinitro-2-methylindole, m.p. 284–285° dec.).

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(11) Analogous to the deformylation which occurred during the nitration of 2-methylindole-3-carboxaldehyde. The probable mechanism of this displacement by nitronium ion has already been discussed.[7]