51–52°. The tan residual oil (0.77 g.) did not yield a crystalline succinyl derivative. The alkaline solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 3.5 days. The product is only slightly soluble in ether and precipitates from refluxing ether as white crystals of high purity. Evaporation of the ether gave 2-methyl-2-(2-methyl-3-indole)succinic acid (1.00 g., 0.00383 mole, 37%), m.p. 219–220° dec. Two recrystallizations from acetonitrile gave white microcrystals, m.p. 223–224° dec., mixed melting point with the sample prepared as described in the preceding section, 222–224° dec. The infrared spectra in Nujol and the ultraviolet spectra were identical.

Anal. Found: neut. equiv. 141; C, 64.53; H, 6.17; N, 5.64.

2-Methyl-2-(2-methyl-3-indole)succinic anhydride (anhydride of XI). 2-Methyl-2-(2-methyl-3-indole)succinic acid (0.66 g., 0.00252 mole) and acetic anhydride (25 cc.) were mixed and set aside at room temperature under a nitrogen atmosphere for 3 days. Since part of the acid remained undissolved, the mixture was warmed on a steam bath for 1 hr. and then set aside for 2 days. Evaporation of the solvent at 73° in a rotary vacuum evaporator left a brown residue, which was dissolved in methylene chloride–petroleum ether (b.p. 60–68°) and set aside in the refrigerator for 3 days. The resulting brownish precipitate (0.31 g., 0.00127 mole, 50%), m.p. 139–141°, was recrystallized four times from methylene chloride-petroleum ether (b.p. 60–68°), yielding 2-methyl-2-(2-methyl-3-indole)succinic anhydride as whitish crystals, m.p. 144°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 223 mμ (log ε 4.49), 282-(3.86), 289(3.80). ν_{NH} 3430, 3400 (doublet); $\nu_{C=O}$ 1846, 1821 (weak), 1770 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{13}NO_3$ (243.25): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.12; H, 5.34; N, 5.70.

(2-Methyl-3-skatyl)succinic anhydride (anhydride of XII) (with William C. Kuryla). 2-Methylindole (12.1 g., 0.0921 mole) and itaconic anhydride (11.2 g., 0.100 mole) were fused on a steam bath for 15 min. The resulting brownish red oil had solidified to a hard glassy mass after 4 days. Crystallization from benzene gave a pinkish white solid (19.42 g., 0.0800 mole, 87%), m.p. 130–134°. Treatment with charcoal and three recrystallizations from benzene yielded (2-methyl-3-skatyl)succinic anhydride as a white solid, m.p. 134–135°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 227 mμ (log ε 4.52), 284(3.85), 291-(3.79). ν_{NH} 3450 in $CHCl_3$, 3390 in Nujol; $\nu_{C=O}$ 1854, 1773 in $CHCl_3$, 1848, 1765 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{13}NO_3$ (243.25): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.00; H, 5.58; N, 5.56.

(2-Methyl-3-skatyl)succinic acid (XIX) (with T. R. Rajagopalan[22]). (2-Methyl-3-skatyl)succinic anhydride (1.50 g., 0.00575 mole) was dissolved in a solution of potassium hydroxide (10.7 g.) in water (37 cc.), and the resulting solution was refluxed for 3.5 hr. The cooled solution was acidified to Congo Red with concd. hydrochloric acid, causing the solution to become turbid. Extraction with ether and evaporation of the ether gave a light brown oil, which solidified after 2 or 3 days at room temperature. The resulting white solid was dissolved in aqueous sodium bicarbonate, the solution was washed with ether, and the aqueous phase was acidified and extracted with ether as previously described. The solidified residue from evaporation of the ether was filtered with the aid of benzene and dried, yielding (2-methyl-3-skatyl)succinic acid as a white solid (1.10 g., 0.00421 mole, 73%), m.p. 149–151° dec. $\lambda_{max}^{95\%\ C_2H_5OH}$: 226 mμ (log ε 4.52), 282 (3.84), 290 (3.79). ν_{NH} 3380, 3340 (stronger band); ν_{OH} 2650; $\nu_{C=O}$ 1698 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{15}NO_4$ (261.27): C, 64.36; H, 5.79; N, 5.36. Found: C, 64.19; H, 5.81; N, 5.34.

The acid was recovered unchanged after attempted decarboxylation at 200–210°. A gas, assumed to be steam resulting from anhydride formation, was evolved at temperatures between the melting point and 210°, but, after alkaline hydrolysis of the cooled melt, the acid was recovered unchanged in 95% yield, as shown by mixed melting point and Nujol infrared comparisons.

(3-Indole)succinic acid (IIa) *from rearrangement under homogeneous conditions of 3-(1-maleyl-2-indolinyl)indole (cis-*Ia, *maleyldiindole*). A solution of maleyldiindole[4,9,10] (10.0 g., 0.0301 mole) in ethanolic 30% potassium hydroxide (30 g. potassium hydroxide in 86 cc. 95% ethanol) was refluxed for 3 hr. The solution was green at first but turned to orange when heating was begun, then back to green after cooling at the end of the reflux period. The ethanol was removed by vacuum distillation, and some indole also codistilled. The residue was washed with ether to remove remaining indole, then acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 5 days. Evaporation of the ether gave (3-indole)succinic acid as a light yellowish solid (4.97 g., 0.0213 mole, 71%), m.p. 197–198.5° dec. The product is obtained in a purer initial state than that resulting from hydrolysis under heterogeneous conditions with aqueous potassium hydroxide.

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[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE AND THE UNIVERSITY OF ALABAMA MEDICAL SCHOOL]

Synthesis of Some 5- and 6-Chloro, 5-Methyl, and 5,6,7-Trimethyl Derivatives of Tryptamine

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The preparation of 5-chloro-*N*,*N*-dimethyl-, 6-chloro-*N*,*N*-dimethyl-, and 6-chlorotryptamine from the corresponding ring-chlorinated indoles has been carried out. A nine-step synthesis of 5,6,7,*N*,*N*-pentamethyltryptamine from 3,4,5-trimethylacetophenone and the preparation of 5,*N*,*N*-trimethyltryptamine from 5-methylindole are discussed. These compounds were prepared for psychopharmacological evaluation.

In a previous communication,[3] we reported that 4-chloro-, 4-methyl-, 3-methyl-, and 3,4,5-trimethyl-β-phenethylamine, at a dose level of 25 mg./kg. (intramuscular), evoked a strong rage response in

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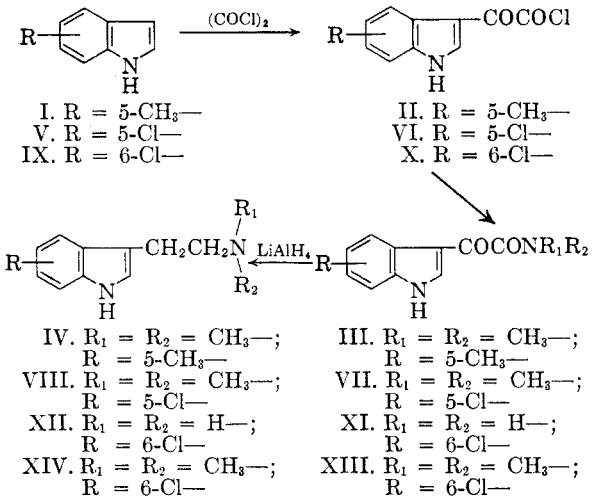
(3) F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Org. Chem.*, **23**, 1979 (1958).

cats. Recent unpublished studies in our laboratories have shown that 5-methoxy-*N*,*N*-dimethyltryptamine (*o*-methylbufotenine) is a more potent rage-producing substance than any of the substituted β-phenethylamines thus far studied. The work reported in this communication was undertaken with the idea of determining whether chloro or methyl groups introduced into the benzenoid ring of *N*,*N*-dimethyltryptamine would yield compounds having psychopharmacological activities comparable with the corresponding substituted β-phenethylamines.

The desired tryptamines were synthesized by application of the general method of Speeter and Anthony[4] to the appropriately substituted indoles as shown in Chart I. None of these reactions requires specific comment beyond the fact that the glyoxalyl chlorides II, VI, and X were isolated without characterization and immediately treated with either ammonia or dimethylamine to give the

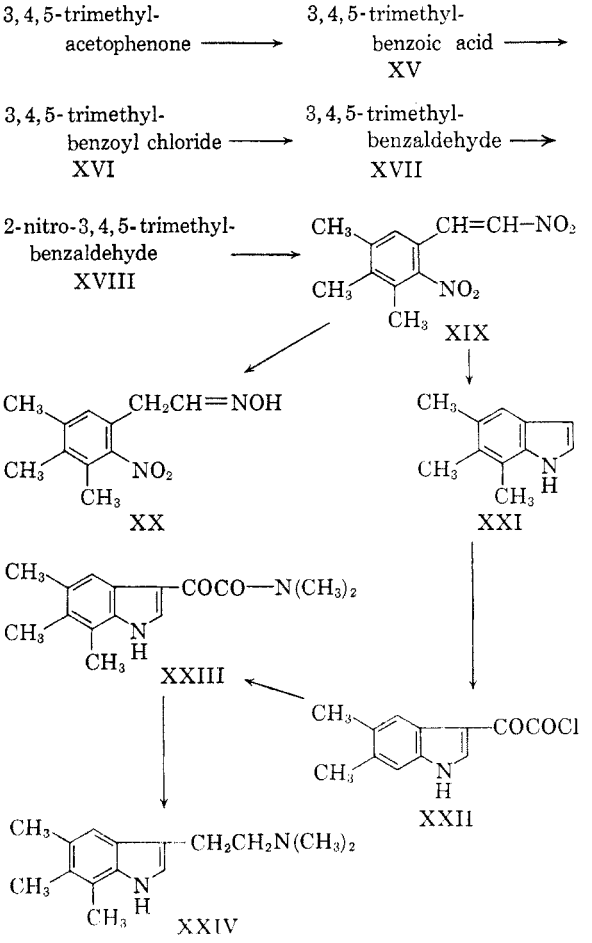
CHART I



more stable glyoxalamides III, VII, XI, and XIII. 5,*N*,*N*-Trimethyltryptamine (IV), which could not be converted to a crystalline hydrochloride, was finally isolated as the hydrogen maleate. The remaining tryptamines, VIII, XII, and XIV, formed stable and well defined crystalline hydrochlorides.

The synthesis of 5,6,7,*N*,*N*-pentamethyltryptamine (XXIV) and 5,6,7-trimethylindole (XXI) was accomplished *via* the route given in Chart II. When 3,4,5-trimethylacetophenone was subjected to a haloform reaction with potassium hypochlorite solution, degradation of the side chain to the expected carboxyl group occurred with simultaneous nuclear halogenation; the resulting compound was identified as 2-chloro-3,4,5-trimethylbenzoic acid. Nuclear halogenation during the Hoffman reaction between certain aromatic amides and sodium hypobromite is well known,[5] and sodium hypochlorite is usually the reagent of choice when this occurs. However, when 3,4,5-trimethylacetophenone[6] was treated with cold sodium hypobromite solution and allowed to react for eighteen hours, the halogen-free 3,4,5-trimethylbenzoic acid (XV) was obtained in 56% yield. After XV had been converted to the acid chloride XVI, the latter compound was changed to the aldehyde XVII by the action of hydrogen in the presence of the usual Rosenmund catalyst. Although the yield of 3,4,5-trimethylbenzaldehyde (XVII) was somewhat variable, depending upon reaction conditions, it was found that, by carrying out this reduction step in refluxing toluene for twenty-five hours, there resulted a 66% yield of the purified aldehyde XVII; a shorter reaction period in refluxing xylene gave lower yields.

CHART II



The nitration of 3,4,5-trimethylbenzaldehyde (XVII) was examined under several reaction conditions in an attempt to obtain 2-nitro-3,4,5-trimethylbenzaldehyde (XVIII). Apparently no reaction occurred between XVII and nitric-acetic

(4) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).

(5) E. S. Wallis and J. F. Lane, *Org. Reactions*, Coll. Vol. III, 267 (1946).

(6) G. Baddely, *J. Chem. Soc.*, 232 (1944).

acid mixture, since only unchanged XVII could be isolated from the final mixture. Nitration with mixed acid at 15°-20° afforded only the dinitration product 2,6-dinitro-3,4,5-trimethylbenzaldehyde. Howefer, by carrying out the nitration of XVII in sulfuric acid by the addition of solid potassium nitrate in accordance with a modification of the procedure given by Eichengrun and Einhorn,[7] the desired 2-nitro-3,4,5-trimethylbenzaldehyde (XVIII) was obtained in 89% yield, based on unrecovered XVII.

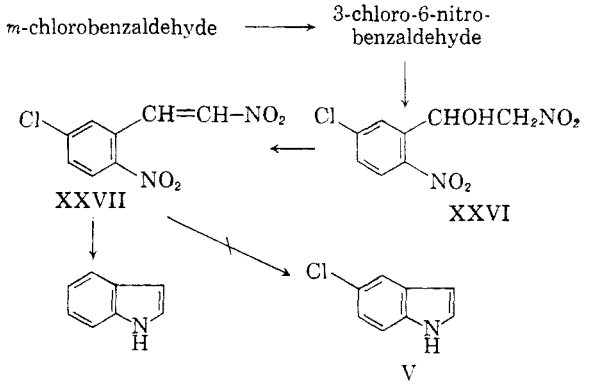
The base-catalyzed condensation of the nitroaldehyde XVIII with nitromethane using the procedure of Huebner *et al.*[8] gave a mixture of the 2,β-dinitrostyrene XIX and the corresponding nitroalcohol. Dehydration of the mixed product with sodium acetate–acetic anhydride gave pure 3,4,5-trimethyl-2,β-dinitrostyrene (XIX) in 76% yield.

Initially, the cyclization of XIX to 5,6,7-trimethylindole (XXI) was attempted using the iron powder–acetic acid procedure of Ek and Witkop,[9] since we had successfully prepared 5,6,7-trimethoxyindole from 3,4,5-trimethoxy-2,β-dinitrostyrene[10] using these reagents. However, none of the desired indole XXI could be isolated from the final reaction mixture. In an alternative approach to this cyclization, XIX in methanol–acetic acid–ethyl acetate solution was subjected to a low-pressure hydrogenation in the presence of a 10% palladium-on-charcoal catalyst.[8] The hydrogen uptake ceased at approximately 60% of the volume calculated to convert XIX completely to XXI. Although the crude reaction product gave a positive Ehrlich reaction, none of the indole XXI could be isolated by conventional methods. There was obtained from this reduction mixture a small amount of 2-nitro-3,4,5-trimethylphenylacetaldoxime(XX). The partial catalytic reduction of β-nitrostyrene in neutral solution to phenylacetaldoxime and polymolecular reduction products has been described by Kohler and Drake,[11] whereas in strongly acid media, complete reduction to β-phenethylamine[12] occurs.

Walker[13] has shown that the course of the reduction of certain *o*-nitrophenylacetonitriles to indoles is drastically influenced by the acidity of the medium. Thus, the intermediate *o*-aminophenylacetonitrile can undergo internal amidine formation and this, in turn, forms a protonated amidinium ion which is resonance stabilized against further reduction to the indole. Since the formation of similar stable protonated ions might be a possibility during the reductive cyclization of XIX in the presence of acetic acid, the hydrogenation was repeated using ethyl acetate–methanol as a reaction medium. The hydrogen uptake was rapid, exothermic, and quantitative. Under these conditions 5,6,7-trimethylindole (XXI) was obtained in 50% yield.

5,6,7,*N*,*N*-Pentamethyltryptamine (XXIV) was obtained *via* the indole glyoxalyl chloride (XXII) and the amide (XXIII), which was reduced by means of lithium aluminum hydride.[4] The free base XXIV was finally converted to the hydrochloride.

3-Chlorobenzaldehyde was selected as the starting material for the synthesis of the intermediate 5-chloroindole (V) required for the preparation of VIII. By following the reaction scheme



the chloroaldehyde was first converted to 2-nitro-5-chlorobenzaldehyde (XXV) in 66% yield by the method[7] already described for the preparation of XVIII. A base-catalyzed condensation of XXV with nitromethane in which tri-*n*-butylamine was used failed to give the nitroolefin XXVII. When the condensation was then repeated following the alcoholic alkali procedure of Worral,[14] α-(2-nitro-5-chlorophenyl)-β-nitroethanol was obtained rather than the expected XXVII. Dehydration of XXVI with anhydrous sodium acetate and acetic anhydride afforded a satisfactory yield of 5-chloro-2,β-dinitrostyrene (XXVII).

When the reductive cyclization of XXVII was attempted in accordance with the method described by Huebner,[8] indole was obtained instead of 5-chloroindole. This result is not surprising in light of the findings of Strel'tsova and Zelinskii,[15] who have demonstrated that hydrogenolysis of the halo group occurs simultaneously with reduction of the nitro group when either 2- or 4-chloronitrobenzene is treated with hydrogen in the presence of a noble-metal catalyst (palladium or platinum).

(7) A. Eichengrun and A. Einhorn, *Ann.*, **262**, 137 (1891).
(8) C. F. Huebner, H. A. Troxell, and D. C. Schroeder, *J. Am. Chem. Soc.*, **75**, 5887 (1953).
(9) A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **76**, 5579 (1954).
(10) R. D. Morin, F. Benington, and L. C. Clark, Jr., *J. Org. Chem.*, **22**, 331 (1957).
(11) E. P. Kohler and N. L. Drake, *J. Am. Chem. Soc.*, **45**, 1281 (1923).
(12) K. Kindler, E. Brandt, and E. Gehlhaar, *Ann.*, **511**, 209 (1934).
(13) G. N. Walker, *J. Am. Chem. Soc.*, **77**, 3844 (1955).
(14) D. E. Worrall, *Org. Syntheses*, Coll. Vol. I. 413 (1941).
(15) A. A. Strel'tsova and N. D. Zelinskii, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 401 (1941); *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 56 (1943).

Since 5-chloroindole became commercially available during this study, this was used in the synthesis of the tryptamine VIII.

The 6-chloroindole (IX) required for the synthesis of XII and XIV was prepared from 2-nitro-4-chlorotoluene following the route of Rydon and Tweedle[16] in which this starting compound is first condensed with ethyl oxalate to give 4-chloro-2-nitrophenylpyruvic acid, which is next cyclized to 6-chloroindole-2-carboxylic acid by treatment with ferrous hydroxide; the acid is finally subjected to thermal decarboxylation in the presence of a copper chromite catalyst to give 6-chloroindole (IX).

EXPERIMENTAL[17]

5,N,N-Trimethyl-3-indoleglyoxalamide (III). A cold stirred solution of 10 g. of I in 200 ml. of dry ether was treated with 12 ml. of oxalyl chloride in 15 ml. of dry ether. The resulting insoluble glyoxalyl chloride (II) was collected, rapidly washed with additional dry ether, and resuspended in the same solvent. To the cold stirred slurry of II there was added dropwise 10.6 g. of anhydrous dimethylamine in dry ether. Stirring was continued for 1 hr. and then the reaction mixture was filtered and washed with additional ether. The crude cake was slurried in water to remove the soluble dimethylamine hydrochloride and finally collected. Recrystallization from hot benzene-ethanol gave 14.4 g. (82.2%) of pure III as colorless needles; m.p. 184–185°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.9; H, 6.10; N, 12.2. Found: C, 68.3; H, 5.9; N, 11.9.

5,N,N-Trimethyltryptamine (IV). To a stirred suspension of 9.9 g. of lithium aluminum hydride in 300 ml. of dry ether was added portionwise and cautiously a slurry of 14.4 g. of III in about 100 ml. of hot, dry benzene using additional dry ether to transfer the last of the solid. The mixture was refluxed for an additional hour, cooled in an ice bath, and cautiously treated with water to decompose excess hydride and the reaction complex. The ether-benzene solution of the product was filtered from the insoluble inorganic salts, dried over anhydrous magnesium sulfate, filtered, and the filtrate treated with hydrogen chloride gas. The precipitated oily salt could not be induced to crystallize and therefore the free base was regenerated with alkali. Vacuum distillation of the crude amine, b.p. 140–142°/0.3 mm., gave a colorless oil which crystallized to give 7.6 g. (59%) of base IV; m.p. 99–100°. To a solution of 6.0 g. of IV in boiling isopropyl acetate there was added a hot solution of 3.0 g. maleic acid in the same solvent. The precipitated salt amounted to 9.0 g. (quant.); m.p. 94–95°.

Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.2; H, 6.9; N, 8.9. Found: C, 63.9; H, 6.8; N, 8.6.

α-(2-Nitro-5-chlorophenyl)-β-nitroethanol (XXVI). 2-Nitro-5-chlorobenzaldehyde (XXV) was obtained in 66.5% yield by adding dropwise 120.4 g. of 3-chlorobenzaldehyde to a stirred solution of 88 g. of potassium nitrate in 1200 ml. of concd. sulfuric acid, while maintaining the reaction temperature between 5–9°. The mixture was stirred for an additional 15 min. at 0–5°, and then poured onto cracked ice. The colorless solid was collected, washed with water, and finally recrystallized from ether–petroleum ether (b.p. 30–60°) as nearly colorless needles; m.p. 78.5–79.5° (reported,[7] m.p. 77.5°).

The nitroaldehyde XXV (122.9 g.) dissolved in a mixture of 40.4 g. of redistilled nitromethane and 132 ml. of methanol was cooled in an ice bath to 10–15°. To this mixture was added a solution of 27.8 g. of sodium hydroxide in 67 ml. of water at such a rate that the internal temperature did not exceed 15°. Following the addition, the entire mixture was kept at about 0–5° for 2 hr. and then the resulting semi-solid mass was dissolved in 700 ml. of an ice water mixture. The resulting clear yellow solution was poured slowly into a solution of 132 ml. of concd. hydrochloric acid in 198 ml. of water. The crude nitroalcohol (XXVI) was collected and washed with water; yield, 72 g. (51%), pure enough for the next reaction step. Poor recovery was experienced in recrystallizing this product from chloroform–petroleum ether. A recrystallized analytical specimen was obtained as light yellow prisms; m.p. 89–90°.

Anal. Calcd. for $C_8H_7ClN_2O_5$: C, 38.9; H, 2.84; Cl, 14.4; N, 11.35. Found: C, 38.95; H, 2.61; Cl, 14.57; N, 11.05.

2-Nitro-5-chloro-β-nitrostyrene (XXVII). Forty-six g. of sodium acetate trihydrate was converted to the anhydrous salt by fusion, ground to a fine powder, and suspended in 90 ml. of acetic anhydride. The nitroalcohol (XXVI) (20 g.) was then added and the mixture refluxed for 5 min. Upon cooling, the resulting solution was poured into 600 ml. of cold water. The precipitated light yellow oil solidified on standing at room temperature for 1 hr. The crude nitrostyrene (XXVII) after collection and air drying amounted to 17.6 g. (95.4%); m.p. 118.5–120°. Recrystallization from ethanol gave light yellow needles; m.p. 124–125°.

Anal. Calcd. for $C_8H_5ClN_2O_4$: Cl, 15.52; N, 12.25. Found: Cl, 15.7; N, 11.8.

Attempted reductive cyclization of XXVII to 5-chloroindole. A solution of 22.9 g. of nitrostyrene XXVII in 185 ml. of ethyl acetate, 20 ml. of ethanol, and 23 ml. of glacial acetic acid containing 2 g. of 10% palladium-on-charcoal catalyst was hydrogenated in a Parr apparatus at room temperature. From an initial pressure of 60 p.s.i., the theoretical value of hydrogen was absorbed within about 2.25 hr. When the hydrogenation mixture was filtered free of ammonium acetate and spent catalyst, the deep blue filtrate was washed three times with 5% sodium bicarbonate solution, dried, and evaporated *in vacuo*. Distillation of the residue gave a main fraction, b.p. 95–98° (0.1 mm.), of a colorless product which was recrystallized from petroleum ether (b.p. 30–60°); 6.1 g.; m.p. 52.5–53°. The product gave a negative Beilstein test for halogen and did not give any depression in a mixed melting point with pure indole (yield 52.1%).

5-Chloro-3-indole-N,N-dimethylglyoxalamide (VII). A solution of 5.0 g. of 5-chloroindole (Aldrich Chemical Co.) in 70 ml. of dry ether was treated with 5.5 ml. of oxalyl chloride in 10 ml. of dry ether, and the glyoxalyl chloride (VI) was isolated and treated with 5 g. of dimethylamine (anhydrous) as described for the preparation of III. The precipitated amide was washed with ether and then water, and the product was air dried. There was obtained 5.5 g. (67%) of VII as colorless needles; m.p. 193–194°. An analytical sample recrystallized from hot benzene-ethanol had the same melting point.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.5; H, 4.4; N, 11.2. Found: C, 57.4; H, 4.6; N, 11.1.

5-Chloro-N,N-dimethyltryptamine (VIII). To a slurry of 3.6 g. of lithium aluminum hydride in 100 ml. of absolute ether was added 5.4 g. of VII as a slurry in 75 ml. of dry benzene. After refluxing and stirring for 1 hr., the product was worked up by the careful addition of enough water to hydrolyze the reaction complex and the excess reagent. After filtration, the ether-benzene layer was dried (magnesium sulfate) and treated with dry hydrogen chloride gas. The crude amine hydrochloride amounted to 5.1 g. (91%) of a nearly colorless powder. Recrystallization twice from hot ethanol-ether afforded 3.0 g. of pure VIII hydrochloride as colorless plates; m.p. 197–198°.

Anal. Calcd. for $C_{12}H_{16}N_2Cl_2$: C, 55.6; H, 6.2; Cl, 27.4. Found: C, 55.8; H, 6.4; Cl, 27.3.

(16) H. N. Rydon and J. C. Tweedle, *J. Chem. Soc.*, 1949 (1955).

(17) All melting points uncorrected.

6-Chloroindole (IX). Following the procedure of Rydon and Tweedle,[16] 2-nitro-4-chlorotoluene was condensed with ethyl oxalate to give 4-chloro-2-nitrophenylpyruvic acid (42%); (m.p. 140–141°; reported 136°). Reductive cyclization of this acid to 2-carboxy-5-chloroindole [m.p. 248–249° dec.; reported m.p. 244° dec.] with ferrous hydroxide afforded this compound in 65% yield (reported 85%). Decarboxylation of this intermediate in hot quinoline containing copper chromite as a catalyst gave the desired 6-chloroindole (66%); m.p. 86–87°; (reported, m.p. 86–87°).

6-Chloro-3-indoleglyoxalamide (XI). To a stirred solution of 22.7 g. of 6-chloroindole (IX) in 400 ml. of dry ether (ice bath) was slowly added 29.6 g. (20 ml.) of oxalyl chloride in 20 ml. of dry ether. The reaction mixture was allowed to stand at room temperature for 2 hr., during which time the glyoxalyl chloride (X) deposited as a yellow solid which, after collecting and washing with ether, amounted to 32 g. (88%). To 500 ml. of 28% ammonium hydroxide was added 32 g. of X under stirring and cooling. After the addition was complete, stirring was continued for half an hour at 40°. After cooling, the resulting mixture was filtered and the cake washed free of ammonium chloride with water. The air-dried amide (XI) weighed 27.8 g. (94.5%). An analytical sample was recrystallized from ethanol as colorless prisms, m.p. 269–270° dec.

Anal. Calcd. for $C_{10}H_7ClN_2O_2$: C, 54.0; H, 3.15; N, 12.6. Found: C, 53.9; H, 3.15; N, 12.5.

6-Chlorotryptamine (XII). To a stirred solution of 13.6 g. of lithium aluminum hydride in 250 ml. of dry ether was added a slurry of 14 g. of XI in hot dry benzene. The hydrolysis was carried out as described for IV and the dry ether-benzene solution of the free base was treated with anhydrous hydrogen chloride gas to precipitate XII as the hydrochloride. The crude salt (4.5 g.; 41%) was recrystallized twice from ethanol-ether to give 4 g. of pure product as colorless crystals; m.p. 224–225°.

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2$: C, 52.0; H, 5.2; N, 12.1. Found: C, 51.8; H, 5.4; N, 11.9.

6-Chloro-3-indole-N,N-dimethylglyoxalamide (XIII). To a stirred suspension of the glyoxalyl chloride (X), obtained from 15.2 g. of 6-chloroindole and oxalyl chloride, in 250 ml. of dry ether was added a solution of 13.5 g. of anhydrous dimethylamine in 25 ml. of dry ether. After stirring for 1 hr., the crude solid product was collected by suction filtration, washed with water and ether, and recrystallized from benzene-ethanol; yield, 21 g. (84%); m.p. 267–268°.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.5; H, 4.4; N, 11.2. Found: C, 57.5; H, 4.4; N, 11.2.

6-Chloro-N,N-dimethyltryptamine (XIV). To a stirred solution of 11.7 g. of lithium aluminum hydride in 300 ml. of dry ether was added portionwise a slurry of 18 g. of XIII in 160 ml. of hot dry benzene. The mixture was stirred at reflux for 3 hr. and hydrolyzed and the product isolated as described for IV. The crude hydrochloride of the product (18 g.) was recrystallized from alcohol-ether; yield, 14.9 g. (80%) of colorless small needles; m.p. 196–197°.

Anal. Calcd. for $C_{12}H_{16}Cl_2N_2$: C, 55.6; H, 6.2; N, 10.8. Found: C, 55.6; H, 6.2; N, 10.8.

Action of potassium hypochlorite on 3,4,5-trimethylacetophenone. A solution of 176 g. of calcium hypochlorite in 880 ml. of water was cooled and treated with a second solution containing 123 g. of anhydrous potassium carbonate, 35 g. of potassium hydroxide, and 350 ml. of water. After standing 0.5 hr., the precipitated calcium carbonate was collected and washed with 40 ml. of cold water. The combined filtrates were heated to 55° (stirring), and 50 g. of 3,4,5-trimethylacetophenone was added in one portion. The resulting exothermic reaction was controlled by occasionally immersing the flask in an ice bath so that the internal temperature remained at 60–70°. When no further temperature rise was noted, the mixture was cooled and stirred for 40 min. at room temperature. The cold solution was first treated with 3 g. of sodium metabisulfite in 120 ml. of water to decompose the excess hypochlorite and then made strongly acid with concd. hydrochloric acid to precipitate the resulting substituted benzoic acid. The crude product was collected, washed with water, and air dried; yield, 59 g.; m.p. 170–200°. After recrystallization from hot benzene, the melting point of the product was 192–193° (reported[18] m.p. for XV, 215–216°). A strong positive Beilstein test indicated the presence of a nuclear chlorine group, since the acid did not give a silver chloride precipitate with warm alcoholic silver nitrate solution. Neut. equiv.: calcd. for 2-chloro-3,4,5-trimethylbenzoic acid: 200. Found: 199.5.

3,4,5-Trimethylbenzoic acid (XV). An aqueous solution of sodium hypobromite was prepared by adding dropwise 79.2 g. of bromine to a mechanically stirred solution of 1200 ml. of 5% sodium hydroxide so that the temperature did not rise above 15°. 3,4,5-Trimethylacetophenone (26.8 g.) was then added, and the mixture stirred for 18 hr.; after this time, no excess reagent was present. The heavy bromoform layer (40.2 g.) was removed, and the aqueous phase was extracted with 200 ml. of ether. The clear alkaline solution was then made strongly acid and the resulting precipitate collected and washed free of salts. After air drying, the crude acid XV weighed 22.0 g. (80%). Since this crude product contained some halogen and melted at 170–185°, it was recrystallized from hot ethanol. The pure XV (halogen-free) amounted to 17.4 g. (64%) and melted at 218–220°. Neut. equiv.: calcd. for $(CH_3)_3C_6H_2CO_2H$: 164. Found: 162.

3,4,5-Trimethylbenzaldehyde (XVII). 3,4,5-Trimethylbenzoyl chloride (XVI) was obtained in 99% yield by refluxing a mixture of 54.6 g. of XV, 100 ml. of purified thionyl chloride, and 50 ml. of dry reagent benzene for 3 hr. After removal of the solvent and excess thionyl chloride under reduced pressure, the residue was vacuum distilled to give 60.2 g. of pure XVIII, b.p. 100–105°/0.1 mm.; m.p. 46–47°.

Rosenmund reduction of XVI was most satisfactory when carried out as described[19] for preparation of 2-ethoxy-3,4-dimethoxybenzaldehyde. To a solution of 120 g. of XVI in 350 ml. of dry toluene was added 10 g. of palladium–on–barium sulfate catalyst. The suspension was mechanically stirred and refluxed while dry hydrogen gas (passed through sulfuric acid) was bubbled through the mixture for a 24-hr. period. After filtering (Norite) free of spent catalyst, the filtrate was stripped at diminished pressure and the residue subjected to a vacuum distillation. Following a small forecut, the aldehyde XVII (72.2 g.; 74%) was collected as a colorless oil (b.p. 80–85°/0.15 mm.) which rapidly crystallized in the receiver. Recrystallization from petroleum ether (b.p. 30–60°) gave 65.2 g. (67%) of colorless needles; m.p. 60–61° (reported[20] m.p. 52°).

2,6-Dinitro-3,4,5-trimethylbenzaldehyde. To a stirred mixture of 15 ml. each of concd. nitric and sulfuric acids, cooled to 15–20°, was added 3.1 g. of XVII. The nitration mixture stood at room temperature for 1 hr. and was poured onto ice and water, and the solid product collected on a filter. After drying, the crude nitration product weighed 4 g.; m.p. 125–135°. Two recrystallizations from hot ethanol afforded 1.7 g. of 2,6-dinitro-3,4,5-trimethylbenzaldehyde as granular yellow crystals, m.p. 154–155°.

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.4; H, 4.2; N, 11.8. Found: C, 50.7; H, 4.5; N, 11.4.

2-Nitro-3,4,5-trimethylbenzaldehyde (XVIII). To 150 ml. of concd. sulfuric acid was added 22.2 g. of finely powdered XVII with stirring and ice bath cooling (internal temperature <8°). When solution was complete (15–30 min.), the flask was placed in a Dry Ice–acetone bath in order to lower the internal temperature to −10° (bath at −25° to −30°). Powdered potassium nitrate was gradually added at a rate to keep the temperature below −5°. The Dry Ice bath was

(18) P. Jannasch and M. Weiler, *Ber.*, **27**, 3444 (1894).

(19) R. H. F. Manske, A. E. Ledingham, and H. L. Holmes, *Can. J. Research*, **23B**, 100 (1945).

(20) H. Kromer, *Ber.*, **24**, 2407 (1891).

then replaced with an ice bath and the temperature kept below 3° for an additional 1.5 hr. The cold nitration mixture was then added to about 1 l. of ice and water to precipitate the crude mononitration product. The solid was collected on a suction filter and washed thoroughly with water. Air drying gave 28.0 g. of crude XVIII which was further purified by vacuum distillation. After removing a forecut of 2.8 g. of unchanged XVII (b.p. 85–120°/0.1 mm.), 23.4 g. of the pure nitroaldehyde XVIII (b.p. 127–130°/0.15 mm.) was collected (89% based on XVII not recovered). The distilled XVIII after recrystallization from ethyl acetate–petroleum ether melted at 87–88°.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.2; H, 5.7. Found: C, 62.3; H, 5.9.

3,4,5-Trimethyl-2,β-dinitrostyrene (XIX). To a stirred solution of 51.3 g. of XVI in 530 ml. of methanol and 20 ml. of redistilled nitromethane which had been precooled to 13° was added 37 ml. of 45% aqueous potassium hydroxide at a rate to maintain the mixture at 15° (ice bath). The resulting mixture was stirred for an additional 20 min. at 11–13° and then poured into a mixture of 175 ml. of concd. hydrochloric acid and ice. The solid which separated was collected, washed with water, and air dried. This product was a mixture of XIX and the corresponding nitroalcohol (m.p. 128–170°), which was dissolved in 50 ml. of acetic anhydride containing 5 g. of fused sodium acetate. The mixture was heated for 10–15 min., poured into cold water, and allowed to stand until the product solidified (1–1.5 hr.). The dried nitrostyrene weighed 47.4 g. (76%); m.p. 176–180°. A sample was purified for analysis by recrystallization from ethanol–ethyl acetate; m.p. 185–186°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 56.0; H, 5.1. Found: C, 56.2; H, 5.0.

5,6,7-Trimethylindole (XXI). To a solution of 5.9 g. of XIX in 250 ml. of hot ethyl acetate was added 2 g. of 10% palladium-on-charcoal catalyst. The hot mixture was placed in a Parr hydrogenation apparatus. From an initial gas pressure of 50 p.s.i. the theoretical amount of hydrogen was absorbed over a period of 13 min.; the effluent gas from the hydrogenation contained ammonia. The resulting hot ethyl acetate solution of the product was treated with Norite, filtered, and evaporated to a small volume of brown oil. This was taken up in 90 ml. of 1:1 benzene–petroleum ether (b.p. 30–60°) and passed through a column of chromatographic alumina (45 g.), which was, in turn, washed with 100 ml. of the same solvent mixture followed by 50 ml. of benzene. The effluent from the column was evaporated *in vacuo* to give a light yellow oil which crystallized when triturated with petroleum ether. Recrystallization from hot petroleum ether (b.p. 30–60°) gave 1.7 g. (42.8%) of colorless prisms, m.p. 66–67°.

Anal. Calcd. for $C_{11}H_{13}N$: C, 83.0; H, 8.2; N, 8.8. Found: C, 82.8; H, 8.2; N, 9.0.

Hydrogenation of XIX in acetic acid–ethyl acetate solution. To a hot solution of 16.5 g. of XIX in 200 ml. of ethyl acetate, 25 ml. of ethanol, and 25 ml. of glacial acetic acid was added 2 g. of 10% palladium-on-charcoal catalyst. The mixture was placed in a Parr hydrogenation apparatus at an initial hydrogen pressure of 60 p.s.i. Over a period of 1.2 hr., 24.4 p.s.i. of hydrogen was taken up (theory 35 p.s.i.) by the sample. The reaction mixture was filtered free of the spent catalyst, and the resulting dark filtrate was washed with 5% sodium bicarbonate. After drying the organic layer over anhydrous magnesium sulfate, the solvent was removed under reduced pressure, and the dark residue distilled. A fraction amounting to 4.2 g. of a semisolid product boiling at 160–165°/0.7 mm. was collected and triturated with benzene–petroleum ether (b.p. 30–60°) to give 1.1 g. of a tan solid; m.p. 153–154°, with preliminary softening. Several recrystallizations from hot benzene afforded 500 mg. of colorless prismatic needles, m.p. 183–184°. This product gave a positive red spot test for an aliphatic oxime group when heated on a steam bath with benzoyl peroxide and the vapors were allowed to impinge on a filter paper which had been treated previously with equal parts of 1% solution of α-naphthylamine and sulfanilic acid in 30% acetic acid.[21] The partial reduction product XIX which was obtained was therefore *2-nitro-3,4,5-trimethylphenylacetaldoxime* (XX).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.3; N, 12.6. Found: C, 59.8; H, 6.5; N, 12.3.

5,6,7,N,N-Pentamethyl-3-indoleglyoxalamide (XXIII). A solution of 7.5 g. of XXI in 100 ml. of absolute ether was treated with 7.5 g. of oxalyl chloride in 10 ml. of the same solvent under stirring. The mixture was stirred for half an hour and the solid orange glyoxalyl chloride collected on a filter and washed with dry ether. The resulting dry powder was resuspended in about 100 ml. of dry ether and then treated with a solution of 6.8 g. of anhydrous dimethylamine in 10 ml. of dry ether (ice bath cooling and stirring). After remaining at room temperature for 1 hr., the crude precipitated amide (XXIII) was collected and washed thoroughly with ether and then with water. After air drying, the dark XXIII weighed 8.2 g. (68%). Recrystallization from hot benzene containing a little ethanol afforded 6 g. (50%) of the pure amide as nearly colorless needles, m.p. 192–193°.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.7; H, 7.0; N, 10.85. Found: C, 70.0; H, 7.1; N, 11.0.

5,6,7,N,N-Pentamethyltryptamine (XXIV). The amide (XXIII) (5.8 g.) in 50 ml. of hot dry benzene was added to a slurry of 3.7 g. of lithium aluminum hydride in 100 ml. of absolute ether and the product worked up in the manner described for the preparation of IV. The resulting dry benzene-ether solution of the base was treated with dry hydrogen chloride gas to precipitate 5.6 g. (93%) of XXIV as an oily compound which was taken up in ethanol; cooling and adding ether induced crystallization of the hydrochloride as nearly colorless prisms weighing 5.1 g. (85%); m.p. 124–125°, with some previous softening.

Anal. Calcd. for $C_{15}H_{23}ClN_2$: C, 67.5; H, 8.6; Cl, 13.3. Found: C, 67.8; H, 8.7; Cl, 13.2.

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