5,7-Dimethoxyindole and Related Compounds

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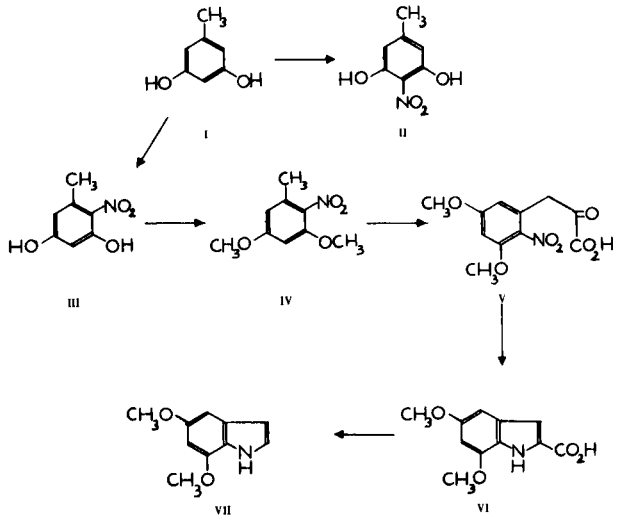
In view of the attempts that have been made to develop structure-activity relationships for substituted tryptamines (1,2) it appeared to be of interest to prepare a new series of these pharmacologically active compounds. The present communication describes the synthesis of 5,7-dimethoxytryptamines not previously prepared.

The key intermediate for these new dimethoxytryptamines is 5,7-dimethoxyindole (VII) and our attention was directed toward its synthesis. Although Süs *et al.*, (3) have reported its preparation by photolytic ring-contraction of an appropriate *o*-quinondiazide we decided to synthesize VII by a simple way *via* a Reissert indole synthesis as illustrated in scheme I.

By nitration of orcinol (I) with nitric acid in ether at 0° (4,5) two isomers were obtained (II and III) which were separated by steam-distillation; methylation of one of these isomers (III) with dimethyl sulphate in acetone with potassium carbonate yielded the required dimethoxy derivative IV (6).

The condensation of IV with diethyl oxalate was carried out with potassium ethoxide in ether and the resulting nitrophenylpyruvic acid (V) without purification was reduced with ferrous sulphate and ammonium hydroxide to afford 5,7-dimethoxyindole-2-carboxylic acid (VI). This carboxylic acid (VI) was carefully freed from sulphate (7) and submitted to decarboxylation with copper chromite in quinoline to yield 5,7-dimethoxyindole (VII).

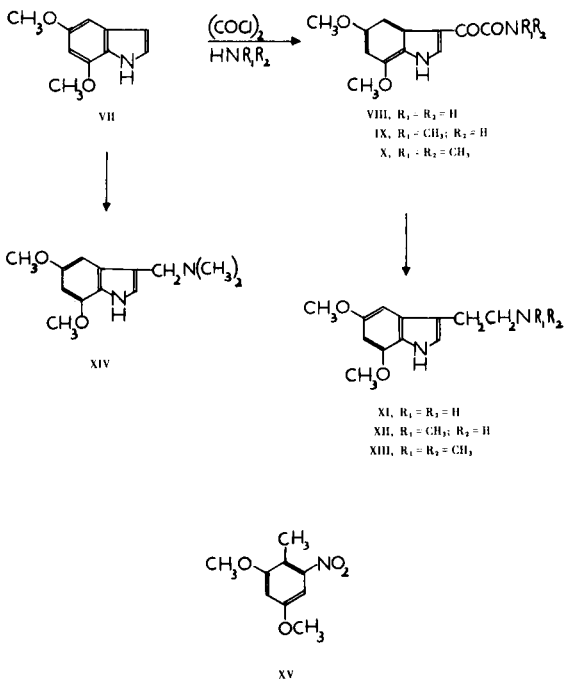
SCHEME I



The melting point of VII (82°) is quite different from that previously recorded (159-160°) (3); our product which was purified by sublimation analyzed correctly and the nmr spectrum is also in good agreement.

Starting with VII and by application of the general method of Speeter and Anthony (8) 5,7-dimethoxytryptamine, *N*-methyl-5,7-dimethoxytryptamine and *N,N*-dimethyl-5,7-dimethoxytryptamine were synthesized, as shown in scheme II.

SCHEME II



By reaction of 5,7-dimethoxyindole with oxalyl chloride in ether the corresponding indolylglyoxalyl chloride was obtained which without isolation was immediately treated with ammonium hydroxide, methylamine or dimethylamine to give the more stable glyoxamides (VIII, IX and X). By reduction of these glyoxamides with LAH in tetrahydrofuran the tryptamines XI, XII and XIII were

obtained. *N,N*-Dimethyl-5,7-dimethoxytryptamine (XIII) was purified by sublimation and the remaining tryptamines (XI and XII) formed crystalline oxalates.

In view of the anomalous behaviour of 4,6-dimethoxyindole toward electrophilic substitution (9) care has been taken to demonstrate that in 5,7-dimethoxyindole, oxalylation had occurred at C-3 rather than in the benzenoid ring.

The nmr spectrum of 5,7-dimethoxyindole (deuteriodimethylsulfoxide) showed, in its aromatic region, signals at δ 6.42 (2H, multiplet, C-3H and one of the aromatic protons), 6.76 (doublet, one of the aromatic protons) and 7.30 (triplet, C-2H); the glyoxamide VIII showed signals at δ 6.62 (1H, doublet), 7.50 (1H, doublet), 7.78 and 8.13 (each 1H, broad signals, $-NH_2$), 8.63 (1H, doublet) and 12.45 (1H, broad signal, NH); by adding deuterium oxide an interesting change was observed in this nmr spectrum. The broad signals at δ 7.78, 8.13 and 12.45 disappeared and the doublet centered at 8.63 became a sharp singlet; this result clearly indicated that the doublet at δ 8.63 corresponds to C-2H and the doublets at δ 7.50 and 7.78 (*meta* coupling) to the benzenoid ring protons. If substitution had taken place at the benzenoid ring no doublets should be observed, the C-2H and C-3H protons should continue to appear as triplets and the aromatic proton (C-4H or C-6H) should become a singlet.

Treatment of VII with formaldehyde and dimethylamine afforded 5,7-dimethoxygramine (XIV). The nmr spectrum of XIV showed three doublets at δ 6.32, 6.70 and 6.98 as expected for a 3-substituted 5,7-dimethoxyindole.

Attempts to synthesize 4,6-dimethoxyindole by the method described above were unsuccessful. The dimethoxy derivative XV, prepared from 2,4,6-trinitrotoluene (10) by selective reductions of the nitro groups, diazotizations and methylations (11), failed to react with diethyl oxalate with potassium ethoxide in ether to give the corresponding nitrophenylpyruvic acid.

Although preliminary tests showed serotonine-like activity, much work should be done before the whole biological activity of these dimethoxy tryptamines (XI, XII and XIII) is established.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Infrared and ultraviolet spectra were recorded on Beckman IR 20A and Beckman DB-G spectrophotometers, respectively. The nuclear magnetic resonance spectra were obtained using a Varian A60 spectrometer using tetramethylsilane as internal reference, at the Departamento de Quimica Organica, Facultad de Ciencias, Universidad de Buenos Aires.

2-Nitro-3,5-dihydroxytoluene (III) (4,5).

Nitric acid (12.6 ml., sp. gr. 1.50) was added gradually to a well stirred solution of I (49 g.) in ether (1700 ml.), the temperature being kept at 0°. After the addition, the mixture was refluxed 45 minutes. The solvent was then removed under reduced pressure to leave a red residue which was steam-distilled. From the steam distillate, II (2.67 g.) separated as orange needles, m.p. 127-128° [lit. (4,5) m.p. 126-127°]. The remaining aqueous mixture was thoroughly extracted with ether. The dried ether extracts (sodium sulfate) were evaporated to dryness *in vacuo* to yield a red semisolid (47 g.) which was used directly in the next step.

2-Nitro-3,5-dimethoxytoluene (IV).

Dimethyl sulphate (66.5 ml.) was added with stirring to a refluxing mixture of III (crude material, 47 g.) and anhydrous potassium carbonate (150 g.) in acetone (600 ml.) over 30 minutes. After refluxing for an additional 30 minutes, water (400 ml.) was added and the acetone was evaporated under reduced pressure to yield a black tarry solid which was filtered, washed with cold water and dried. This product was purified by chromatography on alumina (200 g.) using benzene and benzene-dichloromethane mixtures for elution. A well defined yellow fraction was collected and by evaporation of the solvent under reduced pressure a yellow solid was obtained. Crystallization from benzene-petroleum ether gave IV as pale-yellow crystals (29 g., 37%, based upon the starting orcinol) m.p. 106-107° [lit. (6) m.p. 106°]; nmr (deuteriochloroform) δ 2.28 (3H, singlet, $-CH_3$), 3.81 and 3.83 (6H, 2 OCH_3) and 6.36 (2H, singlet, aromatic protons).

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.83; H, 5.80; N, 6.88.

5,7-Dimethoxyindole-2-carboxylic Acid (VI).

To a solution of dry ether (500 ml.) and absolute ethanol (12 ml.) potassium (3.6 g.) was added and the mixture was stirred until all the potassium dissolved; diethyl oxalate (9.4 ml.) was then added, followed after a few minutes by 2-nitro-3,5-dimethoxytoluene (IV) (12 g.); and the mixture was stirred for 72 hours at room temperature. Water (100 ml.) and benzene (100 ml.) were then added to the red potassium enolate (V) suspension and the organic layer was extracted with 14% ammonium hydroxide until the aqueous extract was almost colorless. The organic layer was dried (sodium sulfate) and evaporated under reduced pressure to yield the starting material IV (4.6 g.), m.p. 105-107°. Ammonium hydroxide (sp. gr. 0.91; 24 ml.) was added to the combined aqueous extracts and with vigorous stirring a hot ferrous sulphate ($FeSO_4 \cdot 7H_2O$) solution (100 g. in 160 ml. of water) was added and the mixture heated at 70-80° on a water-bath for 30 minutes; after refluxing for an additional 30 minutes and while the reaction mixture was still hot, it was filtered. The ferric oxide sludge was boiled five times with 4% ammonium hydroxide (200 ml. per time). The combined filtrates were decolorized with charcoal at 50° and concentrated at reduced pressure. Acidification of the cold concentrate with 5% sulphuric acid yielded a pale yellow solid (7.5 g.), m.p. 212-213°. Crystallization from ethanol gave VI (6.4 g., 48%, based upon the starting dimethoxy derivative IV) m.p. 214-215°; uv (95% ethanol) λ max 234 mμ (log ε = 4.96), 287 (4.81), 325 (4.11); ir cm^{-1} (potassium bromide), 3320 (NH), 1680 (COOH).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.57; H, 5.11; N, 6.60.

By treatment of VI with an ethereal solution of diazomethane the corresponding methyl ester was prepared which without purification gave the following nmr spectrum in deuteriochloroform: δ 3.83 (3H, singlet, OCH_3), 3.91 (6H, singlet, 2 OCH_3), 6.45 (1H,

doublet), 6.65 (1H, doublet) and 7.11 (1H, doublet).

5,7-Dimethoxyindole (VII) (7).

The crude acid (VI, 3 g.) was suspended in water (100 ml.) containing hydrochloric acid (1 ml.) and barium chloride (50 mg.) and extracted with three (40 ml.) portions of ether. The combined ether extracts were washed with water until free from sulphate, dried (calcium chloride) and evaporated to dryness *in vacuo* to yield 5,7-dimethoxyindole-2-carboxylic acid (2.25 g.) m.p. 213-214°.

A mixture of the sulphate-free acid (1.97 g.) and copper chromite (200 mg.) (12) suspended in redistilled quinoline (10 ml.) was heated in an oil-bath at 210-215° (internal temperature) for 2 hours. The reaction mixture was allowed to come to room temperature and poured into water (100 ml.) and thoroughly extracted with ether. The combined ether extracts were washed with 2 *N* hydrochloric acid, 2 *N* sodium bicarbonate and water, dried (sodium sulfate) and concentrated *in vacuo*. The tarry solid residue was sublimed at 70° (3 mm.) giving VII as colorless crystals (920 mg., 58%) m.p. 82° [lit. (3) m.p. 159-160°]; uv (methanol) λ max 220 mμ (log ε = 4.80), 265 (3.86), 291 (3.59); ir cm^{-1} (potassium bromide) 3360 (NH); nmr (deuteriochloroform) δ 3.84 and 3.89 (each 3H, OCH_3), 6.48 (2H, multiplet, C-3H and one of the aromatic protons), 6.75 (doublet, one aromatic proton), 7.12 (triplet, C-2H), 8.37 (NH); the nmr spectrum in deuteriodimethylsulfoxide showed the following signals in the aromatic region: δ 6.42 (2H, multiplet, C-3H and one of the aromatic protons), 6.76 (doublet, one of the aromatic protons) and 7.30 (triplet, C-2H).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.61; H, 6.39; N, 8.11.

5,7-Dimethoxy-3-indolylglyoxamide (VIII).

To a cold stirred solution of VII (567 mg.) in dry ether (10 ml.) was added dropwise oxalyl chloride (1 ml.). The mixture was stirred at room temperature for 30 minutes during which time the indolyl glyoxalyl chloride deposited as a red solid. The suspension of the acid chloride was then added to an ice cold ammonium hydroxide solution (14 ml., sp. gr. 0.91). After the addition was complete, stirring was continued for 30 minutes at 40°. After cooling, the resulting mixture was filtered, washed with water and dried to give VIII (750 mg., 95%). An analytical sample was recrystallized from ethanol, m.p. 219-220°; ir cm^{-1} (potassium bromide), 3440, 3360 and 3280 (NH stretch), 1710 (CO), 1630 (CO); nmr (deuteriodimethylsulfoxide) δ 3.87 and 4.00 (each 3H, OCH_3), 6.62 (1H, doublet), 7.50 (1H, doublet), 7.78 and 8.13 (each 1H, broad signals, NH_2), 8.63 (1H, doublet) and 12.45 (1H, broad signal, NH). By adding a few drops of deuterium oxide the signals at δ 7.78, 8.13 and 12.45 disappeared and the doublet centered at 8.63 became a sharp singlet.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.30; H, 5.14; N, 11.56.

5,7-Dimethoxy-3-indolyl-*N*-methylglyoxamide (IX).

The procedure used to prepare IX was the same as described above for compound VIII. From 5,7-dimethoxyindole (1.34 g.) 5,7-dimethoxy-3-indolyl-*N*-methylglyoxamide IX was obtained (1.42 g., 91%) m.p. 228-229° (from benzene-ethanol); ir cm^{-1} (potassium bromide), 3380 and 3180 (NH stretch), 1680 (CO), 1630 (CO).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.80; H, 5.63; N, 10.80.

5,7-Dimethoxy-3-indolyl-*N*,*N*-dimethylglyoxamide (X).

The procedure used to prepare X was the same as described above for compounds VIII and IX. From 5,7-dimethoxyindole (1.34 g.) 5,7-dimethoxy-3-indolyl-*N*,*N*-dimethylglyoxamide X was obtained (1.81 g., 86%) m.p. 226-227° (from ethanol); ir cm^{-1} (potassium bromide), 3250 (NH), 1660-1630 (broad band, CO).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.09; H, 6.08; N, 10.07.

5,7-Dimethoxytryptamine (XI).

To a suspension of LAH (1 g.) in dry tetrahydrofuran (20 ml.) was added with stirring a solution of VIII (1 g.) in tetrahydrofuran (120 ml.). After refluxing for 16 hours, the mixture was cooled in an ice bath and cautiously treated with cold water (4 ml.) to decompose excess hydride and the reaction complex. The tetrahydrofuran-water solution of the product was filtered from the insoluble inorganic salts, which were washed once with hot benzene (50 ml.). The solutions were evaporated *in vacuo* to give an oily residue which was dissolved in ether (30 ml.). The ether was dried (sodium sulfate) and evaporated to leave a clear syrup (412 mg.) which was dissolved in a small amount of ethanol and treated with oxalic acid. The oxalate was filtered and recrystallized from ethanol-water (390 mg.) m.p. 170-171°.

Anal. Calcd. for $C_{14}H_{18}N_2O_6 \cdot 1\frac{1}{2}H_2O$: C, 49.85; H, 6.23; N, 8.30. Found: C, 50.12; H, 6.28; N, 8.59.

N-Methyl-5,7-dimethoxytryptamine (XII).

The procedure used to prepare XII was the same as described above for compound XI. From 5,7-dimethoxy-3-indolyl-*N*-methylglyoxamide IX (900 mg.) *N*-methyl-5,7-dimethoxytryptamine XII was obtained (721 mg.) as an oil which was crystallized as oxalate (650 mg.) m.p. 197-198° dec. (from methanol).

Anal. Calcd. for $C_{15}H_{20}N_2O_6$: C, 55.55; H, 6.22; N, 8.64. Found: C, 55.80; H, 6.05; N, 8.90.

N,*N*-Dimethyl-5,7-dimethoxytryptamine (XIII).

The procedure used to prepare XIII was the same as described above for compounds XI and XII. From 5,7-dimethoxy-3-indolyl-*N*,*N*-dimethylglyoxamide X (700 mg.) *N*,*N*-dimethyl-5,7-dimethoxytryptamine XIII was obtained (390 mg.). The analytical sample was obtained by sublimation at 100° (0.05 mm.) m.p. 118-119°.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.76; H, 8.41; N, 11.43.

5,7-Dimethoxy-3-dimethylaminomethylindole (5,7-Dimethoxygramine, XIV) (13).

To a stirred mixture of dioxane (4 ml.), acetic acid (4 ml.), 36% aqueous formaldehyde (0.32 ml.) and 12% aqueous dimethylamine (1.8 ml.) at 0° was added dropwise 5,7-dimethoxyindole (709 mg.) in dioxane (4 ml.) over 30 minutes. The solution was stirred for an additional 2 hours at 0° and allowed to stand overnight at room temperature. After cooling in an ice-bath it was alkalized with 10% sodium hydroxide and the suspension was cooled at 5° for several hours. The resulting precipitate was filtered and dried giving XIV (480 mg., 36%) m.p. 118-119°; nmr (deuteriochloroform) δ 2.28 (6H, singlet, $N(CH_3)_2$), 3.57 (2H, singlet, CH_2), 3.81 and 3.87 (6H, singlets, 2 OCH_3), 6.32 (1H, doublet), 6.70 (1H, doublet), 6.98 (1H, doublet) and 8.58 (1H, broad signal, NH). Recrystallization from aqueous ethanol gave an analytical sample, m.p. 121-122°.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.90; H, 8.12; N, 11.81.

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REFERENCES

(1) S. H. Snyder and C. R. Merril, *Proc. Natl. Acad. Sci. U. S.*, 54, 258 (1965).

(2) S. H. Snyder and E. Richelson, *ibid.*, 60, 206 (1968).

(3) O. Süs, M. Glos, K. Müller and H. D. Eberhardt, *Ann. Chem.*, 583, 150 (1953).

(4) F. Henrich and W. Meyer, *Ber.*, 36, 885 (1903).

(5) H. Musso and H. Beecken, *ibid.*, 92, 1416 (1959).

(6) H. Musso, *ibid.*, 91, 349 (1958).

(7) H. N. Rydon and J. C. Tweddle, *J. Chem. Soc.*, 3499 (1955).

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

(9) V. H. Brown, W. A. Skinner and J. I. DeGraw, *J. Heterocyclic Chem.*, 6, 539 (1969).

(10) Kindly supplied by Direccion General de Fabricaciones Militares, Ministerio de Defensa Nacional.

(11) M. Pailer and P. Bergthaller, *Monatsh. Chem.*, 98, 57° (1967).

(12) H. Adkins and R. Connor, *J. Am. Chem. Soc.*, 53, 1091 (1931).

(13) A. Ek and B. Witkop, *ibid.*, 76, 5579 (1954).

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