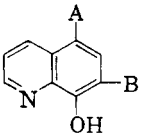
TABLE I

DERIVATIVES OF 5-CARBOXY-8-QUINOLINOL



Compound	A	B	M.P., °C.	Form	Solvent	Formula	Nitrogen Calcd.	Nitrogen Found
I[a]	$-COOC_4H_9$	H	83	Slightly yellow rhombs	EtOH	$C_{14}H_{15}NO_3$	5.71	5.52
II[b]	$-COOC_2H_5$	$-NO_2$	285 (dec.)	Yellow needles	C_6H_6	$C_{12}H_{10}N_2O_5$	10.69	10.30
III[b]	$-COOC_4H_9$	$-NO_2$	220 (dec.)	Yellow columns	C_6H_6	$C_{14}H_{14}N_2O_5$	9.66	10.12
IV[c]	$-COOC_2H_5$	$-NH_2$	132–132.5	Garnet colored needles	Ether	$C_{12}H_{12}N_2O_3$	12.07	12.05
V[c]	$-COOC_4H_9$	$-NH_2$	139–140	Garnet colored columns	Ether	$C_{14}H_{16}N_2O_3$	10.77	10.81
VI[d]	IV Dihydrochloride		254 (dec.)	Orange needles	Dil. HCl	$C_{12}H_{12}N_2O_3 \cdot 2HCl$	9.18	8.76
VII[d]	V Dihydrochloride		211 (dec.)	Orange columns	Dil. HCl	$C_{14}H_{16}N_2O_3 \cdot 2HCl$	8.41	8.94
VIII[e]	$-COOC_2H_5$	$-NH^1COCH_3$	192	Slightly pink needles	C_6H_6	$C_{14}H_{14}N_2O_4$	10.22	10.24
IX[e]	$-COOC_4H_9$	$-NH^1COCH_3$	185–186	Slightly pink needles	C_6H_6	$C_{16}H_{18}N_2O_4$	9.27	9.41
X[f]	$-CONH^1NH_2$	H	268 (dec.)	Colorless needles	MeOH	$C_{10}H_9N_3O_2$	20.69	20.32
XI[d]	I Hydrochloride		239–240 (dec.)	Colorless needles	Dil. HCl	$C_{14}H_{15}NO_3 \cdot HCl$	4.97	5.20

[a] Made by heating a mixture of 5-carboxy-8-quinolinol (1.14 g.), butanol (5 ml.) and concentrated sulfuric acid (0.6 g.) at 120° for 16 hr. until clear dissolution effected, adding water and sodium acetate (2 g.) to the solution, removing butanol by steam distillation, dissolving the residual oil which soon solidified, in dilute hot hydrochloric acid (250 ml.) (just acid to congo red), filtering from dark green amorphous matter and precipitating the free ester (1.08 g., 73%) by sodium carbonate.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.12. Found: C, 68.14; H, 6.37.

[b] Made by heating a mixture of the corresponding ester (0.001 mol.) and 10% nitric acid (4 ml.) at 80° with stirring for 1 hr., yield 88% II and 84% III. [c] Made by stirring a mixture of the corresponding nitro compound (0.001 mol.), ethanol (10 ml.) 2% ammonium hydroxide (14 ml.) and sodium hydrosulfite (2 g.) for 1 hr. at room temperature, removing ethanol by evaporation on a water bath and filtering the resulting crystals on cooling, yield 60% IV and 80% V. [d] Made by concentrating a solution of the corresponding base in dilute hydrochloric acid *in vacuo* over potassium hydroxide at room temperature until crystals began to separate. [e] Made by adding acetic anhydride (0.11 g.) and freshly fused sodium acetate (0.25 g.) to a solution of the corresponding amine (0.001 mol.) in ether (65 ml.), letting the mixture stand at room temperature for 4 days, then evaporating the ether and washing the residue with water in almost quantitative yield. [f] Made by heating a mixture of I (0.25 g.) and 80% hydrazine hydrate (0.5 g.) at 100° for 13 hr. and washing the product with cold benzene, yield 59%.

for 1 hr., phosphorus oxychloride removed *in vacuo* and the residue treated with cold acetone (60 ml.) which had been saturated with ammonia at 0°. The reaction product on treating with dilute ammonia, 0.72 g. of 5-carboxy-8-quinolinol was recovered and the crude XII, when purified through the hydrochloride and finally recrystallized from 90% ethanol gave colorless glistening plates, m.p. 275–276° (dec.),[2] yield 0.32 g. It gives a deep green color with ferric chloride.

Anal. Calcd. for $C_{10}H_8N_2O_2$: N, 14.89. Found: N, 14.63.

On heating 5 hr. instead of 1 hr., the reaction product, on recrystallization from ethanol gave XII (0.17 g.) and from the filtrate of recrystallization XIII (0.4 g.) respectively. XIII gave colorless columns, m.p. 230–231° and no color reaction with ferric chloride.

Anal. Calcd. for $C_{10}H_7ClN_2O$: C, 58.11; H, 3.39; Cl. 17.19. Found: C, 57.91; H, 2.91; Cl, 17.27.

The picrate crystallized from ethanol as plates, m.p. 200–202°.

Anal. Calcd. for $C_{10}H_7ClN_2O \cdot C_6H_3N_3O_7$: N, 16.07. Found: N, 15.51.

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(2) Lit. m.p. 264–265° (dec.). G. R. Clemo and R. Howe, *J. Chem. Soc.*, **1955**, 3552.

Synthesis of *N*-Acetyl-5-methoxytryptamine

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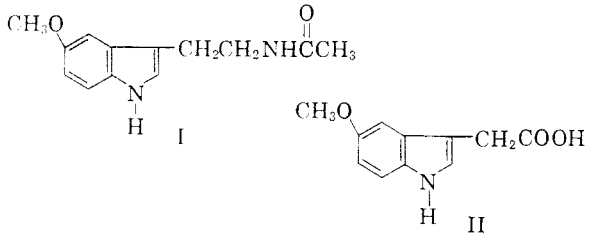
Lerner has reported the isolation[1] from pineal glands and peripheral nerves of an indole derivative, melatonin, which is the most potent agent

(1) A. B. Lerner, J. D. Case, Y. Takahashi, T. H. Lee, and W. Mori, *J. Am. Chem. Soc.*, **80**, 2587 (1958).

known in lightening frog skin. Melatonin and an inactive indole accompanying it in the isolation procedure have since been reported[2,3] to have the structures, 5-methoxy-*N*-acetyltryptamine (I) and 5-methoxyindole-3-acetic acid (II), respectively.

5-Methoxytryptamines seem to be of rare occurrence in nature, the only case we could find being 5 - methoxy - *N* - methyltryptamine, isolated from the grass *Phalaris arundinacea L.*[4]

The infrared spectrum of the methyl ester of naturally occurring II was found to be identical with that of the methyl ester of synthetic II described in the present paper. However, even though the evidence[3] for structure I is quite convincing, it has not been possible to characterize melatonin completely due to its availability from pineal glands in only microgram quantities and in an impure state.



In the present paper we would like to report the synthesis of I by two previously unreported routes. This material has the full activity of natural melatonin when tested on the frog skin.[5]

Previously, 5-methoxytryptamine has been prepared by reaction of *p*-methoxyphenylhydrazine with γ-aminobutyraldehyde diethyl acetal and zinc chloride,[6,7] from 5-methoxyindolemagnesium iodide and chloroacetonitrile[8] followed by reduction with sodium and alcohol,[9,10] and from *p*-methoxyphenyldiazonium chloride and 3-carbethoxy-2-piperidone followed by ring opening and decarboxylation.[11]

5-Methoxy-*N*-acetyltryptamine was used by Späth and Lederer[6] as an intermediate for the preparation of 10-methoxy-3-methyl-5,6-dihydro-4-carbolin, but it was neither purified nor characterized.

Our syntheses were chosen primarily because of the availability of appropriate starting materials. In the first synthesis 5-methoxyindole was converted to the corresponding gramine derivative, followed by displacement with cyanide, lithium aluminum hydride reduction, and acetylation. In the second synthesis, 5-methoxyindole-3-aldehyde was condensed with nitromethane and the resulting unsaturated nitro compound was reduced with lithium aluminum hydride and acetylated.

In connection with the identification of the second pineal-extract product II, we have repeated the preparation of 5-methoxyindole-3-acetic acid according to the literature[7] and converted it to its crystalline methyl ester. Previously II was prepared by alkaline hydrolysis of 5-methoxyindole-3-acetonitrile[12,13] and by the Japp-Klingeman method.[14] It was reported as a urinary excretion product of 5-methoxytryptamine in rats.[15]

EXPERIMENTAL

All melting points (capillary) are uncorrected. Ultraviolet spectra (in mμ) were determined in 95% ethanol using a Cary spectrophotometer, Model 14. Infrared spectra (in $cm.^{-1}$) were determined in Nujol using a Perkin-Elmer recording infrared spectrophotometer, Model 21.

5-Methoxyindole was purchased from Regis Chemical Co., Chicago, Ill.

5-Methoxygramine was prepared according to Cook[16]; m.p. 124–125° (lit., m.p. 124–125°); ultraviolet spectrum mμ (ε): 212 (29,850); 274 (6,250); 295 (4,950); f. 306 (3,700); infrared spectrum: NH: 3200 sh., 3090; *tert.* amine: 2800, 2770 sh.; C=C: 1625, 1590, 1545, 1490; C—O: 1250, 1220, 1070, 1038; aromatic substitution: 854, 830, 750.

5-Methoxyindole-3-acetonitrile was prepared according to the method used previously for the synthesis of indole-3-acetonitrile.[17] A solution of potassium cyanide (27.2 g.; 0.42 mole) in 55 ml. of water was added to a solution of 5-methoxygramine (43 g.; 0.21 mole) in 550 ml. of methanol. Methyl iodide (71 g.; 0.502 mole) was then added during 10 min., keeping the temperature below 20°. The reaction mixture was then stirred at 20–25° for 16 hr. The resulting suspension was evaporated at 35–40°. Water (300 ml.) and ether (500 ml.) were added and the suspension was filtered to give 25.9 g. of a colorless solid which proved to be impure tetramethylammonium iodide (infrared spectra). It was recrystallized from methanol, m.p. >320°.

Anal. Calcd. for $C_4H_{12}IN$: C, 23.89; H, 6.02; I, 63.12; N, 6.97. Found: C, 24.42; H, 6.25; I, 62.71; N, 6.92.

The ultraviolet (λ_{max} 219, ε 13,900) and infrared spectra were identical with those of an authentic sample of tetramethylammonium iodide.

The filtrate was separated into two layers and the ethereal solution was washed with 5% hydrochloric acid (4 × 100

(2) A. B. Lerner, J. D. Case, K. Biemann, R. V. Heinzelman, J. Szmuszkovicz, W. C. Anthony, and A. Krivis, *J. Am. Chem. Soc.*, **81**, 5264 (1959).

(3) A. B. Lerner, J. D. Case, and R. V. Heinzelman, *J. Am. Chem. Soc.*, **81**, 6084 (1959).

(4) S. Wilkinson, *J. Chem. Soc.*, 2079 (1958).

(5) The comparison of natural melatonin and I in the frog skin test was carried out by Dr. A. B. Lerner, Yale University School of Medicine.

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(7) T. Hoshino and T. Kobayashi, *Ann.*, **516**, 81 (1935).

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(9) H. Wieland, W. Konz, and H. Mittasch, *Ann.*, **513**, 1 (1934).

(10) B. Asero, V. Coló, V. Erspamer, and A. Vercellone, *Ann.*, **576**, 69 (1952).

(11) R. A. Abramovitch and D. Shapiro, *Chem. & Ind. (London)*, 1255 (1955).

(12) T. Hoshino and K. Shimodaira, *Bull. Chem. Soc., Japan*, **11**, 221 (1936). *Chem. Abstr.*, **30**, 5982[9] (1936). These authors also reported the ethyl ester, m.p. 97–98°.

(13) B. Asero, V. A. Coló, and A. Vercellone, *Il Farmaco (Pavia) Ed. Sci.*, **11**, 219 (1956); *Chem. Abstr.*, **50**, 13870[e] (1956).

(14) S. P. Findlay and G. Dougherty, *J. Org. Chem.*, **13**, 560 (1948).

(15) V. Erspamer, *J. Physiol. (London)*, **127**, 118 (1955).

(16) J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.*, 1203 (1951).

(17) M. B. Henbest, E. R. H. Jones, and G. F. Smith, *J. Chem. Soc.*, 3796 (1953).

ml.). A gummy impurity separated and after a few minutes was easily removed by decantation. The ether layer was washed in succession with water, sodium bicarbonate solution, water, and saturated salt solution and dried through sodium sulfate to give 25 g. (64% crude yield) of the nitrile as a yellow oil; ultraviolet spectrum: 218 (27,350); 273 (6,500); 295 (4,750); 306 (3,800); infrared spectrum: C≡N: 2240 (m); 2800? (w).

5-Methoxytryptamine. A solution of the crude 5-methoxyindole-3-acetonitrile (19 g., 0.102 mole) in 200 ml. of ether was added during 10 min. to a solution of lithium aluminum hydride (19 g.) in 1200 ml. of ether under nitrogen.

The resulting thick suspension was refluxed for 3 hr. and allowed to stand overnight. The mixture was cooled in ice and decomposed in succession with 20 ml. of water, 20 ml. of 15% aqueous sodium hydroxide, and 60 ml. of water. The resulting suspension was filtered and the cake washed well with ether.

The colorless filtrate was extracted with 5% hydrochloric acid (5 × 100 ml.). Some gummy material precipitated and was easily removed by decantation. The clear yellow extract was cooled in ice and made basic with 30% potassium hydroxide. The resulting oil was extracted three times with ether (total 500 ml.). The ether was washed with water followed by saturated salt solution; it was then dried through sodium sulfate and evaporated under reduced pressure to give a yellow solid, m.p. 119–122° (13.5 g.; 70% yield). Crystallization from benzene gave pale yellow prisms, m.p. 121.5–122.5° (lit.,[9] m.p. 121–122°); ultraviolet spectrum: 223 (25,250); 277 (6,300); 296 (5,050); f 308 (3,450); infrared spectrum: NH: 3310, 3250, 3080; aromatic C=C: 1620, 1585, 1495; C—O: 1240, 1220; aromatic substitution: 860, 850, 813, 793.

N-Acetyl-5-methoxytryptamine (I). 5-Methoxytryptamine (7.6 g.) was added to 35 ml. of acetic anhydride at room temperature. The resulting brown solution became warm and was allowed to stand under nitrogen for 23 hr. Water (200 ml.) was added and the mixture was stirred for 0.5 hr. It was then cooled in ice and neutralized partially by addition of solid sodium carbonate (28 g.). The resulting suspension was filtered and the solid washed with water. It was crystallized from benzene to give 7.6 g. (81.5% yield) of pale yellow leaflets, m.p. 116–118° unchanged on further recrystallization; ultraviolet spectrum: 223 (27,550); 278 (6,300); f. 297 (5,150); f. 308 (3,500); infrared spectrum: NH: 3240; C=O: amide I, 1627; amide II, 1555; aromatic C=C: 1620, 1587, 1492; C—O: 1217, 1180; aromatic substitution: 828, 810, 800.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.27; H, 6.79; N, 11.89.

5-Methoxy-β-indoleninideniumethyl nitronate. A solution of 22 g. of ammonium acetate, 6.0 ml. of acetic anhydride, and 17.6 ml. of acetic acid was stirred for 20 min. and a mixture of 30.0 g. (0.18 mole) of 5-methoxyindole-3-aldehyde (Regis Chemical Co.), 100 ml. of nitromethane, and 120 ml. of acetic acid was added. The solution was brought to reflux and 14 g. of sodium acetate was added. The mixture was refluxed for 2 hr. while 20 ml. of acetic anhydride was added dropwise. The solution was allowed to cool while 45 ml. of water was added dropwise. The mixture was refrigerated and filtered. After recrystallization from alcohol the product weighed 9.6 g. (25%) and melted at 157–158°; infrared spectra: NH/OH: 3215; C=C: 1612, 1585; $-N\langle^{O}_{OH}$: 1297, 1255, 1212, 979; C—O: 1108, 1074; aromatic substitution: 954, 920, 815, 800, 783, 689; ultraviolet spectrum: 224 (19,700); 283 (9100); f. 292 (8250); f. 302 (6550); 405 (20,200).

Anal. Calcd. for $C\alpha\alpha H_{10}N_2O_3$: C, 60.54; H, 4.61; N, 12.84. Found: C, 60.07; H, 4.30; N, 12.65.

5-Methoxytryptamine. A solution of 6.0 g. (0.027 mole) of the nitronate and 50 ml. of tetrahydrofuran was added dropwise to a refluxing mixture of 5.4 g. (0.14 mole) of lithium aluminum hydride and 100 ml. of tetrahydrofuran. The mixture was refluxed for 4 hr. after the addition was complete. It was then cooled and the excess lithium aluminum hydride was decomposed with wet ether followed by concd. potassium hydroxide solution. The solution was decanted and the residue washed thoroughly with ether and added to the original filtrate. The filtrate was dried over potassium carbonate and concentrated. The residue was dissolved in ethyl acetate, refluxed with Nuchar-190-N, and filtered. An approximately equal volume of Skellysolve B was added and the solution was refrigerated overnight. Filtration yielded 1.3 g. (27%) of product which melted at 115–117°. It was identical with the sample obtained by the gramine procedure (infrared, ultraviolet) and on acetylation gave I.

5-Methoxyindole-3-acetonitrile was prepared from the Grignard derivative with chloroacetonitrile.[8]

5-Methoxyindole-3-acetic acid was prepared by hydrolysis of the crude nitrile with aqueous methanolic potassium hydroxide.[12] The acid melted at 145–146°; ultraviolet spectrum: 221 (25,150); 276 (6,300); 296 (4,800); f. 308 (3,400); infrared spectrum: NH: 3,330; OH (carboxyl): 2640, 2560; C=O: 1690, 1670; C—O: 1215, 1175.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.20; H, 5.13; N, 6.62.

Methyl 5-methoxyindole-3-acetate. 5-Methoxy-3-indoleacetic acid (1.0 g.; 0.005 mole) was suspended in 100 ml. of ether and treated with three equivalents of diazomethane in ether. After 2 hr. 1.0 ml. of acetic acid was added. The solution was washed with water, sodium bicarbonate, and then with water. The solution was dried over potassium carbonate and concentrated to yield a dark red oil. This oil was subjected to distillation and the material boiling below 250°/0.03 mm. was collected. The resulting distillate solidified upon scratching. After crystallization from 50% benzene–Skellysolve B the product weighed 0.4 g. (35%) and melted at 73–74°; ultraviolet spectrum: 219 (25,800); 275 (6,350); f. 295 (4,850); f. 307 (3,500); infrared spectrum: NH: 3350; C=O: 1721; aromatic C=C: 1625, 1591, 1495; C—O: 1250, 1221, 1184, 1100, 1064, 1030; aromatic substitution: 825, 806.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.61; H, 5.83; N, 6.73.

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Tropine DL-α-Methyltropate (Methylatropine) and Its Optical Antipodes

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The loss of physiological activity on the ready racemization of natural *l*-hyoscyamine (I R= H)[1–4] led us to search for more stable active anal-

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