Regis Chemical Company

The Syntheses of 5,6-Dihydroxyindole and Some of its Derivatives (1)

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5,6-Dihydroxyindole (VIa) and its two mono *O*-methyl analogs (VIb,c), and their 2-carboxylic acids (XII), tryptamines (XV), and *N*-acetyltryptamines (XVII) have been synthesized. An improved syntheses of the 5,6-dihydroxyindoles has been developed.

The interest in 5,6-dihydroxyindole and its 2-carboxylic acid is great. They are metabolites of the catecholamines and the catecholamine precursors (2), and they undergo enzymatic *O*-methylation (3). Furthermore they are the basis of tests for melanomas (4), and are the melanin precursors (2). Likewise of wide interest is the study of the metabolism of the ubiquitous serotonin (5-hydroxytryptamine), for which 5,6-dihydroxytryptamine (XVa) (5,6) and 6-hydroxymelatonin (7) (*N*-acetyl-6-hydroxy-5-methoxytryptamine) have been reported to be metabolites.

5,6-Dihydroxyindole.

The syntheses of 5,6-dihydroxyindole and its two mono *O*-methyl analogs have been reported by Beer and co-workers (8,9). However, their procedures are not amenable to the preparation of the indoles in the larger quantities requried and the *O*-acetyl protected indoles would not serve as intermediates to the tryptamines. It seemed desirable to prepare the *O*-benzyl protected indoles (V), which would be expected to offer stable intermediates to the highly unstable hydroxyindoles, and would, likewise, be suitable intermediates for the preparations of the tryptamines (XIV).

Examples have appeared in the literature (11,12) of the nitration of 3,4-dialkoxy-β-nitrostyrenes to 4,5-dialkoxy-2,β-dinitrostyrenes, which were reductively cyclized to 5,6-dialkoxyindoles. Therefore, the nitrations of the 3,4-dialkoxy-β-nitrostyrenes (III) were carried out and gave the corresponding 4,5-dialkoxy-2,β-dinitrostyrenes (IV) in high yield. The dinitrostyrenes (IV) could be used without further purification.

As proof that the desired nitration had taken place, samples of IVa and IVb were prepared by the procedure of Schlossberger and Kuch (13), from 6-nitropyrocatechuic aldehyde (14) and 6-nitrovanillin (15). The dinitrostyrenes prepared here were judged to be identical with those previously prepared on the basis of infrared spectra, thin layer chromatography, and mixture melting point.

Stable 5,6-dialkoxyindoles (V) were obtained by a standard iron and acetic acid ring closure. Treatment of V with hydrogen in the presence of palladium on charcoal gave the corresponding hydroxyindoles VI.

5,6-Dihydroxyindole-2-carboxylic Acid.

In a manner similar to the preparation of the above dinitrostyrenes (III), the analogous 3,4-dialkoxytoluenes (VIII) were nitrated to the corresponding 4,5-dialkoxy-2-nitrotoluenes (IX) (see Chart 2). Condensation of the *ortho*-nitrotoluenes (IX) with diethyl oxalate in the presence of potassium ethoxide produced the 2-nitrophenylpyruvic acids (X), which were reductively cyclized to their respective 5,6-dialkoxyindole-2-carboxylic acids (XI). The hydroxyindolecarboxylic acids (XII) were obtained by debenzylation of XI with hydrogen in the presence of palladium on carbon.

5,6-Dihydroxytryptamines.

The syntheses of the 5,6-dialkoxytryptamines (XIV) were accomplished by the lithium aluminum hydride reductions of the indole-3-glyoxylamides (XIII), as outlined in Chart 3.

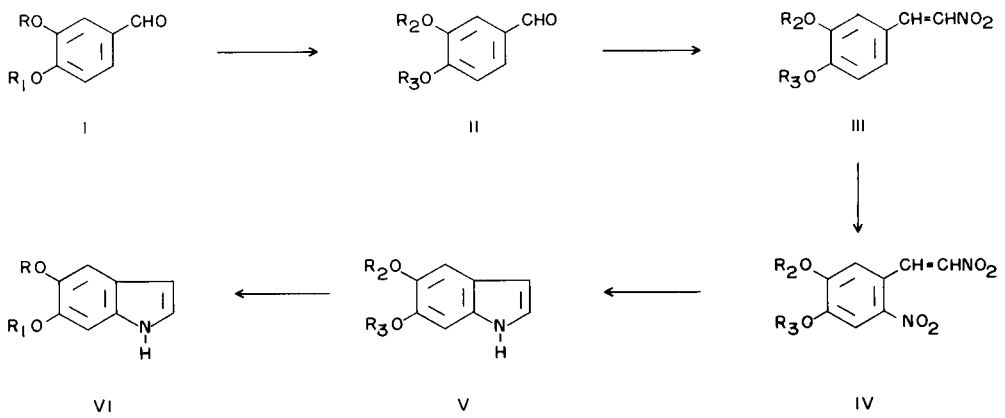
5,6-Dibenzyloxytryptamine (XIVa) was isolated as its hydrogen oxalate salt, however, difficulties were encountered in characterizing 5,6-dihydroxytryptamine (XVa) and purifying 6-benzyloxy-5-methoxytryptamine (XIVb) as its hydrogen oxalate salt. Therefore, formate salts were prepared for the isolation and characterization of these tryptamines.

Debenzylation of the tryptamine formate salts (XIV) produced the corresponding hydroxytryptamine formate salts (XV). 5,6-Dihydroxytryptamine formate (XVa) was found to be hygroscopic and quite difficult to characterize. Indeed the material possessed very low stability even in the solid state. 5-Hydroxy-6-methoxytryptamine formate (XVc) was found to be dimorphic, having melting points of 136-138° and 71-73°. The two samples gave correct elemental analyses and were found to be identical with respect to thin layer chromatography and ultraviolet spectra. The infrared spectra of the two samples in potassium bromide did possess minor differences.

Liberation of the benzylated tryptamines (XIV) from their formate salts, followed by treatment with acetic anhydride, provided the corresponding *N*-acetyltryptamines (XVI). Hydrogenolysis of the *N*-acetyltryptamines (XVI) in the presence of palladium on charcoal yielded the corresponding hydroxy-*N*-acetyltryptamines (XVII). *N*-Acetyl-5,6-dihydroxytryptamine (XVIIa), like 5,6-dihydroxy-

tryptamine formate (XVa), was found to be hygroscopic and unstable to light and air. A sample of the material was isolated and characterized as a stable 1,4-diazabicyclo(2.2.2)octane salt.

CHART 1



Where I and VI

a) $R = R_1 = H$

b) $R = CH_3$, $R_1 = H$

c) $R = H$, $R_1 = CH_3$

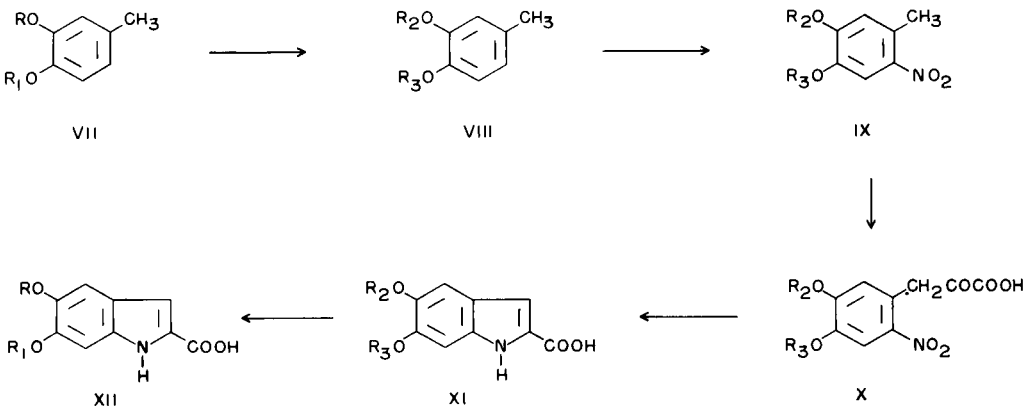
II – V

$R_2 = R_3 = \phi CH_2$

$R_2 = CH_3$, $R_3 = \phi CH_2$

$R_2 = \phi CH_2$, $R_3 = CH_3$

CHART 2



Where VII and XII

a) $R = R_1 = H$

b) $R = CH_3$, $R_1 = H$

c) $R = H$, $R_1 = CH_3$

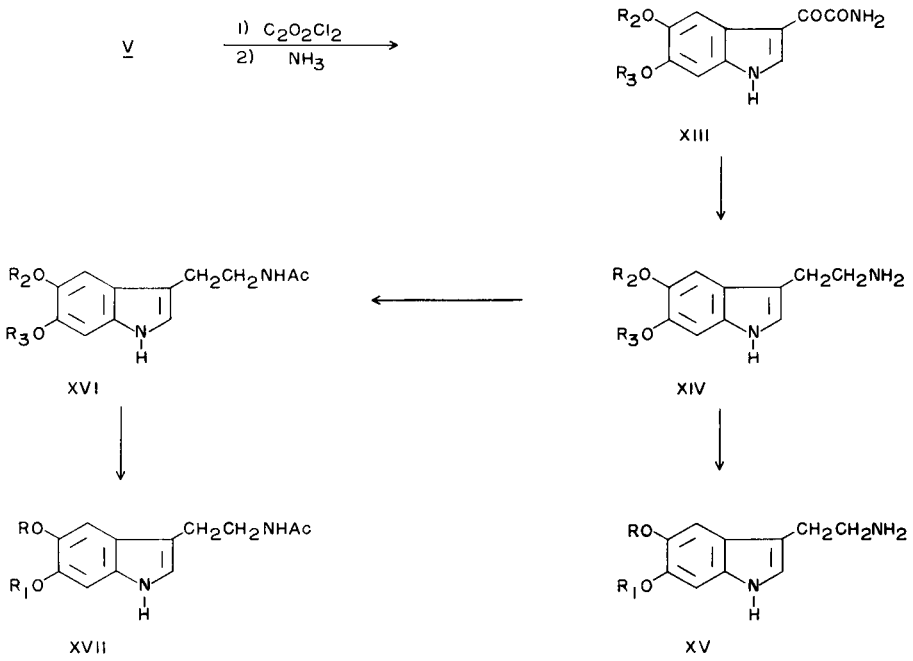
VIII – XI

$R_2 = R_3 = \phi CH_2$

$R_2 = CH_3$, $R_3 = \phi CH_2$

$R_2 = \phi CH_2$, $R_3 = CH_3$

CHART 3



Where V, XIII, XIV, and XVI

a) $R_2 = R_3 = \phi CH_2$

b) $R_2 = CH_3, R_3 = \phi CH_2$

c) $R_2 = \phi CH_2, R_3 = CH_3$

XV and XVII

$R = R_1 = H$

$R = CH_3, R_1 = H$

$R = H, R_1 = CH_3$

XIV and XV isolated as formate salts

XVIIa isolated as 1,4-diazabicyclo(2.2.2)octane salt

TABLE I

Intermediates to 5,6-Dialkoxyindoles (II-IV) and Their 2-Carboxylic Acids (VIII-X)

Compound	% Yield	m.p.	lit. m.p.	Analyses Calculated C	H	N	Found C	H	N
IIa	83	87-89	89-91 (16)						
IIb	110	63-64	64.5 (20)						
IIc	91	63-64	63.5 (20)						
IIIa	71	118-119	118-119 (17)						
IIIb	68	121-122	124-125 (21)						
IIIc	73	129-130	129 (20)						
IVb	72	170-173 (a)		58.18	4.27	8.48	58.55	4.69	8.68
IVc	85	206-208		58.18	4.27	8.48	58.09	4.43	8.53
VIIIa	80	53-54		82.86	6.62		82.70	6.67	
VIIIb	71	46-47	45.6 (22)						
VIIIc	87	55-57		78.91	7.03		78.97	6.97	
IXa	93	153-155	153-154 (13)						
IXb	86	117-118	117-119 (22)						
IXc	85	129-131	131-133 (b)	65.92	5.53	5.13	66.22	5.47	5.13
Xb	54	164-165		59.13	4.38	4.06	58.97	4.18	3.91
Xc	26	158-160	150-153 (19)	59.13	4.38	4.06	59.34	4.40	3.95

(a) Prepared by nitration of IIIb, see Experimental for the preparation from 6-nitrovanillin. (b) See Experimental for the preparation from 4,5-dimethoxy-2-nitrotoluene.

TABLE II

Indoles V, VI, XI, XII

Compound	% Yield	m.p.	lit. m.p.	Analyses Calculated C	H	N	Found C	H	N	Ultraviolet Spectra λ max mμ	ε
Vb	55	148-150		78.86	5.97	5.53	76.28	5.90	5.54	217, 273, 298	31,000, 5,720, 7,840
Vc	50	95-96	96-99 (19)	75.86	5.97	5.53	76.06	6.17	5.74	217, 273, 298	33,200, 5,300, 7,800
VIb	94	111-112	111 (8)							224, 274, 298, 306	12,950, 4,670, 8,400, 7,120
VIc	72	113-114	113 (8)							208, 219, 274, 302	24,100, 23,000, 4,900, 7,360
XIb	35	233-234		68.68	5.09	4.71	68.85	5.20	4.43	212, 298, 313	36,800, 13,750, 17,000
XIc		220-222 dec.	219-222 dec.	68.68	5.09	4.71	68.80	5.38	4.89	215, 294, 313	38,200, 13,000, 17,000
XIIa	77	240 dec.	234 dec.							209, 320	22,400, 16,850
XIIb	78	254-256 dec.		57.96	4.38	6.76	57.90	4.48	6.66	210, 321	24,900, 18,250
XIIc	72	215-217 dec.		57.96	4.38	6.76	58.13	4.42	6.86	209, 299, 315	27,200, 13,000, 14,700

TABLE III

Compounds XIII-XVII

Compound	% Yield	m.p.	Analyses Calculated C	H	N	Found C	H	N	Ultraviolet: (95% EtOH) λ max mμ	ε	Infrared (KBr) μ
XIIa	69	256-257 dec.	63.82	4.28	14.89	63.58	4.46	14.90	252, 259, 292, 332	10,000, 9,800, 15,200, 9,800	2.98, 5.99, 6.13
XIIc	59	232 dec.	66.66	4.97	8.64	66.39	5.06	8.38	214, 250, 258, 292, 332	26,900, 7,280, 7,050, 11,700, 7,500	2.95, 3.1, 5.99, 6.20
XIVa (t, w)	51	145-146	71.74	6.26	6.70	72.03	6.25	6.86	215, 220, 280 infl., 298	40,200, 38,300, 6,700, 8,920	3.1, 3.3-4.5, 6.48
XIVc	38	161-163	66.65	6.48	8.18	66.78	6.64	8.10	219, 278 inflt., 293	32,700, 5,362, 8,600	3.05, 3.3-4.3, 6.45
XVa (t, x)	30	92-95	55.46	5.92	11.76	54.76	6.15	11.59	219, 282, 304	22,200, 5,860, 3,370	
XVc (y)	72	136-138	57.13	6.39	11.11	56.91	6.38	11.37	222, 283 inflt., 299-311	19,800, 4,300, 6,500	
XVIa	90	118-119	75.34	6.32	6.76	75.22	6.30	6.97	217, 225, 300	37,300, 35,800, 8,800	3.0, 6.1
XVIc	91	138-139	70.98	6.55	8.28	71.19	6.48	8.11	224, 299 inflt., 298	31,200, 5,230, 8,000	2.95, 3.01, 6.11
XVIIa (z)		73-76	61.53	6.02	11.96	60.52	6.06	11.50	210, 221, 303	18,000, 18,100, 6,640	
XVIIc	70	162-164	62.88	6.50	11.28	63.09	6.55	11.22	208, 222, 303	24,400, 25,500, 7,900	3.01, 3.2, 6.15

(t) Analyzed as formate salts. (w) Hydrogen oxalate, m.p. 194-196° (dec.) lit. (12) 193-195° (dec.). (y) Dimorphic, m.p. 71-73°. (x) Material hygroscopic and unstable to light and air.
(z) Hygroscopic and unstable to air and light, see experimental for characterization as 1,4-diazabicyclo(2.2.2)octane salt.

EXPERIMENTAL

Melting points were taken on a Hoover Thomas Uni-Melt capillary apparatus and are corrected. Ultraviolet spectra were determined on a Perkin-Elmer recording spectrophotometer Model 202. Infrared spectra were run on a Perkin-Elmer Infracord Model 137. Elemental analyses were performed by either Midwest Microlab, Inc., Indianapolis, Indiana, or Micro-Tech Laboratories, Skokie, Ill.

Benzylation of Benzaldehydes (I).

The hydroxy benzaldehydes were benzylated according to the procedure of Schlossberger and Kuch (13).

Preparation of β-Nitrostyrenes (III). 3,4-Dibenzyloxy-β-nitrostyrene (IIIa).

A solution of 15.9 g. (0.05 mole) of 3,4-dibenzyloxybenzaldehyde (IIa), 9.2 g. (0.15 mole) of nitromethane, 8 g. (0.1 mole) of good quality ammonium acetate, and 80 ml. of acetic acid was stirred and refluxed for 2 hours. The dark solution was allowed to cool to room temperature. A copious yellow solid precipitated which was collected, washed with ethanol and air-dried. The yield of 3,4-dibenzyloxy-β-nitrostyrene (IIIa), m.p. 118-119°, (lit. (17) m.p. 118-119°) was 13 g. (71%). Infrared: ($CHCl_3$) 6.18 μ (C = C); 6.3, 6.4 μ doublet (conjugated aromatic); 6.7-7.55 μ (NO_2); 7.95 μ (aryl ether). The product was nitrated without further purification.

Preparation of 2,β-Dinitrostyrenes (IV). 4,5-Dibenzyloxy-2,β-dinitrostyrene (IVa).

To a stirred suspension of 4.5 g. (0.013 mole) of 3,4-benzyloxy-β-nitrostyrene (IIIa), and 100 ml. of glacial acetic acid was added 25 ml. of fuming nitric acid (d. 1.5). The initial temperature of the mixture was 25°; during the addition of the nitric acid the temperature rose to 35-40°, and solution resulted. The mixture was cooled to 30° and the remainder of the acid added. On stirring 3 hours a yellow solid precipitated. It was poured into water, collected, washed well with water, and air-dried. Recrystallization of the solid from ethanol yielded 4.5 g. (85%) of 4,5-dibenzyloxy-2,β-dinitrostyrene (IVa), m.p. 162-163° (lit. (13) m.p. 162°). Infrared: ($CHCl_3$) 6.6 and 7.5 μ (NO_2), 6.15 μ (C = C), 6.25 and 6.4 μ (conjugated aromatic), and 7.85 μ (aryl ether).

4,5-Dibenzyloxy-2,β-dinitrostyrene (IVa).

This compound was also prepared by the method of Schlossberger and Kuch (13) from 4,5-dihydroxy-2-nitrobenzaldehyde, obtained by the procedure of Parijs (14). The materials prepared by independent routes gave a nondepressed mixed melting point, 163°, and their infrared spectra and thin layer chromatograms indicated they were identical.

Alternate Synthesis of 4-Benzyloxy-5-methoxy-2,β-nitrostyrene (IVb).

6-Nitrovanillin was obtained in 0.3% yield by the nitration of vanillin acetate (15). Benzylation by the usual procedure (13) gave 4-benzyloxy-5-methoxy-2-nitrobenzaldehyde m.p. 123-125° from ethanol.

Anal. Calcd. for $C_{15}H_{13}NO_5$: C, 62.70; H, 4.56; N, 4.88. Found: C, 62.83; H, 4.53; N, 4.91.

4-Benzyloxy-5-methoxy-2,β-dinitrostyrene (IVb) was prepared from the above aldehyde in 67% yield, m.p. 172-173° recrystallized from ethyl acetate. Infrared: ($CHCl_3$) 6.1 μ (C = C); 6.22, 6.35 μ (conjugated aromatic); 6.58, 6.62, 7.45, 7.52 μ (2 NO_2).

Anal. Calcd. for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.55; H, 4.79; N, 8.68.

This material was compared with that prepared by the nitration of IIIb, and gave a non-depressed mixed melting point, and their infrared spectra and thin layer chromatograms indicated they were identical.

Ring Closure of the 2,β-Dinitrostyrenes (IV). 5,6-Dibenzyloxyindole (Va).

To a refluxing mixture of 140 g. (2.5 moles) of iron powder and 500 ml. of glacial acetic acid was added a hot solution of 40 g. (0.098 mole) of 4,5-dibenzyloxy-2,β-dinitrostyrene (IVa) and 700 ml. of glacial acetic acid. The addition was carried out so as to maintain a controlled vigorous reflux. The mixture was refluxed for an additional hour on completion of the addition. The reaction mixture was filtered while hot into a solution of 208 g. of sodium meta bisulfite in 2 l. of water. The filtrate and the inorganic materials were extracted with chloroform. The combined extracts were dried over sodium sulfate, filtered, and evaporated under reduced pressure. The resulting dark oil was filtered through a 250 g. alumina column with 70:20 benzene-chloroform. The eluate was evaporated under reduced pressure to a dark semi-solid, which was taken up in benzene and treated with Filtrol. White crystalline 5,6-dibenzyloxyindole, (Va), 13.0 g. (40%) m.p. 113° (lit. (13) m.p. 115°), was obtained by the addition of hexane. A second crude crop of material (about 4 g.) was obtained by eluting the column with ethyl acetate. A sample was recrystallized to m.p. 113-114°. The bulk of the material was sufficiently pure to use in the next reaction.

Ultraviolet: (95% EtOH) λ max 212, 216, and 298 mμ; ε, 42,500; 51,500; and 8,500, respectively. Infrared: ($CHCl_3$) 2.89 μ (NH).

Debenzylation of 5,6-Dialkoxyindoles V. 5,6-Dihydroxyindole (VIa).

To a Parr low pressure hydrogen bottle was added 1.0 g. (0.0033 mole) of 5,6-dibenzyloxyindole (Va), 0.3 g. of 5% palladium on charcoal, 120 ml. of ethyl acetate, and the mixture was hydrogenated at room temperature for 4 hours, filtered and evaporated under reduced pressure to a red oil. A tan solid resulted on the addition of hexane. The product was taken up in benzene (charcoal) and crystallized by the addition of hexane to the cloud point. The yield of 5,6-dihydroxyindole (VIa), m.p. 142-144° (dec.), (lit. (8) m.p. 140° dec.), was 0.4 g. (89%).

The product was again recrystallized in the same manner to give a white granular material, m.p. 143-144° (dec.).

Ultraviolet: (95% EtOH) λ max 209, 275, and 302 mμ: ε, 18,800; 3,970; and 6,110, respectively. Infrared: (KBr) 2.87 μ broad band (NH and OH).

Chromatography: Thin layer, Silica Gel G, CCl_4-pyridine (7:2), detection, 50% H_2SO_4 and heat, shows a single spot, Rf 0.28.

Anal. Calcd. for $C_8H_7NO_2$: C, 64.43; H, 4.73; N, 9.39. Found: C, 64.43; H, 4.87; N, 8.96.

Benzylation of Toluenes VII.

The benzylations of the hydroxytoluenes VII were accomplished as described above for the hydroxybenzaldehydes I.

Preparation of 4,5-Dialkoxy-2-nitrotoluenes (VIII). 4,5-Dibenzyloxy-2-nitrotoluene (VIIIa).

To a solution of 10 g. (0.033 mole) of 3,4-dibenzyloxytoluene (VIIa) and 100 ml. of acetic acid cooled to 20° was added with stirring 3.5 ml. (0.073 mole) of fuming nitric acid (d. 1.5). The temperature was kept under 30° during the additions. The copious yellow precipitate was stirred 15 minutes and poured into 200 ml. of water. The yellow solid was collected, washed with water, and air-dried. The yield of 4,5-dibenzyloxy-2-nitrotoluene, (VIIIa), m.p. 102-103° was 10.5 g. (93%). Recrystallization from ethanol gave pale yellow needles, m.p. 103-104°, (lit. (13) m.p. 102-103°).

Infrared: ($CHCl_3$) 6.65, 7.58 μ (NO_2); 7.95 μ (aryl ether).

Preparations of 4,5-Dialkoxy-2-nitrophenylpyruvic Acids (X).

These were accomplished by the procedure of Schlossberger and Kuch (13).

5,6-Dialkoxyindole-2-carboxylic Acids (XI). 5,6-Dibenzyloxyindole-2-carboxylic Acid (XIa).

To a refluxing mixture of 17 g. (0.30 mole) of iron powder, 50 ml. of acetic acid, and 50 ml. of ethanol was added a hot solution of 10 g. (0.0238 mole) of 4,5-dibenzyloxy-2-nitrophenylpyruvic acid (Xa), 50 ml. of acetic acid, and 50 ml. of ethanol. The mixture was stirred and refluxed for 1 hour and filtered hot into 200 ml. of water containing 50 g. of sodium meta-bisulfite. The solids and the filtrate were extended with chloroform. The wet chloroform extracts were allowed to stand to permit the product to crystallize. There resulted 5.0 g. of solid, m.p. 180-185° dec. The solid was crystallized from acetic acid with a charcoal treatment giving 3.5 g. (40%) of 5,6-dibenzyloxyindole-2-carboxylic acid (XIa), m.p. 203-205° dec. Recrystallization from ethyl acetate gave white crystals, m.p. 204-206° (lit. (13) m.p. 196-197°).

Ultraviolet: (95% EtOH) λ max 220, 316 mμ; ε, 22,200, 15,700, respectively. Infrared: (KBr) 2.9 μ (NH); broad band 3 μ region (COOH); 6.09 μ (COOH).

Anal. Calcd. for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13. Found: C, 73.85; H, 5.13.

Debenzylation of 5,6-dialkoxyindole-2-carboxylic acids (XI) to the corresponding hydroxy compounds (XII) was accomplished as described above.

Alternate Synthesis of 6-Benzyloxy-4-methoxy-2-nitrotoluene (IXc).

Benzylation of 5-hydroxy-4-methoxy-2-nitrotoluene (18) in the usual manner gave the product (IXc), m.p. 130-131° (lit. (19), m.p. 131-133°). This material was found to be identical with that prepared by the nitration of 3-benzyloxy-4-methoxytoluene (VIIIc).

5,6-Dialkoxyindole-3-glyoxylamides (XIII). 6-Benzyloxy-5-methoxyindole-3-glyoxylamide (XIIIb).

To a solution of 15.0 g. (0.0595 mole) of 6-benzyloxy-5-methoxyindole (Vb), 350 ml. of ether and 300 ml. of tetrahydrofuran at 0° was added 17 g. (0.134 mole) of oxalyl chloride. The mixture was stirred for 15 minutes, diluted with 400 ml. of hexane and the dark solid collected.

The acid chloride was added to a solution of 500 ml. of ether and 50 ml. of ammonia, and the mixture stirred for 45 minutes. The yellow 6-benzyloxy-5-methoxyindole-3-glyoxylamide (XIIIb), which was collected, washed well with water, and air-dried, amounted to 13.5 g. (70%), m.p. 237-238° dec. A sample was recrystallized twice from fifty percent dioxane and water (charcoal) to give yellow needles, m.p. 242-244° dec.

Ultraviolet: (95% EtOH) λ max 213, 252, 259, 292 and 332 mμ: ε, 32,700, 10,000, 9,770, 16,100 and 9,770, respectively. Infrared: (KBr) 2.95, 3.1 μ (NH); 5.99 μ (C = O); 6.20 μ (C = O).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.56; H, 4.95; N, 8.76.

5,6-Dialkoxytryptamines (XIV). 6-Benzyloxy-5-methoxytryptamine Formate (XIVb).

A solution of 13.6 g. (0.358 mole) of lithium aluminum hydride and 600 ml. of dry tetrahydrofuran was allowed to reflux through a Soxhlet extractor containing 10.0 g. (0.031 mole) of 6-benzyloxy-5-methoxyindole-3-glyoxylamide (XIIIb). The mixture was stirred and refluxed for 15 hours. While hot, 19 ml. of water in 50 ml. of tetrahydrofuran was cautiously added to the stirring mixture, and the reaction mixture stirred and refluxed an additional half hour. The inorganic salts were filtered and extracted by boiling with fresh tetrahydrofuran. The combined filtrates were evaporated to an oil, which was taken up in ether and extracted with dilute sodium hydroxide solution. The ether solution was dried and evaporated, and the oil dried by distilling with benzene. The dark oil was taken up in a small amount of chloroform and a few drops of 100% formic acid added to form a crystalline salt. The yield of tan crystalline 6-benzyloxy-5-methoxytryptamine formate (XIVb) was 3.0 g. (32%), m.p. 143°. Recrystallization twice from ethanol-ether gave a crystalline solid, m.p. 155-156°.

Ultraviolet: (EtOH) λ max 222, 297, 279 mμ (inflt.): ε, 29,600, 8,000, 5,270, respectively. Infrared: (KBr) 3.08 μ (NH); broad band 3.3-4.3 μ (amine salt); 6.45 μ (carboxylate).

Anal. Calcd. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.80; H, 6.55; N, 7.98.

Hydroxytryptamines (XV). 6-Hydroxy-5-methoxytryptamine Formate (XVb).

To a 500 ml. Parr low pressure bottle was added 0.8 g. (0.0023 mole) of 6-benzyloxy-5-methoxytryptamine formate (XIVb), 0.32 g. of 5% palladium on charcoal, 130 ml. of ethanol, and the mixture was shaken with hydrogen at room temperature for 4 hours, filtered, and evaporated under reduced pressure. A colorless oil was obtained which was dissolved in a minimum of hot methanol containing a few drops of 100% formic acid. Upon the addition of ether an off-white solid, 0.4 g. (69%), m.p. 207° (dec.), was obtained. Recrystallization twice from ethanol-ether gave an off-white crystalline 6-hydroxy-5-methoxytryptamine formate (XVb), m.p. 207-208°.

Ultraviolet: (95% EtOH) λ max 220, 280, (inflt.) 298-309 mμ: ε, 25,000, 5,200, 8,300, respectively. Infrared: (KBr) 3.2-4.3 μ strong broad band; 6.35 μ (carboxylate).

Chromatography: Thin layer-alumina, methanol-acetic acid (5 ml. -1 drop), detection heat, single spot, Rf 0.36, silica gel G gave Rf 0.26.

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.11. Found: C, 57.12; H, 6.58; N, 10.91.

N-Acetyl-5,6-dialkoxytryptamines (XVI). *N*-Acetyl-6-benzyloxy-5-methoxytryptamine (XVIb).

6-Benzyloxy-5-methoxytryptamine formate (XIVb) (1.2 g., 0.0032 mole) was taken up in ethanol, made basic with 5% sodium hydroxide, and diluted with water. The aqueous mixture was extracted with ether, and the ether dried and evaporated. The light yellow oil was taken up in 20 ml. of acetic anhydride and allowed to stand overnight at room temperature. The mixture was diluted with 250 ml. of water heated to boiling, cooled, 25 g. of potassium carbonate added, and the resulting solution placed in the refrigerator to crystallize. There resulted 0.7 g. (58.3%) of white crystalline *N*-acetyl-6-benzyloxy-5-methoxytryptamine (XVIb), m.p. 139-140°. Recrystallization twice from benzene gave a crystalline solid, m.p. 148-149° (23).

Ultraviolet: (95% EtOH) λ max 228, 298 mμ; ε, 21,700, 5,280, respectively. Infrared: ($CHCl_3$) 2.89, 3.0 μ (NH), 6.02 μ (C = O).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 71.06; H, 6.68; N, 8.23.

N-Acetylhydroxytryptamines (XVII). *N*-Acetyl-6-hydroxy-5-methoxytryptamine (XVIIb). (6-Hydroxymelatonin).

To a 500 ml. Parr low pressure hydrogenation bottle was added 0.2 g. (0.0053 mole) of *N*-acetyl-6-benzyloxy-5-methoxytryptamine (XVIb), 0.07 g. 5% palladium on charcoal, 100 ml. of ethanol. The mixture was hydrogenated at room temperature for 5 hours, filtered, and evaporated. There resulted 0.11 g. (72%) of solid, m.p. 172-174° dec. Recrystallization from ethanol-hexane gave white crystalline 6-hydroxymelatonin (XVIIb), 174-175°.

Ultraviolet: (95% ethanol) λ max 208, 220, 303 mμ; ε, 24,000, 25,400, 7,800, respectively. Infrared: (KBr) 3.0, 3.15, 3.2 μ (OH and NH), 6.22 μ (C = O).

Chromatography: Thin layer, silica gel G, ethanol, detection, 50%, H_2SO_4 and heat, showed a single spot, Rf 0.65.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.50; N, 11.28. Found: C, 62.48; H, 6.62; N, 11.10.

5,6-Dihydroxy-*N*-acetyltryptamine 1,4-Diazabicyclo-(2.2.2)octane Salt.

5,6-Dibenzyloxy-*N*-acetyltryptamine (XVIa) (0.8 g., 0.0019 mole) was debenzylated as described above. The resulting oil was taken up in a minimum of ethanol and an ethereal solution of 1,4-diazabicyclo(2.2.2)octane was added. The product was precipitated by the addition of ether to yield 0.48 g. (66.8%) of 5,6-dihydroxy-*N*-acetyltryptamine 1,4-diazabicyclo(2.2.2)octane salt, m.p. 169-171°. The material was recrystallized from a mixture of 2-butanone and ether, m.p. 156-160°.

Ultraviolet: (95% EtOH) λ max 210, 220, 305 mμ; ε, 24,400, 24,600, 8,500, respectively. Infrared: (KBr) broad strong absorption from 3.1-4.3 μ; 6.4 μ (carboxylate).

Anal. Calcd. for $C_{18}H_{26}N_4O_3$: C, 62.41; H, 7.56. Found: C, 62.14; H, 7.82.

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