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SYNTHESIS OF ALKYLAMINE DERIVATIVES OF 1-ARYL-5-HYDROXYINDOLE

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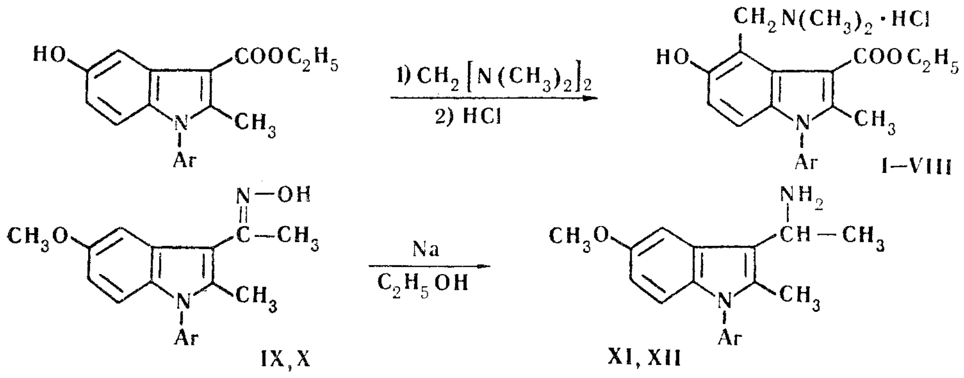
Condensing substituted 1-aryl-5-hydroxyindoles with bisdimethylaminomethane, or sodium-alcohol reduction of 1-aryl-2-methyl-3-acetyl-5-methoxyindoles gives 4-dimethylaminomethyl and 3-alkylamino derivatives of 1-aryl-5-hydroxy(methoxy) indole, isolated as the hydrochlorides.

An American patent [1] states that alkylamine derivatives obtained from 1-alkyl-5-hydroxyindoles which we synthesized [2, 3], are useful as central nervous system stimulants. We have also offered a convenient method of synthesizing 4-alkylamino derivatives of 5-hydroxybenzofuran, 5-hydroxynaphthofuran, and 5-hydroxybenzindole, by condensing the corresponding benzofurans, naphthofurans, and benzindoles with bismethylenaminomethane [4, 5]. Continuing these researches, in a search for new medicinals, from 1-aryl-5-hydroxyindoles [6] we have prepared a number of hydrochlorides of 4-alkylamino derivatives of 1-aryl-5-hydroxyindole (I-VIII).



I—VIII

IX, X

XI, XII

Furthermore, sodium-alcohol reduction of oximes IX-X, synthesized from 1-aryl-2-methyl-3-acetyl-5-methoxyindoles [7] gives hydrochlorides of derivatives of 3-alkylaminoindole (XI-XII).

Experimental

1-Phenyl-2-methyl-3-carboethoxy-4-dimethylaminomethyl-5-hydroxyindole hydrochloride (I). A mixture of 5.42 g (0.02 mole) 1-phenyl-2-methyl-3-carboethoxy-5-hydroxyindole, 3 g (0.03 mole) bisdimethylaminomethane, and 15 ml dry dioxane was refluxed for 2 hr 30 min, on a water bath. Then the dioxane and excess bisdimethylaminomethane were distilled off under reduced pressure. The oily liquid product was dissolved in 3 ml dioxane and 60 ml dry ether, the solution cooled, and a solution of hydrogen chloride in dry ether added. The crystals of I which formed were separated off and recrystallized from a mixture of MeOH, Me_2CO, and dry Et_2O. The other alkylamine derivatives of 5-hydroxyindole (II–VIII) were synthesized similarly (table).

1-Phenyl-2-methyl-3-acetyl-5-methoxyindole oxime (IX). 8 g (0.028 mole) 1-phenyl-2-methyl-3-acetyl-5-methoxyindole and 5.6 g (0.08 mole) hydroxylamine hydrochloride were added to a solution of 6.4 g (0.16 mole) NaOH in 120 ml EtOH. The mixture was boiled for 1 hr, diluted with water, cooled, and made acid to congo red with dilute HCl. The crystals of oxime which formed were separated off, and recrystallized from aqueous MeOH. Yield of IX 6.2 g (74%), mp 171°-172° C (ex MeOH). Found: C 73.50, 73.65; H 6.39, 6.25; N 9.35, 9.54%. Calculated for $C_{18}H_{18}N_2O_2$: C 73.47; H 6.12; N 9.52%.

1-(p-Anisyl)-2-methyl-3-acetyl-5-methoxyindole oxime (X). 7 g (0.023 mole) 1-(p-anisyl)-2-methyl-3-acetyl-5-methoxyindole, 6.4 g (0.16 NaOH, 120 ml EtOH, and 5.6 g (0.08 mole) $NH_2OH \cdot HCl$ were brought to react as in the previous experiment. Yield of oxime X 6 g (82%) mp 132°–133° C (ex MeOH). Found: C 69.80, 69.96; H 6.31, 6.40; N 8.52, 8.64%. Calculated for $C_{19}H_{20}N_2O_3$: C 70.34; H 6.21; N 8.63%.

1-Phenyl-2-methyl-3-(1'-aminoethyl)-5-methoxyindole hydrochloride (XI). A three-necked flask was fitted with a Dimroth reflux condenser and an effective stirrer, a solution of 8.8 g (0.03 mole) oxime IX in 300 ml dry EtOH refluxed, and 30 g (1.3 g at) Na added in large pieces in 5-10 min. Then the reaction mixture was stirred and heated for

Hydrochlorides of 4-Alkylamino Derivatives of 1-Aryl-5-hydroxyindole

Compound No.	Ar	Mp, °C (recrystal-lization solvent)*	Formula	Found, %			Calculated, %			yield, %
				C	H	N	C	H	N	
I	C_6H_5	184—185 (1 : 1 : 3)	$C_{21}H_{24}N_2O_3 \cdot HCl$	64.45 64.77	6.59 6.52	7.37 7.41	64.85	6.48	7.20	71
II	*o*-CH_3—C_6H_4	156 —157 (ex Me_2CO)	$C_{22}H_{26}N_2O_3 \cdot HCl$	65.54 65.41	6.74 6.86	6.93 7.12	65.55	6.75	6.95	68
III	*p*-CH_3—C_6H_4	147.5—148 (1 : 1 : 10)	$C_{22}H_{26}N_2O_3 \cdot HCl$	65.75 65.45	6.83 6.87	6.71 6.64	65.55	6.75	6.95	63
IV	*m*-Cl—C_6H_4	189—190 (ex Me_2CO)	$C_{21}H_{23}ClN_2O_3 \cdot HCl$	59.93 59.57	5.89 5.85	6.74 6.65	59.57	5.71	6.62	66
V	*p*-Cl—C_6H_4	192.5—193 (1 : 10 : 12)	$C_{21}H_{23}ClN_2O_3 \cdot HCl$	59.64 59.56	5.53 5.66	6.51 6.42	59.57	5.71	6.62	67
VI	*m*-CH_3O—C_6H_4	177—178 (1 : 10 : 15)	$C_{22}H_{26}N_2O_4 \cdot HCl$	62.94 63.28	6.34 6.34	6.55 6.74	63.07	6.49	6.68	74
VII	*p*-CH_3O—C_6H_4	180—181 (1 : 1 : 6)	$C_{22}H_{26}N_2O_4 \cdot HCl$	63.32 63.13	6.46 6.63	6.38 6.59	63.07	6.49	6.68	70
VIII	*p*-CH_3CONH —C_6H_4	203—204 (1 : 10: 10)	$C_{23}H_{27}N_3O_4 \cdot HCl$	61.91 61.70	6.38 6.14	9.40 9.45	61.94	6.18	9.42	77

* MeOH-Me_2CO-dry Et_2O in the given ratio used for recrystallizing.

15–20 min until the Na dissolved completely, diluted with water, the EtOH distilled off under reduced pressure, and the water emulsion extracted with ether. The ether extract was dried over KOH. Addition of an ether solution of HCl* to a well cooled solution of the amine gave XI hydrochloride, yield 4.1 g (48%), mp 155°–157°C (ex MeOH-Me_2CO-dry Et_2O 1:3 :8). Found: C 68.22, 68.56; H 6.63, 6.72; N 8.94, 9.04%. Calculated for $C_{18}H_{20}N_2O \cdot HCl$: C 68.23; H 6.76; N 8.96%.

<u>1-(p-Anisyl)-2-methyl-3-(1'-aminoethyl)-5-methoxyindole hydrochloride (XII).</u> 5.7 g (0.018 mole) oxime X, 17.6 g (0.76 g at) Na, and 180 ml dry EtOH were used in this experiment, the conditions being the same as those used in the previous experiment. Yield of XII 2.4 g (38%), mp 202°–203° C (ex MeOH-dry Et_2O 1:1). Found: C 66.84, 67.03; H 6.87, 6.68; N 8.25, 8.15%. Calculated for $C_{19}H_{22}N_2O_2 \cdot HCl$: C 66.74; H 6.77; N 8.08%.

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* Addition of excess ethereal HCl leads to tar formation.