SYNTHESIS OF AMINOALKYL DERIVATIVES OF 2-BENZYL-5-HYDROXYINDOLE

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Derivatives of 2-benzyl-5-methoxyindole-3-carboxylic acid are decarboxylated on heating and are converted to the corresponding 2-benzyl-5-methoxyindoles. 2-Benzyl-5-methoxygramine hydrochlorides were obtained from the latter and used to obtain (2-benzyl-5-methoxy-3-indolyl)acetonitriles. The nitriles were converted to 2-benzyl-5-methoxytryptamines by hydrogenation. A number of Mannich bases were obtained by aminomethylation of 2-benzyl-3-carbomethoxy-5-hydroxyindole derivatives.

While aminoalkyl derivatives of 2-methyl-5-hydroxy(methoxy)indole are widely accessible [1], aminoalkyl derivatives of 2-benzyl-5-hydroxy(methoxy)indole have not yet been obtained. The synthesis of the latter apparently merits attention since aminoalkyl derivatives of 2-methyl-5-hydroxy(methoxy)indole, for example, 1-benzyl-2-methyl-5-methoxytryptamine, are of interest as serotonin antimetabolites [2, 3]. In this paper we present the synthesis of 2-benzyl-5-hydroxy(methoxy)indole derivatives which contain aminoalkyl substituents in the 3- and 4- positions. The 1-methyl- and 1-phenyl-2-benzyl-3-carbomethoxy-5-hydroxyindoles (I, II) [4] as well as 1-benzyl-and 1-(p-tolyl)-2-benzyl-3-carbomethoxy-5-methoxyindoles (V-VII) were obtained by methylation of hydroxyindoles I-III with dimethyl sulfate; V and VII are described by us in [4]. Fusion of V-VII with potassium hydroxide leads to 1-methyl-1-benzyl-, and 1-phenyl-2-benzyl-5-methoxyindole-3-carboxylic acids (VIII-X); we described VIII and X in [4]. Acids VIII-X are decarboxylated on heating to the melting point and are converted to 2-benzyl-5-methoxyindoles XI-XIII, which undergo the Mannich reaction to give 2-benzyl-5-methoxygramines (XIV-XVI). (2-Benzyl-5-methoxy-3-indolyl)-acetonitriles (XVII-XIX) are obtained from the methiodides of XIV-XVI. A fivefold excess of potassium cyanide should be used to obtain optimum yields of XVII-XIX. Hydrogenation of nitriles XVII-XIX over Raney nickel gives 2-benzyl-5-methoxytryptamines (XX-XXII). Aminomethylation of 2-benzyl-3-carbomethoxy-5-hydroxyindoles I-IV leads to 4-aminomethyl derivatives XXIII-XXVI.

Absorption bands at 2650-2750 cm^{-1} (ν_{OH}) and 1650-1660 cm^{-1} ($\nu_{C=O}$) are observed in the IR spectra of indole-3-carboxylic acids VIII-X. A peak near 2250-2260 cm^{-1} ($\nu_{C\equiv N}$) is observed for (3-indolyl)acetonitriles XVII-XIX. The IR spectra of mineral oil suspensions of 4-dimethylaminomethyl derivatives XXIII-XXVI do not contain the absorption band for a hydroxyl group at 3000-3600 cm^{-1}, which is observed in the starting compounds. This can apparently be explained by the involvement of the hydroxyl group in a hydrogen bond. The IR spectra of these compounds in dilute carbon tetrachloride solutions (0.0005 M, layer thickness 0.5 cm) were obtained to investigate the nature of the hydrogen bond. In this case also, no valence vibrations of the hydroxyl group were observed in the spectra of XXIII-XXVI, which attests to the absence of an intermolecular hydrogen bond in the structures of the Mannich bases and to the presence in them of an intramolecular hydrogen bond. It is well known that for every association one observes a shift in the band of the valence vibration of the OH group to lower frequencies, and the size of this shift may be a measure of the hydrogen bond energy [5]. In our case, the absence of a band characteristic for the OH group attests to the presence of a rather strong intramolecular hydrogen bond, so that only bands of the valence vibrations of the aromatic C–H bonds are observed at 2850-2960 cm^{-1} in the IR spectra of these compounds.

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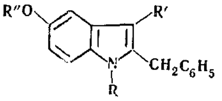
TABLE 1. 2-Benzyl-5-hydroxyindole Derivatives



Compound	R	R′	R″	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
						C	H	N	C	H	N	
III	$CH_2C_6H_5$	$COOCH_3$	H	217—218,5[a]	$C_{24}H_{21}NO_3$	77,4	5,6	3,7	77,6	5,7	3,8	25
IV	p-$CH_3C_6H_4$	$COOCH_3$	H	168—169[b]	$C_{24}H_{21}NO_3$	77,8	5,6	3,9	77,6	5,7	3,8	11
VI	$CH_2C_6H_5$	$COOCH_3$	CH_3	127—128[b]	$C_{25}H_{23}NO_3$	78,2	6,0	3,6	77,9	6,0	3,6	96
IX	$CH_2C_6H_5$	COOH	CH_3	208—209[c] (dec.)	$C_{24}H_{21}NO_3$	77,5	5,7	3,7	77,6	5,7	3,8	99
XI	CH_3	H	CH_3	106—107[b]	$C_{17}H_{17}NO$	81,3	6,9	5,6	81,2	6,8	5,6	98
XII	$CH_2C_6H_5$	H	CH_3	88—89[b]	$C_{23}H_{17}NO$	84,1	6,4	4,4	84,4	6,5	4,3	~100
XIII	C_6H_5	H	CH_3	57—58[b]	$C_{22}H_{19}NO$	84,6	6,3	4,6	84,3	6,1	4,5	~100

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[a] From dichloroethane.

[b] From methanol.

[c] From methanol–dioxane (2:1).

The bands of the OH bond are probably shifted to ~ 2900 cm^{-1} and are masked by the intense bands of the aromatic C–H bonds there. To confirm this assumption, we investigated the IR spectra of the hydrochlorides of the 2-benzyl-3-carbomethoxy-4-dimethylaminomethyl-5-hydroxyindoles. An intense band at 3110-3120 cm^{-1} is observed in the spectra of these compounds in the region of the valence vibrations of the OH group, which indicates the absence of an intramolecular association. In addition, bands appear at 2715-2730 cm^{-1}, which are apparently due to the NH and NH...Cl vibrations [6]. From what has been stated, it follows that $\Delta\nu$ of the hydroxyl group (which is involved in an intramolecular hydrogen bond in the investigated compounds), like the Mannich bases in the phenol series [7], amounts to ~ 700 cm^{-1}.

Three intense absorption maxima are observed at 217 nm (log ε 4.60), 247 nm (log ε 4.33), and 293 nm (log ε 4.09) in the UV spectrum of 1-methyl-2-benzyl-3-carbomethoxy-5-hydroxyindole (I). Replacement of the alkyl substituent on the nitrogen of the indole ring by aryl substituents leads to the disappearance of the absorption band at 217 nm, while no definite changes in the positions of the maxima at 245-247 nm (log ε 4.31-4.35) and 293 nm (log ε 4.09-4.13) are observed. There is an intense absorption at 276-285 nm (log ε 3.94-4.33) in the UV spectra of 2-benzyl-5-methoxyindoles XI-XIII and of their derivatives (XIV-XXII), which contain dimethylaminomethyl, cyanomethyl, or aminoethyl groups in the 3-position. In addition, an absorption maximum at 224-228 nm (log ε 4.18-4.54) is also characteristic for the corresponding 1-methyl-2-benzyl-5-methoxyindole derivatives. The introduction of a dimethylaminomethyl group into 2-benzyl-3-carbomethoxy-5-hydroxyindole derivatives I-III leads to a bathochromic shift and a decrease in the intensity of the absorption band at 244-247 nm (log ε 4.31-4.38) to 250-259 nm (log ε 4.28-4.33) and does not affect the position of the maximum at 291-293 nm (log ε 4.09-4.15), but lowers its intensity (log ε 4.01-4.11).

EXPERIMENTAL

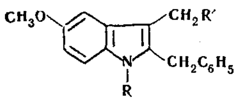
The IR spectra of mineral oil suspensions of the compounds and of some of their carbon tetrachloride solutions were obtained with a UR-10 spectrophotometer. The UV spectra of alcohol solutions were obtained with an EPS-3 spectrophotometer.

1-Benzyl-and 1-(p-tolyl)-2-benzyl-3-carbomethoxy-5-hydroxyindoles (III, IV), 1,2-dibenzyl-3-carbomethoxy-5-methoxyindole (VI), and 1,2-dibenzyl-5-methoxyindole-3-carboxylic acid (IX) were obtained via the methods described in [4]. The data for III, IV, VI, and IX are presented in Table 1.

2-Benzyl-5-methoxyindoles (XI-XIII). Compounds VIII-X (0.1 mole) were heated at 240-250 deg in a flask equipped with an air condenser fitted with a Bunsen valve until the evolution of bubbles of carbon dioxide ceased. The resulting oily liquid (XI-XIII) crystallized on cooling. The data for the 2-benzyl-5-methoxyindoles (XI-XIII) are presented in Table 1.

2-Benzyl-5-methoxygramine Derivatives (XIV-XVI). A mixture of 0.1 mole of XI-XIII, 0.2 mole of dimethylamine hydrochloride (25% aqueous solution), 0.2 mole of 40% formalin, and 160 ml of dioxane was

TABLE 2. 3-Aminoalkyl and 3-Cyanomethyl Derivatives of 2-Benzyl-5-methoxyindoles



Compound	R	R′	mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	halogen	N	C	H	halogen	N	
XIV	CH_3	$N(CH_3)_2$	104—105[a]	$C_{20}H_{24}N_2O$	77,7	7,7	—	9,0	77,9	7,8	—	9,1	—
		$N(CH_3)_2 \cdot HCl$	202—203[b] (dec.)	$C_{20}H_{24}N_2O \cdot HCl$	—	—	10,2	8,2	—	—	10,3	8,1	84
		$\overset{+}{N}(CH_3)_3I^-$	>150 (dec.)	$C_{21}H_{27}IN_2O$	—	—	27,7	6,3	—	—	28,2	6,2	97
XV	$CH_2C_6H_5$	$N(CH_3)_2$	90—91[a]	$C_{26}H_{28}N_2O$	81,2	7,2	—	7,2	81,2	7,3	—	7,3	—
		$N(CH_3)_2 \cdot HCl$	207—208[c] (dec.)	$C_{26}H_{28}N_2O \cdot HCl$	74,1	7,1	8,3	6,6	74,2	6,9	8,4	6,6	98
		$\overset{+}{N}(CH_3)_3I^-$	183—185[a] (dec.)	$C_{27}H_{31}IN_2O$	60,9	6,1	24,3	5,1	61,6	5,9	24,1	5,3	97
XVI	C_6H_5	$N(CH_3)_2$	101—102[a]	$C_{25}H_{26}N_2O$	81,2	7,2	—	7,5	81,0	7,1	—	7,6	—
		$N(CH_3)_2 \cdot HCl$	174—175[d]	$C_{25}H_{26}N_2O \cdot HCl$	—	—	8,5	6,6	—	—	8,7	6,9	81
		$N(CH_3)_3I^-$	154—155[a] (dec.)	$C_{26}H_{26}IN_2O$	—	—	24,9	5,5	—	—	24,8	5,5	95
XVII	CH_3	CN	97—98[e]	$C_{19}H_{18}N_2O$	78,7	6,3	—	9,7	78,6	6,2	—	9,6	93
XVIII	$CH_2C_6H_5$	CN	121—122[a]	$C_{25}H_{22}N_2O$	81,9	6,1	—	7,8	81,9	6,0	—	7,6	99
XIX	C_6H_5	CN	121—121,5[a]	$C_{24}H_{28}N_2O$	81,6	6,0	—	7,8	81,8	5,7	—	7,9	96
XX	CH_3	$CH_2NH_2 \cdot HCl$	249—250[f] (dec.)	$C_{19}H_{20}N_2O \cdot HCl$	69,1	7,1	10,5	8,6	69,0	7,0	10,7	8,5	81
XXI	$CH_2C_6H_5$	$CH_2NH_2 \cdot HCl$	197—198,5[g]	$C_{25}H_{26}N_2O \cdot HCl$	73,7	6,8	8,5	6,9	73,8	6,7	8,7	6,9	80
XXII	C_6H_5	$CH_2NH_2 \cdot HCl$	209—210[h] (dec.)	$C_{24}H_{24}N_2O \cdot HCl$	73,4	6,2	8,6	7,2	73,4	6,4	9,0	7,1	70

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[a] From methanol.

[b] From methanol–ether (5:1).

[c] From acetone–methanol–ether (2:1:2).

[d] From acetone–methanol (5:1).

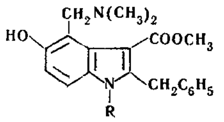
[e] From petroleum ether–benzene (5:1).

[f] From methanol–acetone–ether (1:3:2).

[g] From methanol–acetone–ether (1:10:10).

[h] From methanol–acetone (1:4).

TABLE 3. 2-Benzyl-3-carbomethoxy-4-dimethylaminomethyl-5-hydroxyindoles



Compound	R	Base or hydrochloride	mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	Cl	N	C	H	Cl	N	
XXIII	CH_3	Base	134—135 [a]	$C_{21}H_{24}N_2O_3$	71,6	6,8	—	7,7	71,6	6,9	—	7,9	
		Hydrochloride	212—213 [b]	$C_{21}H_{24}N_2O_3 \cdot HCl$	—	—	8,9	7,0	—	—	9,1	7,2	62
XXIV	$CH_2C_6H_5$	Base	144—145 [a]	$C_{27}H_{28}N_2O_3$	75,5	6,8	—	6,4	75,7	6,6	—	6,5	
		Hydrochloride	204—205 [c] (dec.)	$C_{27}H_{28}N_2O_3 \cdot HCl$	69,2	6,5	7,5	6,0	69,7	6,3	7,6	6,0	74
XXV	C_6H_5	Base	134,5—136 [a]	$C_{26}H_{26}N_2O_3$	75,2	6,2	—	6,6	75,3	6,3	—	6,8	
		Hydrochloride	201—202 [d] (dec.)	$C_{26}H_{26}N_2O_3 \cdot HCl$	69,3	6,1	7,7	6,2	69,2	6,0	7,9	6,2	63
XXVI	*p*-$CH_3C_6H_4$	Base	134—135 [a]	$C_{27}H_{28}N_2O_3$	75,5	6,6	—	6,3	75,7	6,6	—	6,5	
		Hydrochloride	145—146 [e] (dec.)	$C_{27}H_{28}N_2O_3 \cdot HCl$	—	—	7.1	5,8	—	—	7,6	6,0	76

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[a] From methanol.
[b] From methanol–acetone–ether (1:2:1).
[c] From acetone–methanol (6:1).
[d] From methanol–acetone–ether (1:3:3).
[e] From acetone.

stirred at 40-45 deg for 4 h (6 h at 60-65 deg for hydrochloride XVI), after which the solvent was removed by vacuum distillation. The residue was mixed thoroughly with a small amount of water and filtered. The XIV-XVI hydrochlorides on the filter were washed with water and acetone. To obtain the bases a methanol solution of the hydrochlorides was made alkaline and diluted with water. The methiodides of XIV-XVI were obtained by the usual method. The data for bases XIV-XVI, their hydrochlorides, and their methiodides are presented in Table 2.

(2-Benzyl-5-methoxy-3-indolyl)acetonitriles (XVII-XIX). A suspension of 0.04 mole of the methiodides of XIV-XVI and 0.2 mole of potassium cyanide in a mixture of 80 ml of water and 24 ml of dioxane was refluxed for 2 h. The reaction mixture was then cooled and diluted with two volumes of water. The precipitate was filtered, washed with water, and dried. The data for XVII-XIX are presented in Table 2.

2-Benzyl-5-methoxytryptamine Hydrochlorides (XX-XXII). Compounds XVII-XIX (0.02 mole) were dissolved in 300 ml of absolute ethanol saturated with ammonia and hydrogenated over a Raney nickel catalyst in an autoclave with stirring at room temperature and 90 atm. An alcohol suspension (15 ml) of the catalyst was used. The catalyst was filtered, and the alcohol was removed from the filtrate by vacuum distillation. The residue was dissolved in absolute ether and filtered. The filtrate was acidified with an ether solution of hydrogen chloride until it gave an acid reaction. The resulting hydrochloride precipitate was filtered. Data on XX-XXII are presented in Table 2.

2-Benzyl-3-carbomethoxy-4-dimethylaminomethyl-5-hydroxyindole Derivatives (XXIII-XXVI). A mixture of 0.02 mole of I-IV and 0.03 mole of bis(dimethylamino)methane in 30 ml of absolute dioxane was heated for 6-7 h on a water bath. The dioxane and excess bis(dimethylamino)methane were then removed by vacuum distillation. The residue was dissolved in absolute ether, and the solution was cooled and acidified with an ether solution of hydrogen chloride until it gave an acid reaction. The resulting crystals of the hydrochlorides of XXIII-XXVI were filtered, washed with ether, and dried. Bases XXIII-XXVI were obtained from the corresponding hydrochlorides by the usual method. The data for bases XXIII-XXVI and their hydrochlorides are presented in Table 3.

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