DERIVATIVES OF 1-ARYL-5-METHOXYINDOLES

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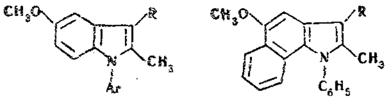
By fusion with potassium hydroxide, derivatives of 1-aryl-3-ethoxycarbonyl-5-methoxy-2-methylindole are converted into the corresponding indole-3-carboxylic acids. When the indole-3-carboxylic acids are heated to their melting points, they are readily converted into derivatives of 1-arylindoles with unsubstituted β-positions. A similar cycle of conversions has been carried out for 3-ethoxycarbonyl-5-methoxy-2-methyl-1-phenylbenzoindole. The reactions of derivatives of 1-aryl-5-methoxy-2-methylindoles with formaldehyde and dimethylamine hydrochloride gives Mannich bases.

In one of our papers [1] it was shown that derivatives of 1-aryl-3-ethoxycarbonyl-2-methyl-5-hydroxyindoles are widely accessible. Their synthesis is readily carried out by the condensation of p-benzoquinone with acetoacetic ester and aromatic amines. On the other hand, in view of the interest in derivatives of 5-hydroxyindole, which include Dimekarbin and other substances with a prolonged hypertensive effect that we have obtained [2], a broadening of studies in the 1-aryl-5-hydroxyindole series also deserves attention.



I Ar=o-$CH_3C_6H_4$; R=$COOC_2H_5$
II Ar=p-$CH_3C_6H_4$; R=$COOC_2H_5$
III Ar=p-$CH_3OC_6H_4$; R=$COOC_2H_5$
IV Ar=C_6H_5; R=COOH
V Ar=o-$CH_3C_6H_4$; R=COOH
VI Ar=p-$CH_3C_6H_4$; R=COOH
VII Ar=p-$CH_3OC_6H_4$; R=COOH
IX Ar=C_6H_5; R=H
X Ar=o-$CH_3C_6H_4$; R=H
XI Ar=p-$CH_3C_6H_4$; R=H
XII Ar=p-$CH_3OC_6H_4$; R=H
XIV Ar=C_6H_5; $R=CH_2{-}N(CH_3)_2\cdot HCl$
XV Ar=o-$CH_3C_6H_4$; $R=CH_2{-}N(CH_3)_2\cdot HCl$
XVI Ar=p-$CH_3C_6H_4$; $R=CH_2{-}N(CH_3)_2\cdot HCl$
XVII Ar=p-$CH_3OC_6H_4$; $R=CH_2{-}N(CH_3)_2\cdot HCl$

VIII R=COOH
XIII R=H

In the present work we have studies the hydrolysis of O-methyl derivatives of 1-aryl-3-ethoxycarbonyl-2-methyl-5-hydroxyindoles. 5-Hydroxyindole derivatives are unstable under conditions of alkaline hydrolysis. The synthesis of the 1-aryl-3-ethoxycarbonyl-5-methoxy-2-methylindoles (I–III) was carried out from the corresponding hydroxy derivatives by the action on them of dimethyl sulfate in an alkaline medium. The hydrolysis of the methoxy derivatives I–III and also of 3-ethoxycarbonyl-5-methoxy-2-methyl-1-phenylindole [3] and 3-ethoxycarbonyl-5-methoxy-2-methyl-1-phenylbenzoindole [4], which do not undergo hydrolysis under the usual conditions, for example with alcoholic alkali, was carried out by fusing them with potassium hydroxide. A number of indole-3-carboxylic acids (IV–VII) and benzoindole-3-carboxylic acid (VIII) have been obtained in high yield. We have found that when the acids IV–VIII are heated above their melting points they readily undergo decarboxylation, being converted in almost quantitative yield into the indole derivatives IX–XII and the benzoindole XIII, which have an unoccupied β-position. The 1-aryl-5-methoxy-2-methylindoles IX–XII that we have obtained are of interest as starting materials for the synthesis of analogs of natural and biologically active substances. The action of bis(dimethylamino)methane on the indole derivatives IX–XII under the conditions for the aminomethylation of 5-hydroxyindoles in position 4 [5] led to no reaction. Reaction with formaldehyde and dimethylamine hydrochloride gave the hydrochlorides of the 1-aryl-5-methoxy-2-methylgramines XIV–XVII.

EXPERIMENTAL

3-Ethoxycarbonyl-5-methoxy-2-methyl-1-o-tolylindole (I). A suspension of 46.5 g (0.15 mole) of 3-methoxycarbonyl-5-hydroxy-2-methyl-1-o-tolylindole in 75 ml of dioxane was treated with 150 ml (0.3 mole) of 2 N sodium hydroxide and then with 41.5 g (0.33 mole) of dimethyl sulfate in one portion. The reaction mixture was stirred vigorously for 40–50 min and was diluted with 3 volumes of water. The oily layer was separated off, diluted with 1 volume of water, and left overnight at 0° to +3° C. The semicrystalline mass that formed was separated from the aqueous layer and treated with a small amount of methanol. The crystals were separated off and recrystallized twice from methanol.

Table 1

1-Aryl-5-methoxy-2-methylindole-3-carboxylic Acids

Compound	Mp, °C*	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
V	Above 205 (decomp.)	$C_{18}H_{17}NO_3$	73.68· 73,55	5.98; 6.07	4.86; 5,02	73.23	5.80	4.74	85
VI	Above 225 (decomp.)	$C_{18}H_{17}NO_3$	73.49; 73.65	5.77; 5.56	4.85; 5.12	73.23	5.80	4.74	.83
VII	Above 220 (decomp.)	$C_{18}H_{17}NO_4$	69.6[illegible]; 69.59	5.60; 5.70	4.41; 4.32	69.44	5.50	4.49	81
VIII	Above 270 (decomp.)	$C_{21}H_{17}NO_3$	76.10; 75.84	4.95; 4.85	4.31; 4.32	76.12	5.17	4.23	70

*From dioxane

Table 2

1-Aryl-5-methoxy-2-methylindoles

Compound	Bp, °C (pressure, mm)	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
X	200 (3.5)	—	$C_{17}H_{17}NO$	80,90; 81,20	6,67; 6,90	5,65; 5,70	81,24	6,82	5,57	93
XI	213 (5)	65—66	$C_{17}H_{17}NO$	80.92; 81.00	6.51; 6.71	5.61; 5.38	81,24	6.82	5.57	95,6
XII	229—230 (5)	103—104	$C_{17}H_{17}NO_2$	76,80; 76.73	6,47; 6,38	5.24; 5.23	76.39	6.41	5,25	95
XIII	360 (4)	—	$C_{20}H_{17}NO$	83.55; 83.85	5.64; 5,59	4,96; 4.78	83,56	5,96	4.87	60

Table 3

Hydrochlorides of 1-Aryl-5-methoxy-2-methylgramines

Hydrochlorides of compounds	Mp, °C*	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
XV	215—217 (decomp.)	$C_{20}H_{24}N_2O \cdot HCl$	69.58; 69,67	7,18; 7,05	7.80; 7.72	69,65	7.36	8,12	75
XVI	212—213 (decomp.)	$C_{20}H_{24}N_2O \cdot HCl$	69.66; 69,80	7,07; 7,13	8.11; 7,90	69.65	7,36	8,12	63
XVII	210—211 (decomp.)	$C_{20}H_{24}N_2O_2 \cdot HCl$	66.28; 66,40	6,82; 6,73	7.24; 7.38	66.56	6.98	7,76	66

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*From methanol

The yield of I was 30 g (75%), mp 71°–72° C. Found, %: C 74.18; 74.00; H 6.20; 6.31; N 4.45; 4.35. Calculated for $C_{20}H_{21}NO_3$, %: C 74.27; H 6.54; N 4.33.

3-Ethoxycarbonyl-5-methoxy-2-methyl-1-p-tolylindole (II). From 77.2 g (0.25 mole) of 3-ethoxycarbonyl-5-hydroxy-2-methyl-1-p-tolylindole, 68.7 g (0.55 mole) of dimethyl sulfate, and 250 ml (0.5 mole) of 2 N sodium hydroxide in 100 ml of dioxane was obtained 70 g (86%) of II, mp 131°–132° C (from acetone). Found, %: C 74.12; 74.37; H 6.55; 6.41; N 4.36; 4.62. Calculated for $C_{20}H_{21}NO_3$, %: C 74.27; H 6.54; N 4.33.

3-Ethoxycarbonyl-5-methoxy-1-p-methoxyphenyl-2-methylindole (III). From 81.3 g (0.25 mole) of 3-ethoxycarbonyl-5-hydroxy-1-p-methoxyphenyl-2-methylindole, 68.7 g (0.55 mole) of dimethyl sulfate, and 250 ml (0.5 mole) of 2 N sodium hydroxide in 100 ml of dioxane was obtained 64 g (74%) of III, mp 70°–71° C (from methanol). Found, %: C 70.70; 71.16; H 6.32; 6.02; N 4.03; 4.04. Calculated for $C_{20}H_{21}NO_4$, %: C 70.77; H 6.23; N 4.12.

5-Methoxy-2-methyl-1-phenylindole-3-carboxylic acid (IV). To a solution of 56 g (1 mole) of potassium hydroxide in 14 ml of water heated to 155°–160° C was added 30.9 g (0.1 mole) of 3-ethoxycarbonyl-5-methoxy-2-methyl-1-phenylindole [3]. The reaction mixture was stirred well at 155°–170° C for 25–30 min. Then the temperature of the melt was raised to 200°–210° C and it was heated at this temperature with stirring until it solidified. The solid mass formed was cooled and dissolved in 700 ml of water. The resulting solution was neutralized with 2 N hydrochloric acid (to Congo Red). The precipitate of the acid IV was filtered off, washed with distilled water on the filter, and then dried, the water being eliminated in the form of the azeotrope with benzene (Dean and Stark trap). The yield of IV was 25 g (89%), mp 240° C (decomp., from a mixture of methanol and dioxane, 1:1). Found, %: C 72.24; 72.20; H 5.62; 5.40; N 5.03; 5.08. Calculated for $C_{17}H_{15}NO_3$, %: C 72.58; H 5.37; N 4.98.

Data on the other indolecarboxylic acids V–VIII are given in Table 1.

5-Methoxy-2-methyl-1-phenylindole (IX). In a distillation flask, 28.1 g (0.1 mole) of the acid IV was heated at 230°–245° C for 5–10 minutes until the evolution of carbon dioxide ceased. The indole IX formed was distilled in vacuum. The yield of IX was 22.3 g (94%), bp 199°–200° C (5 mm). Found, %: C 81.04; 81.25; H 6.42; 6.29; N 6.00; 5.87. Calculated for $C_{16}H_{15}NO$, %: C 80.97; H 6.37; N 5.90.

Data on the other 1-arylindoles X–XIII are given in Table 2.

Hydrochloride of 5-methoxy-2-methyl-1-phenylgramine XIV. A mixture of 7.1 g (0.03 mole) of the indole IX, 4 g (0.05 mole) of dimethylamine hydrochloride (in the form of a 25% solution in water), 1.6 g (0.05 mole) of formaldehyde (4 ml of a 40% solution), and 23 ml of dioxane was shaken in a closed vessel for 4 hr and was then cooled to 10° C, after which the crystals of the hydrochloride XIV were separated off and recrystallized from methanol. The yield of XIV was 9 g (90%), mp 195°–196° C (decomp.). Found, %: C 68.66; 68.81; H 6.79; 6.97; N 8.68; 8.60. Calculated for $C_{19}H_{22}N_2O \cdot HCl$, %: C 68.97; H 7.05; N 8.46.

Data on the hydrochlorides of the other 1-aryl-5-methoxy-2-methylgramines XV–XVII are given in Table 3.

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