STUDIES IN THE QUINONE FIELD

XLI. Synthesis of Derivatives of 1-Benzyl-5-hydroxyindole*

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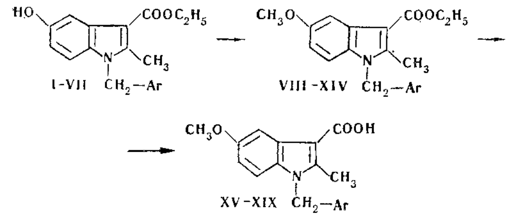
The condensation of p-benzoquinone with substituted N-benzyl-β-aminocrotonic esters has been studied. A series of derivatives of 1-benzyl-5-hydroxyindole containing various substituents in the benzene nucleus of the benzyl radical has been obtained.

The condensation of quinones with β-aminocrotonic esters is the most effective method for the synthesis of derivatives of 5-hydroxyindole. This reaction, which has been developed in recent years by one of us together with his co-workers [1], has enabled a large number of compounds possessing high biological activity to be obtained [2]. Furthermore, in one of our investigations [3] this reaction was used in an original synthesis of the preparation BAS, which is of considerable interest as a serotonin antagonist [4–6].

In the present paper the condensation of p-benzoquinone with substituted N-benzyl-β-aminocrotonic esters containing various substituents in the benzene nucleus of the benzyl radical, which leads to the formation of 1-benzyl-3-ethoxycarbonyl-5-hydroxy-2-methylindoles (**I–VII**) is studied. The substituted N-benzyl-β-aminocrotonic esters obtained from acetoacetic ester and nuclear-substituted benzylamines [7–9] were not subjected to purification. The 1-benzyl-3-ethoxycarbonyl-5-hydroxy-2-methylindole derivatives (**I–VII**) were converted by the action of dimethyl sulfate in alkaline solution into the corresponding methoxy derivatives (**VIII–XIV**). The latter are stable to hydrolysis under the usual conditions. By saponifying the ethoxycarbonyl group in some of them by fusion with an excess of caustic soda at 180–220° C, a number of indole-3-carboxylic acids (**XV–XIX**) have been obtained.



I, VIII, XV Ar=p-$CH_3C_6H_4$;

II, IX, XVI Ar=o-$CH_3OC_6H_4$;

III, X, XVII Ar=p-$CH_3OC_6H_4$;

IV, XI Ar=p-BrC_6H_4;

V, XII Ar=p-$NO_2C_6H_4$;

VI, XIII, XVIII Ar=2′,4′-$(CH_3)_2C_6H_3$;

VII, XIV, XIX Ar=3′,4′-$(CH_3O)_2C_6H_3$

EXPERIMENTAL

3-Ethoxycarbonyl-5-hydroxy-2-methyl-1-(p-methylbenzyl)indole. (I). A mixture of 24.2 g (0.2 mole) of p-methylbenzylamine, 26 g (0.2 mole) of acetoacetic ester, and one drop of concentrated hydrochloric acid was heated in the water bath for 1 hr and treated with 80 ml of dichloroethane, and the water liberated was distilled off in the form of the azeotropic mixture with dichloroethane (60 ml). After 25–30 min, a solution of 20.4 g of p-benzoquinone in 220 ml of dichloroethane was added to the reaction mixture without the cessation of the distillation of the azeotropic mixture (a total of 230–250 ml was distilled off). The reaction mixture was left overnight and the precipitate was filtered off and washed with methanol. Yield 13.8 g (22%), mp 231–233° C (from a mixture of ethyl acetate and dioxane). Found, %: C 74.11, 74.41; H 6.62, 6.87. Calculated for $C_{20}H_{21}NO_3$, %: C 74.28; H 6.55. Compounds **II–VII** were obtained similarly (Table 1).

Table 1

Derivatives of 1-Benzyl-3-ethoxycarbonyl-5-hydroxy-2-methylindole

Compound	Mp, °C (solvent for crystallization)	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
II	203—204 (ethyl acetate)	$C_{20}H_{21}NO_4$	70.84 70.72	6.13 6.26	4.37 4.28	70.78	6.26	4.13	21
III	214—215 (dioxane)	$C_{20}H_{21}NO_4$	70.82 70.62	6.54 6.54	—	70.78	6.26	—	29
IV	204—206 (dioxane)	$C_{19}H_{18}BrNO_3$	58.82 59.04	4.88 5.10	—	58.78	4.77	—	16
V	222—224 (dimethylformamide)	$C_{19}H_{18}N_2O_5$	64.51 64.63	5.23 5.25	7.66 7.85	64.40	5.12	7.91	23
VI	236—237 (dimethylformamide)	$C_{21}H_{23}NO_3$	74.65 74.51	7.09 6.91	4.38 4.57	74.75	6.87	4.15	26
VII	154—155 (dioxane)	$C_{21}H_{23}NO_5$	68.33 68.33	6.47 6.37	—	68.27	6.27	—	18

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*For part XL, see [1].

Table 2

Derivatives of 1-Benzyl-3-ethoxycarbonyl-5-methoxy-2-methylindole

Compound	Mp, °C (solvent for crystallization)	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
IX	105—107 (isopropanol)	$C_{21}H_{23}NO_4$	—	—	3.98 4.15	—	—	3.96	91
X	108—109 (isopropanol)	$C_{21}H_{23}NO_4$	71.68 71.50	6.84 6.79	—	71.37	6.56	—	86
XI	146—148 (dioxane)	$C_{20}H_{20}BrNO_3$	59.62 59.77	5.10 5.22	3.63 3.51	59.70	5.01	3.48	72
XII	153—155 (dioxane)	$C_{20}H_{20}N_2O_5$	65.02 65.05	5.67 5.51	7.70 7.90	65.19	5.48	7.60	84
XIII	114—115 (ethanol)	$C_{22}H_{25}NO_3$	74.89 74.71	7.07 7.16	3.87 4.10	75.19	7.14	3.99	83
XIV	119—121 (ethanol)	$C_{22}H_{25}NO_5$	69.32 69.43	6.71 6.63	—	68.91	6.57	—	77

Table 3

Derivatives of 1-Benzyl-5-methoxy-2-methylindole-3-carboxylic Acid

Compound	Mp (decomp.), °C (solvent for crystallization)	Empirical formula	Found, %		Calculated, %		Yield, %
			C	H	C	H	
XVI	210—213 (ethyl acetate–dioxane)	$C_{19}H_{19}NO_4$	70.36 70.07	5.73 5.69	70.13	5.88	71
XVII	195—197 (dimethylformamide)	$C_{19}H_{19}NO_4$	70.21 70.22	6.01 6.05	70.13	5.88	90
XVIII	201—203 (dioxane)	$C_{20}H_{21}NO_3$	74.51 74.32	6.86 6.72	74.27	6.55	86
XIX	179—181 (dioxane–ethanol)	$C_{20}H_{21}NO_5$	67.93 67.81	6.28 6.29	67.58	5.96	67

3-Ethoxycarbonyl-5-methoxy-2-methyl-1-(p-methylbenzyl)indole (VIII). To a solution of 3.53 g (0.011 mole) of I in a mixture of 12 ml of 2 N NaOH and 20 ml of dioxane 10–15 minutes after its preparation was added 1.5 ml of freshly-distilled dimethyl sulfate, and the mixture was stirred at 20° C for 1 hr and poured into 200 ml of water. The oil that separated out crystallized on being rubbed with a rod. The crystals were filtered off and washed with water. Yield 3.27 g (87%), mp 99–100° C (from dioxane). Found, %: C 74.92, 74.72; H 6.88, 7.03. Calculated for $C_{21}H_{23}NO_3$, %: C 74.75; H 6.87.

The other 5-methoxyindoles **IX-XIV** were obtained similarly (Table 2).

5-Methoxy-2-methyl-1-(p-methylbenzyl)indole-3-carboxylic acid (XV). To a melt of 6.4 g (0.16 mole) of caustic soda and 1.2 ml of water was added 4.42 g (0.013 mole) of VIII. The reaction mixture was stirred vigorously at 200–220° C for 10–15 min. The cooled melt was dissolved with heating in 70 ml of water, the hot solution was filtered, and the filtrate was cooled and acidified with dilute hydrochloric acid. Yield 3.63 g (73%); mp 212–214° C (decomp., from dioxane). Found, %: N 4.47, 4.42. Calculated for $C_{19}H_{19}NO_3$, %: N 4.52.

The other indolecarboxylic acids (XVI-XIX) were obtained similarly (Table 3).

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