SYNTHESIS AND AMINOMETHYLATION OF 6-HYDROXYINDOLES

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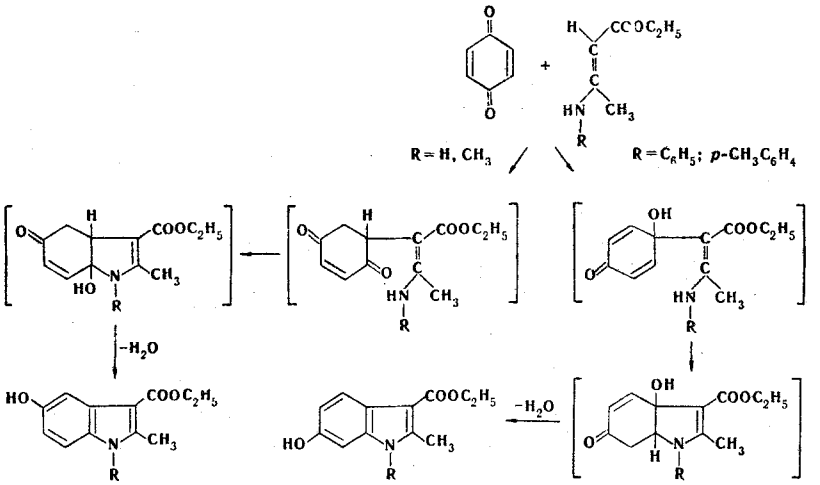
Condensation of p-benzoquinone with N-aryl-β-aminocrotonic esters was used to synthesize N-aryl-2-methyl-3-carbethoxy-6-hydroxyindoles, aminomethylation of which gave N-aryl-2-methyl-3-carbethoxy-6-hydroxy-7-dimethylaminomethylindoles.

Cooling of the mixture from the reaction of p-benzoquinone with p-chlorophenylaminocrotonic ester in acetic acid gives N-(p-chlorophenyl)-2-methyl-3-carbethoxy-6-hydroxyindole (I) [1], i.e., the reaction proceeds anomalously as compared with the other known (up until now) examples of the Nenitzescu reaction [2].

We have found that the reaction of p-benzoquinone with β-aminocrotonic esters and nitrogen-substituted β-aminocrotonic esters at 0°C in acetic acid–dichloroethane leads to derivatives of 5-hydroxy- or 6-hydroxyindole. 5-Hydroxyindole derivatives (II-III) are obtained by the action of β-aminocrotonic of N-methyl-β-aminocrotonic ester on p-benzoquinone. Under the same conditions, p-benzoquinone and N-aryl-β-aminocrotonic esters give 6-hydroxyindole derivatives (IV-V) rather than the 5-hydroxyindole derivatives that are usually obtained in the condensation (with heating) of p-benzoquinone with N-aryl-β-aminocrotonic esters [3]. Consequently, at 0° in the presence of acetic acid the direction of addition of substituted β-aminocrotonic esters to the double bond or to the carbonyl group of p-benzoquinone depends on the character of the substituent attached to the nitrogen of the β-aminocrotonic ester. 6-Hydroxy-7-dimethylaminomethylindole derivatives (VI-VIII) are formed in the reaction of 6-hydroxyindole derivatives I, IV, and V with bisdimethylaminomethane.



The structures of the derivatives obtained were proved by means of the PMR spectra. The spectrum of III contains (in the weak-field region) the doublet of a 4-H proton (7.5 ppm, $J_{4,6} = 2.5$ Hz), a 7-H doublet (7.21 ppm, $J_{7,6} = 9.0$ Hz), and a 6-H quartet (6.72 ppm, $J_{6,7} = 9.0$ Hz, $J_{6,4} = 2.5$ Hz). The position of the hydroxyl group attached to the $C_{(5)}$ atom in III was proved by means of calculation of the chemical shifts

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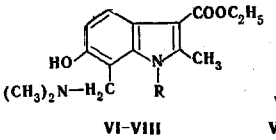


VI–VIII

VI R = *p*-ClC$_6$H$_4$;
VII R = –C$_6$H$_5$;
VIII R = *p*-CH$_3$C$_6$H$_4$

of the aromatic ring protons via an additive scheme [4] and by comparison of its PMR spectrum with the spectrum of the 5-hydroxy derivative previously obtained in [5]. A comparison of the data from the spectrum of IV with the spectrum of the substance obtained in [3], in which the hydroxyl group is attached to the $C_{(5)}$ atom, and with the results of calculation of the chemical shifts of the protons showed that the OH group in IV is in the 6 position. The signal at weakest field is that of the 4-H proton (7.88 ppm, $J_{4,5}$ = 9.0 Hz), and a 5-H quartet ($J_{5,4}$ = 9.0 Hz, $J_{5,7}$ = 2.5 Hz) and a 7-H doublet ($J_{7,5}$ = 2.5 Hz) are observed at 6.74 ppm and 6.38 ppm, respectively. The signals of the phenyl ring are situated at 7.26–7.55 ppm. The spectrum of V is similar. The presence in the spectrum of VII of two doublets with J = 9.0 Hz at 8.01 and 6.22 ppm proves that the dimethylaminomethyl group is in the 7 position. The protons of the phenyl ring have signals at 7.25–7.70 ppm. The 4-H doublets in the spectra of VI and VIII are found at 7.96 and 7.95, respectively, while the 5-H doublets are at 6.67 and 6.75, respectively.

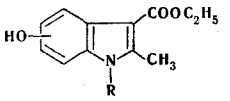
It is interesting that the substituent enters the 5 position of the indole ring in the bromination and nitration of derivatives of 6-methoxy- and 6-acetoxyindole [6]. The different orientations of the substituents in bromination and nitration, on the one hand, and in aminomethylation, on the other, can be explained by the fact that these processes occur under different conditions: bromination and nitration occur in acidic media, probably through a step involving protonation of the indole nitrogen atom, while aminomethylation proceeds in alkaline media.

EXPERIMENTAL

The PMR spectra were recorded with S-60 and JNM-4H-100 spectrometers with tetramethylsilane as the internal standard.

The spectra of III and VIII were obtained from deuterodimethylformamide solutions, while the spectra of VI and VII were obtained from deuteroacetone solutions.

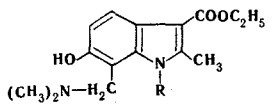
TABLE 1



Comp.	R	mp, °C (recrystalliz. solvent)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
III	CH_3	212–213* (acetone)	—	—	—	—	—	—	—	21
IV	C_6H_5	162–163 (methanol)	$C_{18}H_{19}NO_3$	72,8	5,9	4,7	73,2	5,8	4,7	10,3
V	*p*-$CH_3C_6H_4$	186–187 (methanol)	$C_{19}H_{19}NO_3$	73,5	6,0	4,5	73,8	6,2	4,5	13,5

*Identical to the compound obtained by the method in [5].

TABLE 2



Comp.	R	mp, °C (recrystallization solvent)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
VII	C_6H_5	142–143 (from acetone)	$C_{21}H_{24}N_2O_3$	71,2	6,8	7,2	71,6	6,9	7,9	61
VIII	*p*-$CH_3C_6H_4$	139–140 (from acetone)	$C_{22}H_{26}N_2O_3$	72,0	7,0	7,6	72,1	7,2	7,6	50

2-Methyl-3-carbethoxy-5-hydroxyindole (II). A solution of 17.8 g (0.165 mole) of p-benzoquinone in 125 ml of glacial acetic acid was added gradually at 0° to a cooled (to 0°) solution of 17.25 g (0.15 mole) of β-aminocrotonic ester in 20 ml of dichloroethane, after which the mixture was stirred for another 6 h at 0° and 12 h at room temperature. The precipitate was removed by filtration, washed with methanol, and dried to give 8.1 g (25%) of a product with mp 202-203° (from acetone). No melting-point depression was observed for a mixture of II with a sample of 2-methyl-3-carbethoxy-5-hydroxyindole synthesized by the method in [7].

Data on III, IV, and V, which were similarly obtained, are presented in Table 1.

1-(p-Chlorophenyl)-2-methyl-3-carbethoxy-6-hydroxy-7-dimethylaminomethylindole (VI). A solution of 4.5 g (0.014 mole) of 1-(p-chlorophenyl)-2-methyl-3-carbethoxy-6-hydroxyindole [1] and 2.1 g (0.021 mole) of bisdimethylaminomethane in 14 ml of absolute dioxane was heated for 2.5 h on a water bath. The solvent and excess bisdimethylaminomethane were removed in vacuo, and the residue was treated with methanol, removed by filtration, and dried to give 5 g (96%) of a product with mp 171-172° (from acetone). Found,%: C 65.1; H 5.8; N 7.3; Cl 8.9. $C_{21}H_{23}N_2 \cdot ClO_3$. Calculated,%: C 65.2; H 6.0; N 7.2; Cl 9.2.

Compounds VII and VIII were similarly obtained; see Table 2 for data on these compounds.

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