CHEMISTRY OF INDOLE

XXXIV.* BROMINATION OF 5-SUBSTITUTED INDOLES

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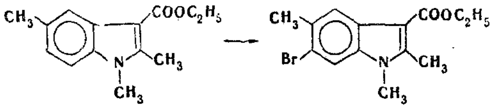
Bromination of various 5-hydroxyindole derivatives gives 6-bromo-5-hydroxyindole. Bromination in the 4 position is observed when the 6 position is occupied.

It has been previously noted that the steric requirements of the reagent in both bromination and nitration are different, a consequence of which may be a change in the orientation during introduction of a substituent [2]. It is known that the nitro group enters primarily the 6 position (i.e., the 4 position for the ordinary indole molecule) in the nitration of 7-benzyloxy-2,3-dihydro-9-formyl-1H-pyrrolo[1,2-*a*]indole [3]. There are data that indicate that bromine enters the 6 position in the bromination of 2-methyl-3-carbethoxy-5-hydroxyindole [4]; however, if there is no substituent in the benzene ring, bromination proceeds at the 5 position [2].

Our experiments have shown that the bromine atom in the bromination of 1,2-dimethyl-3-carbethoxy-5-hydroxyindole (I) in acetic acid is directed to the 6 position to give 1,2-dimethyl-3-carbethoxy-5-hydroxy-6-bromoindole (II). Bromination in the 4 position is observed only when the 6 position is occupied (XIII-XV, Table 1). Similarly, if there is a methyl group in the 5 position of the indole molecule rather than a hydroxyl group, the bromine enters the 6 position: for example, the bromination of 1,2,5-trimethyl-3-carbethoxyindole (III) gives 1,2,5-trimethyl-3-carbethoxy-6-bromoindole (IV).



III IV

Bromination with dioxane dibromide in the case of 1,2-dimethyl-3-carbethoxy-5-hydroxyindole (I) also gives the 6-bromo isomer, which, according to the UV and IR spectra, is identical to the previously obtained bromoindole (II). In the PMR spectrum of II, the aromatic region has two singlets at 7.07 and 7.38 ppm, which are characteristic for protons in the 7 and 4 positions, respectively. The PMR spectrum of 1,2-dimethyl-3-carbethoxy-5-methoxy-6-bromoindole (V) also contains two singlets (7.07 and 7.45 ppm), which correspond to the protons in the 4 and 7 positions, respectively. The change in the chemical shift of the proton in the 7 position ($\Delta\delta$ 0.24 ppm) on introduction of bromine into the 6 position is in agreement with the usual shift of the proton signal under the influence of bromine in the ortho position [5]. The 7-H shift ($\Delta\delta$ 0.06 ppm) on introduction of bromine into the 4 position of structures XIII-XV is also in good agreement with the literature data.

1,2-Dimethyl-3-carbethoxy-5-benzoyloxy-6-bromoindole (VI) was obtained both by bromination of 1,2-dimethyl-3-carbethoxy-5-benzoyloxyindole (VII) and by benzoylation of 1,2-dimethyl-3-carbethoxy-5-hydroxy-6-bromoindole (II). Similarly, 1-phenyl-2-methyl-3-carbethoxy-5-acetoxy-6-bromoindole

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[*] See [1] for communication XXXIII.

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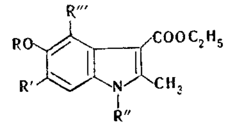
TABLE 1

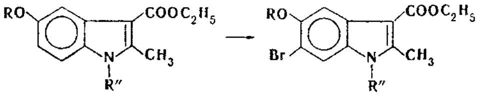


Compound	R	R′	R″	R‴	mp, °C	Empirical formula	Found, %	
							C	H
II	H	Br	CH_3	H	220—221	$C_{13}H_{14}BrNO_3$	50,1	4,6
XI	CH_3CO	Br	CH_3	H	172—174	$C_{15}H_{16}BrNO_4$	50,7	4,4
V	CH_3	Br	CH_3	H	164—165	$C_{14}H_{16}BrNO_3$	51,5	5,0
VI	C_6H_5CO	Br	CH_3	H	180—181	$C_{20}H_{18}BrNO_4$	57,9	4,6
X	H	Br	C_6H_5	H	187—188	$C_{18}H_{16}BrNO_3$	57,9	4,5
VIII	CH_3CO	Br	C_6H_5	H	136—137	$C_{20}H_{18}BrNO_4$	57,2	4,3
XII	CH_3	Br	C_6H_5	H	146—147	$C_{19}H_{18}BrNO_3$	58,8	4,5
XIII	H	CH_3	CH_3	Br	131—132 (dec.)	$C_{14}H_{16}BrNO_3$	51,5	4,9
XIV	CH_3CO	CH_3	CH_3	Br	179—180	$C_{16}H_{18}BrNO_4$	52,4	4,9
XV	CH_3	CH_3	CH_3	Br	140—141	$C_{15}H_{18}BrNO_3$	53,3	5,2

Compound	Calc., %		UV spectrum		$\nu_{C=O}$, (ν_{OH}), cm^{-1}	δ, ppm (singlets)		Yield, %
	C	H	λ_{max}, nm	lg ε		4-H	7-H	
II	50,2	4,5	218 251 295 304	4,73 4,54 4,20 4,22	1650	7,38	7,07	82
XI	50,9	4,5	227* 292 300	4,57* 4,05 4,03	1765, 1680	7,61	7,31	85
V	51,6	4,9	218* 242 288 300 313	4,59* 4,43 4,09 4,11 3,98	1700	7,07	7,45	80
VI	57,8	4,4	222 292	4,65 3,94	1745, 1685	7,78	7,38	78
X	57,8	4,3	216 244 292	4,62 4,52 4,20	1650, (3250)	—	—	35
VIII	57,7	4,4	224 234 290 297	4,59 4,60 4,20 4,15	1770, 1695	7,69	7,04	73
XII	58,8	4,7	238 288 298	4,48 4,06 4,04	1670	7,66	6,97	78
XIII	51,6	4,9	221* 308	4,36* 4,08	1685, (3420—3410)	—	—	50
XIV	52,3	4,9	224 290 298	4,61 4,10 4,08	1760, 1695	—	7,57	54
XV	53,1	5,3	220 240 288 297	4,56 4,33 4,07 4,06	1700	—	7,48	58

* These are the spectra of isooctane solutions; for XV in isooctane λ_{max}, nm (log ε): 222 (4.62), 240 (4.42), 286 (4.08), 297 (4.04).

(VIII) was obtained by bromination of 1-phenyl-2-methyl-3-carbethoxy-5-acetoxyindole (IX) and acetylation of 1-phenyl-2-methyl-3-carbethoxy-5-hydroxy-6-bromoindole (X).



II, V, VI, VIII, X, XI, XII

The UV spectrum of 1,2-dimethyl-3-carbethoxy-5-hydroxy-6-bromoindole (II) differs from that of 1,2-dimethyl-3-carbethoxy-5-hydroxyindole (I) by an increase in the extinction and a small bathochromic shift of the absorption maximum to the long-wave region. The UV spectra of 1,2,5-trimethyl-3-carbethoxy-

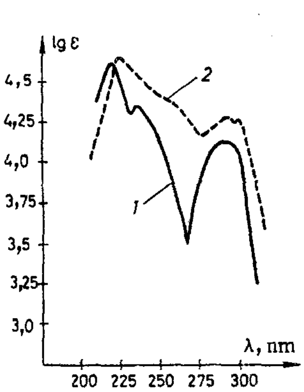


Fig. 1

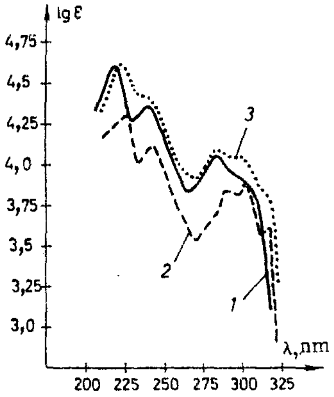
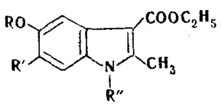


Fig. 2

Fig. 1. UV spectra in alcohol: 1) 1,2,5-trimethyl-3-carbethoxyindole (III); 2) 1,2,5-trimethyl-3-carbethoxy-6-bromoindole (IV).

Fig. 2. UV spectra in isooctane: 1) 1,2-dimethyl-3-carbethoxy-5-methoxyindole (XVII); 2) 1,2-dimethyl-3-carbethoxy-5-methoxy-6-bromoindole (V); 3) 1,2,6-trimethyl-3-carbethoxy-4-bromo-5-methoxyindole (XV).

TABLE 2



Compound	R	R′	R″	mp, °C[a]	PMR spectra: δ, ppm, positions in indole								Yield, %
					1	2	3		4[b]	5	6	7	
							CH$_3$	CH$_2$					
I[c]	H	H	CH$_3$	209[8]	—	—	1,78	—	7,94	—	7,20	7,64	60
XVI[d]	CH$_3$CO	H	CH$_3$	127—128	3,16	2,02	1,07	4,04	7,34	2,23	6,49	6,84	97
XVII[e]	CH$_3$	H	CH$_3$	114—115[11]	3,91	2,15	1,03	4,02	7,21	3,05	6,47	6,72	95
XII[f]	C$_6$H$_5$CO	H	CH$_3$	167—168	3,50	2,57	1,30	4,31	7,84	8,04 7,40	6,87	7,17	95
IX[g]	CH$_3$CO	H	C$_6$H$_5$	129—131	7,39 7,10	2,36	1,30	4,33	7,67	2,23	—	—	88
XXI[h]	CH$_3$CO	CH$_3$	CH$_3$	128—129	3,43	2,17	1,37	4,30	6,94	2,53	2,36	7,51	95

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[a] Compounds I and IX were recrystallized from acetone, while the rest were recrystallized from methanol. [b] For all of the compounds, $J_{46} = 2$ Hz, and $J_{67} = 8$-9 Hz. [c] UV spectrum: λ_{max}, nm (log ε): 217 (4.51), 244 (4.30), 288 (4.08). IR spectrum: 1660 (CO); 3225-3300 (OH) cm^{-1}. The PMR spectrum in hexametapol was recorded with an RS-60 spectrometer at 70°. [d] Found: C 66.0; H 6.2; N 5.2%. $C_{15}H_{17}NO_4$. Calculated: C 66.1; H 6.2; N 5.1%. UV spectrum: λ_{max}, nm (log ε): 217 (4.60); 286 (4.15). [e] UV spectrum: λ_{max}, nm (log ε): 217 (4.59); 240 (4.34); 283 (4.04). [f] Found: C 71.2; H 5.7; N 4.1%. $C_{20}H_{19}NO_4$. Calculated: C 71.3; H 5.7; N 4.2%. [g] Found: C 71.1; H 5.8; N 4.0%. $C_{20}H_{19}NO_4$. Calculated: C 71.3; H 5.7; N 4.2%. [h] Found: C 66.4; H 6.5; N 4.6%. $C_{16}H_{19}NO_4$. Calculated: C 66.5; H 6.6; N 4.8%.

indole (III) and 1,2,5-trimethyl-3-carbethoxy-6-bromoindole (IV) differ substantially. An increase in extinction and the appearance of an additional absorption maximum (Fig. 1) are observed in the UV spectrum of IV at 300 nm. The UV spectrum of 5-methoxy-6-bromoindole (V) in isooctane has the character of the spectrum of 5-methoxyindole (XVII) and has a fine structure at 250-320 nm. The UV spectra of the 4-bromoindole (XV) and the 6-bromoindole (V) are practically identical (Fig. 2).

In the case of nitration of diphenyl-2-carboxylic acid with nitrogen pentoxide, it was shown that the carboxyl group may serve as a nitronium-ion carrier by determining the entry of the nitro group into the ortho position [6]. A similar phenomenon is also apparently observed in the nitration of 3-carbethoxyindole derivatives; it determines entry of the nitro group into the 4 position. Coordination with the carbethoxy group during the action of bromine probably does not play a substantial role, and substitution therefore proceeds in the 6 position (in accordance with the distribution of the electron density in such structures).

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with IKS-22 and UR-10 spectrophotometers. The UV spectra of alcohol solutions were recorded with a Cary-15 spectrophotometer. The PMR spectra of trifluoroacetic acid solutions were recorded with a Varian S-60T spectrometer with hexamethyldisiloxane as the external standard. The R_f values from chromatography of the bromo derivatives on activity-II aluminum oxide (Brockmann scale) in two to three different systems did not differ from the R_f values of the starting compound. The same thing was observed during chromatography on Silufol.

1,2-Dimethyl-3-carbethoxy-5-hydroxy-6-bromoindole (II). A. A 23.3-g (0.1 mole) sample of 1,2-dimethyl-3-carbethoxy-5-hydroxyindole (I) was suspended in 200 ml of glacial acetic acid, and 16 g (0.1 mole) of bromine was added dropwise with vigorous stirring at room temperature. The mixture was then stirred for 2 h and poured into water. The resulting precipitate was removed by filtration, washed with water, dried on the filter, washed with a small amount of ether, and recrystallized from dioxane to give 25.5 g (82%) of colorless crystals of II with mp 220-221° (dec.).

B. Compound II [mp 218-219° (dec., from dioxane)] was obtained in 76% yield by bromination of I with dioxane dibromide in dioxane at room temperature. The samples were identical with respect to melting point, IR and UV spectra (Table 1).

1,2,5-Trimethyl-3-carbethoxyindole (III). A 2.7-g (0.02 mole) sample of 1-methyl-1-(p-tolyl)hydrazine [7] was heated with 5.16 g (0.04 mole) of acetoacetic ester on a boiling-water bath for 1 h. The water and excess acetoacetic ester were then removed by distillation, 10 ml of absolute diethyl ether was added, and dry hydrogen chloride was passed through the mixture for 20-30 min. The alcohol was removed by distillation, and the reaction mass was poured into water. The resulting precipitate was removed by filtration and recrystallized from heptane to give 2.76 g (60%) of colorless crystals with mp 106-107° and R_f 0.8 on aluminum oxide in benzene–ethyl acetate–heptane (4 : 1 : 3). Found: C 72.4; H 7.3; N 6.4%. $C_{14}H_{17}NO_2$. Calculated: C 72.6; H 7.4; N 6.1%. IR spectrum: 1670 cm^{-1} (CO). UV spectrum: λ_{max}, nm (log ε): 218 (4.59), 236 (4.34), 289 (4.13). PMR spectrum (in CCl_4): 7.68 (4-H, singlet), 6.8 (6,7-H_2, singlet, 2H), 4.27 (CH_2, quartet), 3.30, 2.45, 2.39 (5-CH_3, N–CH_3, 2-CH_3, singlets), 1.33 (3-CH_3, triplet) ppm.

1,2,5-Trimethyl-3-carbethoxy-6-bromoindole (IV). 1,2,5-Trimethyl-3-carbethoxyindole (III) was brominated as in the case of I in acetic acid to give colorless crystals with mp 141-142° in 97% yield. Found: C 54.2; H 5.0; N 4.4%. $C_{14}H_{16}BrNO_2$. Calculated: C 54.2; H 5.2; N 4.5%. IR spectrum: 1670 cm^{-1} (CO). UV spectrum: λ_{max}, nm (log ε): 222 (4.66), 292 (4.26), 300 (4.24). PMR spectrum: 7.51, 6.94 (4-H, 7-H, singlets), 4.28 (CH_2, quartet), 3.17, 2.37, 2.23 (N–CH_3, 5-CH_3, 2-CH_3, singlets), 1.37 (3-CH_3, triplet) ppm.

The remaining bromo derivatives (Table 1) were similarly obtained by bromination in acetic acid. Compound VI was recrystallized from dioxane–methanol, II was recrystallized from dioxane, and the rest were recrystallized from methanol.

1-Phenyl-2-methyl-3-carbethoxy-5-hydroxyindole (XVIII). This compound was obtained in 53% yield [8] and had mp 203-204° (from acetone).

1-Phenyl-2-methyl-3-carbethoxy-5-methoxyindole (XIX). This compound was obtained in 75% yield [9] and had mp 88-90°.

1,2,6-Trimethyl-3-carbethoxy-5-hydroxyindole (XX). This compound was obtained in 20% yield [10] and had mp 222-225° (from ethanol).

1,2,6-Trimethyl-3-carbethoxy-5-methoxyindole (XXII). This compound was obtained in 91% yield and had mp 134° (from methanol). Found: C 69.2; H 7.2; N 5.2%. $C_{15}H_{19}NO_3$. Calculated: C 69.2; H 7.3; N 5.4%.

The physical constants of the remaining starting compounds are given in Table 2.

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