

XXV.* BROMINATION OF THE BENZENE RING OF ALKYLINDOLES

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Indoles that have alkyl groups in the pyrrole ring are brominated in the 5 position in sulfuric acid. The introduction of an alkyl group into the 7 position may change the orientation and result in the formation of the 6-bromo isomer.

The 3 position is attacked during the reaction of halogens with indole and its alkyl derivatives; this is in agreement with the distribution of electron density in the indole ring. The cation formed in the case of indole and 3-alkylindoles is predominantly converted to a polymer, but, in the case of 2-alkyl- and 2,3-dialkylindoles, it is stabilized with the formation of the product of the addition of halogen to the C₂-C₃ double bond [2]. The preparative replacement of hydrogen by halogen is successful only by means of complexed halogen [3] or other special reagents. However, 2-alkyl- and 2,3-dialkylindoles are nitrated smoothly in the benzene ring in sulfuric acid [2,4]. This difference in the behavior during electrophilic attack is associated with the fact that the indole molecule undergoes prior protonation to form a cation with an indolenine structure. In this sort of system, the elevated electron density is retained only in the benzene ring, and electrophilic attack is directed to the 5 position as in the nitration of 2-alkyl- and 2,3-dialkylindoles [5].

Thus, by prior protonation of the indole molecule, one can exclude the electrophilic addition at the double bond of the pyrrole ring, and, by selecting the conditions, one can restrict polymerization and direct the reaction to favor substitution of the hydrogen atom of the benzene ring, which, despite protonation of the molecule, has a rather high electron density. In fact, in acetic acid, 2,3-dimethylindole adds bromine at the double bond [2], while, as we demonstrated in [6], 5-bromo-2,3-dimethylindole is formed in sulfuric acid.

Continuing our study of this problem, we have investigated the behavior of a number of alkylindoles during bromination in concentrated sulfuric acid. For successful electrophilic substitution of the hydrogen atom of the benzene ring, it was desirable to not only protonate the pyrrole portion of the molecule but

* See [1] for communication XXIV.

TABLE 1. Chemical Shifts (δ , ppm) of the Protons of the Benzene Ring of Bromoalkylindoles in CCl₄

Compound	Name	4-H	5-H	6-H	7-H
I	5-Bromo-2-methylindole	7,44	—	7,05	6,90
II	5-Bromo-2,3-dimethylindole	7,38	—	7,00	6,78
III	5-Bromo-1,2,3-trimethylindole	7,23	—	6,80	6,48
IV	6-Bromo-1,2,3,4-tetrahydrocarbazole	7,40	—	6,98	6,58
V	5-Bromo-2,3-dimethyl-1,7-ethanoindole	7,00	—	6,33	—
VI	6-Bromo-2,3-dimethyl-1,7-trimethyl-eneindole	6,95	6,95	—	—
VII	5-Bromo-2,3-dimethyl-1,7-trimethyl-eneindole	7,63	—	7,09	—
VIII	6-Bromo-1,2,3,7-tetramethylindole	6,90	6,90	—	—

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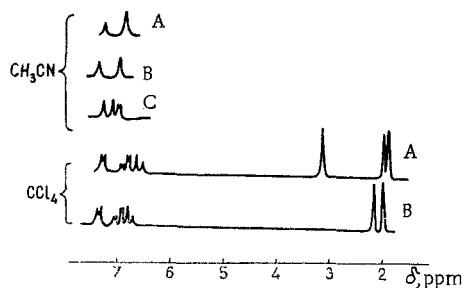
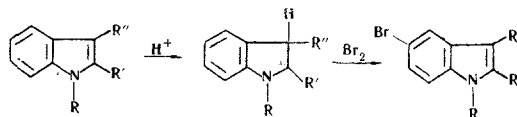


Fig. 1. PMR spectra: A) 5-bromo-1,2,3-trimethylindole (III); B) 5-bromo-2,3-dimethylindole (II); C) 6-bromo-2,3-dimethylindole (IX).

also to facilitate the formation of the Br^+ cation. The process was therefore carried out in the presence of silver sulfate. Under these conditions, 2-methyl-, 2,3-dimethyl-, and 1,2,3-trimethylindoles are brominated smoothly to form the corresponding 5-bromo derivatives. 1,2,3,4-Tetrahydrocarbazole reacts similarly.



The structures of I, II, and IV were established on the basis of the PMR spectra (Table 1). Compounds II and IV [7] were also synthesized from p-bromophenylhydrazine and the appropriate ketone.

An examination of the spectrum of bromoindole III (Fig. 1) does not give an unambiguous answer regarding the position of the bromine atom. In fact, the aromatic protons in the spectrum of III give two doublets (6.48 and 6.80 ppm) and a singlet (7.23), and one of the doublets (6.80 ppm) and the singlet have additional second-order splitting. This form of the spectrum does not contradict the 5-bromo derivative structure, but a priori one might expect a similar spectrum for the 6-isomer. The solution of the problem was obtained by a comparison of the spectrum of bromoindole III with the spectra of authentic 5- (II) and 6-bromo-2,3-dimethylindoles (IX). The latter is slightly soluble in carbon tetrachloride, and its spectra were therefore recorded from acetonitrile solutions. The position of the absorption signals of the aromatic protons of these compounds depends substantially on the solvent, and the spectra are therefore not amenable to simple analysis. However, the character of the change in the spectra and their overall form make it possible to assert that bromine enters the 5 position of molecules of III.

In the case of V, which was chromatographically homogeneous, the PMR spectrum excludes any other compounds except 5-bromo-2,3-dimethyl-1,7-ethanoindole. It was unexpected that the bromination of 2,3-dimethyl-1,7-trimethyleneindole would lead to the 6-bromo derivative (VI), which was identical to the samples obtained from the corresponding indoline (X) by bromination in sulfuric acid and subsequent dehydrogenation, as well as from nitroindoline XI by reduction to the corresponding amino derivative, conversion of the latter to the bromo derivative via the Sandmeyer reaction, and dehydrogenation.

For comparison, we synthesized 5-bromo isomer VII via the route indicated in the scheme below. Two solitary signals of the aromatic protons are observed in the PMR spectrum (Table 1) of VII (which confirms the assigned position of bromine), while the spectrum of the 6-bromo isomer (VI) contains a

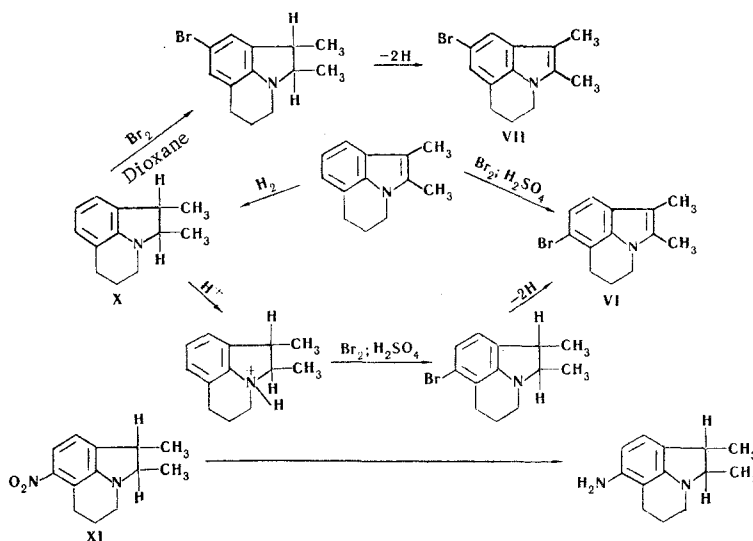


TABLE 2. Relative Intensities and m/e Values of the Principal Fragment Ions in the Mass Spectra of 5- and 6-Bromo-2,3-dimethylindoles

5-Bromo-2,3-dimethylindole(II)		6-Bromo-2,3-dimethylindole (IX)	
m/e	$I, \%$	m/e	$I, \%$
225	93,0	225	93,5
224	70,3	224	68,2
223	100,0	223	100,0
222	60,5	222	62,0
210	33,0	210	31,8
208	34,4	208	33,4
144	12,4	144	15,9
143	37,6	143	39,7

solitary signal with an intensity of two proton units. Bromine apparently strongly deshields the proton in the 5 position and less strongly deshields the proton in the 4 position. Since the proton in the 4 position in the spectrum of the starting indole is situated at weaker field than the proton in the 5 position, bromine equalizes the chemical shifts of both protons, and they become practically equivalent.

Similarly, 1,2,3,7-tetramethylindole also is brominated in the 6 position, since the PMR spectrum of the product of the reaction of VIII is similar to the spectrum of VI. No trace of the 5-isomer was detected in the reaction mass.

Thus the 6-bromo derivatives are formed by the action of bromine on 2,3-dimethyl-1,7-trimethyleneindole and 1,2,3,7-tetramethylindole in sulfuric acid. This sort of specificity in the electrophilic substitution is associated with the +I effect of the alkyl group in the 7 position. However, the nitration of 2,3-dimethyl-1,7-trimethyleneindole gives the 5-nitro isomer under similar conditions [8]. This might have been explained by the difference in the nature of the attacking agent and in its steric requirements, but 2,3-dimethyl-1,7-ethanoindole is nitrated and brominated in the 5 position. The direction of the reaction consequently depends on both the attacking agent and the substrate. We do not have sufficient data to accurately estimate their effect on the course of the process. The transition states during nitration and bromination apparently have different positions on the reaction coordinate.

The UV spectra of 5- and 6-nitro derivatives are very similar and cannot be used successfully for identification purposes. As demonstrated in the case of the 5- and 6-bromo-2,3-dimethylindoles, the mass spectra are practically identical (Table 2). The primary process in the disintegration of the molecular ions (M^+) of II and IX is detachment of H to form the rearranged $(M-1)^+$ ions characteristic for methylindoles, which apparently have the quinoline structure, as well as the formation of ions with m/e 208 (210) and 144 as a result of loss of a CH_3 and Br, respectively, by the molecular ion. The $(M-1)^+$ ions then eliminate Br to form ions with m/e 143, which can also be formed from $(M-Br)^+$ ions after elimination of a H atom and corresponding rearrangement to the quinoline structure.

It might have been expected that II and IX, which have a substituent in different positions, would give an appreciable difference in the relative intensities of the molecular and fragment ions [here, we primarily have in view the M^+ , $(M-1)^+$, and $(M-CH_3)^+$ ions], but the mass spectra were obtained under rather severe conditions (at an ionizing voltage of 70 eV and a sample-admission temperature of 200°C), and, within the limits of experimental error, no differences are observed in the disintegrations of II and IX. The subsequent disintegration of II and IX proceeds via the scheme in [9].

EXPERIMENTAL

The UV spectra of methanol solutions were recorded with an SF-4A spectrometer. The PMR spectra were recorded with an RS-60 spectrometer with hexamethyldisiloxane as the internal standard. The mass spectra were obtained with an MKh-1303 spectrometer.

The synthesis of 5-bromo- (II) and 6-bromo-2,3-dimethylindole(IX) was described in [6]. Compound II was synthesized from p-bromophenylhydrazine and methyl ethyl ketone via the method in [8]. Chromatography in a thin layer of aluminum oxide [petroleum ether-ether (1:1)] was used to evaluate the purities of the compounds obtained.

5-Bromo-2-methylindole (I). Gaseous bromine [2.4 g (0.015 mole)], volatilized by means of a current of air, was bubbled into a vigorously stirred solution of 2 g (0.015 mole) of 2-methylindole and 2.3 g (0.015 mole) of silver sulfate in 40 ml of concentrated sulfuric acid. The mixture was then stirred at room temperature for 1 h and poured over ice. The resulting precipitate was removed by filtration and washed with ether, and the filtrate was extracted with ether. The combined ether extracts were washed with water and dried with magnesium sulfate. The ether was removed and the residue was dissolved in hexane. The solution was passed through a layer of aluminum oxide, and the solvent was removed by distillation to give 1.9 g (62%) of colorless crystals of I with mp 98–99° (from hexane) (mp 96–97° [10]).

5-Bromo-1,2,3-trimethylindole (III). Similarly, 1.5 g (63%) of III with mp 40° (from hexane) was obtained from 1.6 g of 1,2,3-trimethylindole, 1.6 g of silver sulfate in 30 ml of concentrated sulfuric acid, and 1.6 g of bromine. UV spectrum: λ_{\max} 233,293 nm (log ϵ 4.63; 3.76). Found: C 55.3; H 5.2%. $C_{11}H_{12}BrN$. Calculated: C 55.5; H 5.0%.

6-Bromo-1,2,3,4-tetrahydrocarbazole (IV). A) As described above, 1.3 g (60%) of IV with mp 153–154° (from hexane) was obtained from 1.5 g of 1,2,3,4-tetrahydrocarbazole, 1.5 g of silver sulfate in 30 ml of sulfuric acid, and 2 g of bromine at room temperature.

B) A solution of 9.5 g (0.015 mole) of p-bromophenylhydrazine and 5 g (0.015 mole) of cyclohexanone in alcohol was refluxed for 40 min. The alcohol was removed in vacuo, and 100 ml of 20% sulfuric acid was added to the residue. The mixture was heated on a boiling-water bath for 20 min, and the resulting precipitate was recrystallized from alcohol to give 9.2 g (74%) of bromocarbazole IV with mp 153° [7]. Chromatography and IR spectroscopy confirmed that this product was identical to the sample described above. In addition, it did not depress the melting point of the above sample.

5-Bromo-2,3-dimethyl-1,7-ethanoindole (V). Following the general method, 1.2 g (86%) of colorless crystals of V with mp 138–139° (from hexane) was obtained from 1 g of 2,3-dimethyl-1,7-ethanoindole, 1 g of silver sulfate in 20 ml of sulfuric acid, and 2 g of bromine at room temperature. UV spectrum: λ_{\max} 244,297 nm (log ϵ 4.50; 3.78). Found: C 57.6; H 4.8%. $C_{12}H_{12}BrN$. Calculated: C 57.6; H 4.8%.

6-Bromo-2,3-dimethyl-1,7-trimethyleneindole (VI). A) Following the general method, 2.8 g (0.015 mole) of 2,3-dimethyl-1,7-trimethyleneindole was brominated by means of 2.4 g of bromine and 2.4 g of silver sulfate in 30 ml of sulfuric acid. Recrystallization of the product from heptane gave 3.1 g (75%) of VI with mp 94°. UV spectrum: λ_{\max} 237,290 nm (log ϵ 4.51; 3.90). Found: C 59.0; H 5.4%. $C_{13}H_{14}BrN$. Calculated: C 59.1; H 5.3%.

B) A mixture of 2.6 g (0.014 mole) of 2,3-dimethyl-1,7-trimethylene-2,3-dihydroindole (X) was brominated by the action of 2.3 g (0.014 mole) of bromine in 40 ml of concentrated sulfuric acid. The reaction mass was poured over ice, and the precipitate was removed by filtration. The filtrate was made alkaline and extracted with ether. The extract was dried with magnesium sulfate, the ether was removed by distillation, and the residue was vacuum-distilled to give 1.6 g (45%) of 6-bromo-2,3-dimethyl-1,7-trimethylene-2,3-dihydroindole with bp 165–167° (15 mm), which, without further purification, was dehydrogenated by refluxing for 0.5 h in xylene with an equimolar amount of chloranil. The solution was washed successively with alkali, water, dilute (1 : 1) hydrochloric acid, and water, and dried with magnesium sulfate. The solvent was removed in vacuo, and the residue was crystallized from heptane to give 17% of VI with mp 93°. This product did not depress the melting point of the sample obtained in method A, and was chromatographically identical to it.

C) A saturated aqueous solution of 1.4 g of sodium nitrite was added dropwise at 5° to a solution of 4 g (0.02 mole) of 6-amino-2,3-dimethyl-1,7-trimethylene-2,3-dihydroindole [8] in 20 ml of concentrated hydrobromic acid. The resulting solution of diazonium compound was added slowly to a freshly prepared solution of 2 g of copper bromide in hydrobromic acid. The reaction mixture was held at 50–60° until gas evolution ceased. The mixture was cooled, made alkaline with concentrated ammonium hydroxide, and extracted with ether. The extract was dried with magnesium sulfate and the ether was evaporated. The residue was dissolved in xylene, 5 g of chloranil was added, and the mixture was refluxed for 30 min. The xylene solution was washed successively with 20% sodium hydroxide solution, water, dilute hydrochloric acid, and water, and the xylene was vacuum-evaporated. The residue was dissolved in hexane and passed through a 4–5-cm layer of aluminum oxide. The hexane was removed to give 0.5 g (10%) of bromo derivative VI with mp 93–94°.

5-Bromo-2,3-dimethyl-1,7-trimethyleneindole (VII). A 1-g sample of potassium hydroxide in the minimum amount of water was added to a solution of 3.5 g (0.019 mole) of 2,3-dimethyl-1,7-trimethylene-2,3-dihydroindole in 150 ml of dioxane, and a solution of 4.6 g (0.019 mole) of dioxane dibromide in 200 ml of ether was added dropwise with vigorous stirring while maintaining the temperature at $\sim 10^\circ$. The ether layer was then washed with water and dried with magnesium sulfate. The ether was removed, and the residue was vacuum-fractionated to give 1.7 g (40%) of 5-bromo-2,3-dimethyl-1,7-trimethylene-2,3-dihydroindole with bp $132-134^\circ$ (1 mm), n_D^{20} 1.5882, d_4^{20} 1.3526, and MR_D 66.20 (calc. 65.94). The picrate had mp 147° . Found: C 46.3; H 3.9%. $C_{13}H_{16}BrN \cdot C_6H_3N_3O_7$. Calculated: C 46.3; H 3.8%. Dehydrogenation of 1.7 g of this compound with chloranil via the method described above for the dehydrogenation of the 6-bromo isomer yielded 0.6 g of VII with mp 110° (from heptane). UV spectrum: λ_{max} 237; 290-293 nm (log ϵ 4.60; 3.93). Found: C 59.1; H 5.4%. $C_{13}H_{14}BrN$. Calculated: C 59.1; H 5.3%.

6-Bromo-1,2,3,7-tetramethylindole (VIII). Similarly, 1.8 g (62%) of VIII with mp $124-125^\circ$ (from hexane) was obtained from 2 g of 1,2,3,7-tetramethylindole, 2 g of silver sulfate in 40 ml of sulfuric acid, and 3 g of bromine at $5-10^\circ$. UV spectrum: λ_{max} 237, 292 nm (log ϵ 4.34; 3.81). Found: C 56.8; H 5.3%. $C_{12}H_{14}BrN$. Calculated: C 57.1; H 5.6%.

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