AMIDOMETHYLATION OF THE BENZENE RING OF INDOLES

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The benzene ring of indoles was amidomethylated by various agents in the presence of sulfuric acid. The amidomethylation of 2-methyl- and 2,3-dimethylindoles takes place in the 5 position. When there is a methyl or methoxy group in the 5 or 7 position, the substituent enters the 6 position. Hydrazinolysis or hydrolysis of the amidomethylation products gives 5- or 6-aminomethylindoles.

Electrophilic substitution reactions involving the hydrogen atom of the benzene portion of indoles usually proceed in strongly acidic media, in which the dimerization and trimerization of the indole are alternatively possible. It is therefore necessary to completely protonate the pyrrole ring; substitution then occurs in the 5 position, unless there is a readily protonated substituent in this ring, in which case attack may take place at the $C_{(6)}$ or $C_{(4)}$ atom, as demonstrated, for example, in the case of nitration [1]. This is valid for strongly electrophilic inorganic reagents; however, acetylation of the benzene ring under Friedel—Crafts conditions gives the products in very low yields [2]. Correspondingly, Vilsmeier formylation can be carried out only when there is an electron-donor group in the benzene ring [3]. The Mannich reaction, which requires the presence of a hydroxy group, proceeds with even greater difficulty [4, 5]. Consequently, one encounters considerable difficulties in attempts to attach a hydrocarbon chain to the benzene ring of indole.

In this connection, we made a study of the possibility of amidomethylation of indoles. This reaction presents relatively low requirements for the nucleophilicity of the aromatic ring undergoing attack [6]. It was found that in sulfuric acid, in which the pyrrole ring of 2-alkyl- or 2,3-dialkylindoles is completely protonated (3-alkylindoles can be isomerized to the 2-alkyl isomers under these conditions [7]), 5-aminomethylindoles can be obtained in good yields. These data served as the subject of our inventor's certificate in 1970 [8]. A paper by Freter and co-workers [9], who described the amidomethylation of several indoles, was published in 1976, and this compelled us to publish our data in greater detail.

If the benzene ring of 2,3-dialkylindole does not contain additional activating groups, amidomethylation by means of N-hydroxymethylacetamide or N-hydroxymethylbenzamide does not occur. The compounds were recovered unchanged even after heating for many hours in sulfuric or phosphoric acid (100°C). The use of hydroxymethyl derivatives of trichloroacetamide or phthalimide, which leads to amides (imides) of the I or II type, is considerably more effective. In this case the reaction with N-hydroxymethyltrichloroacetamide is sensitive to a change in the temperature: for example, the amidomethylation of 2,3-dimethylindole goes to completion faster (in 6-8 h instead of 24 h) when the temperature is raised from 20 to 60°C, whereas it requires 15-16 h both at 20 and 100°C in the reaction with N-hydroxymethylphthalimide. Nevertheless, the yields are higher in the latter case. Substitution takes place at the $C_{(5)}$ atom in both variants. 1,2,3,4-Tetrahydrocarbazole also undergoes amidomethylation in the 6 position (see Table 1).

It is known [6] that the N-hydroxymethyl derivative of chloroacetamide is a weaker reagent than those described above. Consequently, it is less effective for amidomethylation of the benzene ring of indoles (in sulfuric or phosphoric acid); however, when there is a 5-methoxy group in the ring, the reaction takes place sufficiently smoothly and makes it possible to obtain amide VI.

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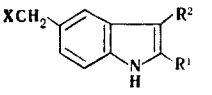
TABLE 1. Amidomethylindoles

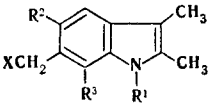
Compound	mp, °C	Found, % C	Found, % H	Empirical formula	Calc., % C	Calc., % H	R_f of the system	λ_{max}, nm (lg ε)	Yield, % (synthetic method)
Ia	195—196[a 9, 12]	—	—	$C_{19}H_{16}N_2O_2$	—	—	0,53[b]	287 (4,0)[c]	49 (A)
Ib	226—227[a 9, 11]	—	—	$C_{18}H_{14}N_2O_2$	—	—	0,37[d]	276 (3,84), 281 (3,83)[c]	74 (A)
Ic	186—187[a 11]	—	—	$C_{21}H_{18}N_2O_2$	—	—	0,56[b]	287 (3,70)[c]	80 (A)
IIa	120—122[e]	48,5	3,9	$C_{13}H_{13}Cl_3N_2O$	48,8	4,1	0,32[f]	233 (4,68), 286 (3,92)[g]	86 (B)
IIb	103—104[e]	—	—	$C_{12}H_{11}Cl_3N_2O$[h]	—	—	0,35[f]	225 (4,65), 277 (3,87), 283 (3,80), 294 (3,73)[g]	63 (B)
IIc	134—135[e]	—	—	$C_{15}H_{15}Cl_3N_2O$[i]	—	—	0,44[f]	232 (4,66), 286 (3,91)[g]	58 (B)
IIIa	235—236[j]	75,6	5,8	$C_{20}H_{18}N_2O_2$	75,5	5,7	0,24[b]		63 (A)
IIIb	204—205[k]	76,1	6,1	$C_{21}H_{20}N_2O_2$	75,9	6,0	0,47[l]	234 (4,74), 292 (3,95)[c]	56 (A)
IVa	188—189[i]	51,0	4,5	$C_{14}H_{15}Cl_3N_2O$	51,0	4,4	0,36[n]	235 (3,71), 291 (3,13)[c]	35 (B)
IVb	168—170[m]	51,8	4,8	$C_{15}H_{17}Cl_3N_2O$	51,9	4,9	0,38[n]	237 (4,58), 294 (3,83)[c]	39 (B)
Va	161—162[m]	78,4	6,9	$C_{19}H_{20}N_2O$	78,1	6,8	0,39[o]	235 (4,44), 283 (3,97), 289 (3,96)[p]	71 (C)
Vb	172—174[e]	78,4	6,7	$C_{20}H_{22}N_2O$	78,6	6,6	0,45[o]	238 (4,72), 292 (3,93)[c]	57 (C)
Vc	162—163[q]	73,8	6,6	$C_{19}H_{20}N_2O_2$	74,0	6,5	0,41[o]	230 (4,48), 293 (4,01)[p]	68 (C)
VI	149—151[r]	60,2	6,2	$C_{14}H_{17}ClN_2O_2$	59,9	6,0	0,35[s]	230 (4,29), 287 (3,98)[c]	57 (D)

[a]From acetone—chloroform (5:1). [b]Benzene—methanol (9:1). [c]In chloroform. [d]Benzene—ether (4:1). [e]From heptane. [f]Benzene—ethanol (9:1). [g]In methanol. [h]Found: N 9.0%. Calculated: N 9.1%. [i]Found: N 7.8%. Calculated: N 8.1%. [j]From heptane—benzene (7:3). [k]From benzene—petroleum ether. [l]Benzene—ether (1:1). [m]From benzene. [n]Benzene—petroleum ether—ether (3:2:1). [o]Benzene—ether (3:1). [p]In ethanol. [q]From benzene—heptane (7:3). [r]From benzene—heptane (10:1). [s]Benzene—ether (1:1).

The incorporation of the substituent in the 5 position does not raise any doubts, since aminomethylindoles identical to those previously synthesized by reduction of the corresponding amides [10] or nitriles [11] or by dehydrogenation of 5-aminomethylindolines [12] are obtained by hydrazinolysis of imides I or amides II. Freter and co-workers [9] obtained imides Ia, b with the same constants.



I, II



III–VI

I X=$C_6H_4(CO)_2N$; II X=CCl_3CONH; I, II a $R^1=R^2=CH_3$; b $R^1=CH_3$, $R^2=H$, c $R^1—R^2=(CH_2)_4$; III X=$C_6H_4(CO)_2N$; IV X=CCl_3CONH; V X=C_6H_5CONH; VI X=$ClCH_2CONH$; III—VI a $R^1=R^3=H$, $R^2=CH_3$; b $R^1=R^3=CH_3$; $R^2=H$, c $R^1=R^3=H$, $R^2=CH_3O$

Under the conditions indicated above we did not observe the formation of bisamidomethylation products. Phthalyl derivative Ia and the corresponding 2,3-dimethyl-5-acetamidomethylindole [11] are recovered virtually unchanged when they are heated with N-hydroxymethylphthalimide in sulfuric or phosphoric acid (at 100°C for 24 h). Thus an amidomethyl group attached to the benzene ring hinders the incorporation of a second such grouping; this is evidently associated with the formation of complexes through the amide or imide carbonyl group. Typical electron-donor groups facilitate the process appreciably. Thus 2,3,5-trimethylindole undergoes amidomethylation not only by the above-indicated reagents but also by N-hydroxymethylbenzamide at room temperature in sulfuric acid to give amide Va. However, N-hydroxymethylacetamide does not amidomethylate this compound even in the case of heating with concentrated sulfuric acid.

One might have expected the formation of 4 and 6 isomers for 5-substituted indoles; however, we were able to isolate only the 6 isomers (IIIa, IVa, and Va, c), although a sec-

ond substance can be detected in the reaction mixture by chromatography. The signals of the aromatic protons in the spectrum of 2,3,5-trimethylindole (in $CDCl_3$) lie at 7.22 (4-H), 6.82 (6-H), and 7.18 ppm (7-H, $J_{6,7}$ = 7.5 Hz). However, when a trichloroacetamidomethyl group is introduced (amide IVa), the signals of both the 4-H and 7-H protons are shifted to 7.37 ppm; this corresponds to the shift of the signals when a CH_2 group is introduced. Similarly, if there is a methyl group in the 7 position, substitution evidently takes place at the $C_{(6)}$ atom (as usual in the case of indoles under electrophilic attack). Thus amide IVb is obtained from 1,2,3,7-tetramethylindole. The PMR spectrum of the starting compound (in CCl_4) contains a multiplet of aromatic protons centered at 7.04 (4-H), 6.69 (5-H), and 6.54 ppm, whereas two doublets of protons at 7.10 and 6.80 ppm (J = 7.5 Hz) are apparent in the PMR spectrum of amide IVb.

The same 6-aminomethyl-1,2,3,4-tetrahydrocarbazole (Ic, IIc, X = NH_2) is obtained in the hydrazinolysis or hydrolysis of Ic and IIc. Similarly, known amines are formed from Ia and IIa and Ib and IIb. Thus the orientation does not change when the amidomethylating reagent is changed. The structures of amides IIIa, IVa, and Va are confirmed by hydrolysis to 2,3,5-trimethyl-6-aminomethylindole (X = NH_2), the Sommelet oxidation [13] of which leads to the known aldehyde.

Thus the direct amidomethylation of the benzene ring of the indole molecule can be carried out with 2-alkyl- or 2,3-dialkylindoles under the influence of strong acidic agents. The substituent enters the ring in accordance with the principles usually observed for indole in the case of electrophilic attack.

EXPERIMENTAL

The individuality of the compounds obtained was monitored by thin-layer chromatography on a loose layer of Al_2O_3 (activity III). The PMR spectra were recorded with a PC-60 or T-60 (Varian) spectrometer. The UV spectra were recorded with a Cary-15 spectrophotometer.

Amidomethylation of Substituted Indoles

A. Reaction with N-Hydroxymethylphthalimide. A solution of 3.42 g (0.02 mole) of N-hydroxymethylphthalimide in 20 ml of sulfuric acid was added dropwise in the course of 1 h to a solution of 2.74 g (0.02 mole) of 2-methylindole in 20 ml of concentrated sulfuric acid, and the mixture was stirred at room temperature for 12 h. It was then poured over ice, and the precipitate was removed by filtration, washed with water, and dried to give 4.3 g (74%) of 2-methyl-5-phthalimidomethylindole (Ib). No melting-point depression was observed for a mixture of this product with a sample obtained from 2-methyl-5-aminomethylindole with a known structure [11]. It was also identical with respect to the results of TLC and its IR spectrum (see also [9]).

B. Reaction with N-Hydroxymethyltrichloroacetamide. As in the preceding experiment, solutions of the reagents in sulfuric acid were mixed in the course of 30 min, after which the mixture was heated at 50°C for 7 h. It was then poured over ice, and the aqueous mixture was made alkaline with ammonium hydroxide. The precipitate was separated to give 3.8 g (63%) of 2-methyl-5-trichloroacetamidomethylindole (IIb).

C. Reaction with N-hydroxymethylbenzamide. As in the preceding experiment, an equimolar amount of finely ground N-hydromethylbenzamide was added to a solution of 2,3,5-trimethylindole in concentrated sulfuric acid, and the mixture was stirred at room temperature for 12 h and allowed to stand overnight. The usual workup gave 2,3,5-trimethyl-6-benzamidomethylindole (Va).

D. Reaction with N-Hydroxymethylchloroacetamide. Similarly, solutions of 2,3-dimethyl-5-methoxyindole and N-hydroxymethylchloroacetamide in 85% sulfuric acid were mixed, after which the mixture was stirred at room temperature for 10 h and allowed to stand overnight. The usual workup gave 2,3-dimethyl-5-methoxy-6-chloroacetamidomethylindole (VI).

6-Aminomethyl-1,2,3,4-tetrahydrocarbazole (VII). A mixture of 2 g (6 mmole) of phthalimide derivative Ic, 2 ml of hydrazine hydrate, and 50 ml of methanol was refluxed for 3 h, after which it was cooled, and the precipitated phthalazinedione was separated. The amine hydrochloride was precipitated from the filtrate by the addition of excess 18% hydrochloric acid. It was then washed with water and decomposed with concentrated ammonium hydroxide. The mixture was extracted with ether, the extract was dried with potassium

hydroxide, and the ether was removed to give 0.6 g (51%) of amine VII with mp 143-144°C (from heptane) [10]. UV spectrum (in methanol), λ_{max} (log ε): 232 (4.59) and 285 (3.88). Found: C 78.3; H 7.9%. $C_{13}H_{16}N_2$. Calculated: C 78.0; H 8.0%. An additional amount of the amine can be isolated from the methanol layer combined with the wash waters. The same compound was obtained by alkaline hydrolysis of amide IIc.

2-Methyl-5-aminomethylindole. A 1-g (3.6 mmole) sample of amide IIb was refluxed for 1.5 h, after which the methanol was removed by distillation, and cold water was added. The mixture was extracted with ether, the extract was dried with potassium hydroxide, and the ether was removed to give 0.46 g (88%) of the amine with mp 140-142°C (from heptane) [9, 11]. The same substance (mp 141-142°C) was obtained in 68% yield after refluxing phthalimide derivative Ib with hydrazine hydrate in methanol (for 3 h).

Similarly, the alkaline hydrolysis of amide IIa gave 2,3-dimethyl-5-aminomethylindole, with mp 152-153°C (from heptane) [9, 12], in 74% yield. The same amine (mp 154-155°C) was obtained in 53% yield by hydrazinolysis of phthalimide derivative Ia.

LITERATURE CITED

1. L. G. Yudin, A. N. Kost, E. Ya. Zinchenko, and A. G. Zhigulin, Khim. Geterotsikl. Soedin., No. 8, 1070 (1974).
2. N. N. Suvorov, N. P. Sorokina, and Yu. N. Sheinker, Zh. Obshch. Khim., 29, 979 (1959).
3. V. I. Shvedov, A. K. Chizhov, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 3, 339 (1971).
4. F. Troxler, Helv. Chim. Acta, 51, 1214 (1968).
5. V. I. Shvedov, G. N. Kurilo, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 2, 208 (1971).
6. H. E. Zaugg, Synthesis, No. 1, 49 (1970).
7. V. A. Budylin, A. N. Kost, and E. D. Matveeva, Khim. Geterotsikl. Soedin., No. 1, 55 (1972).
8. A. N. Kost, L. G. Yudin, and M. Abdullaev, USSR Inventor's Certificate No. 339161 (1972); Byul. Izobr., No. 46, 171 (1975).
9. K. Freter, F. Hess, and K. Grozinger, Ann., No. 2, 241 (1976).
10. A. G. Terzyan and G. T. Tatevosyan, Izv. Akad. Nauk Arm. SSR, 13, 193 (1960).
11. M. Abdullaev, A. N. Kost, and L. G. Yudin, Vestn. Mosk. Gos. Univ., Ser. Khim., No. 1, 113 (1972).
12. A. N. Kost, L. G. Yudin, and M. Abdullaev, Khim. Geterotsikl. Soedin., No. 10, 1339 (1975).
13. A. N. Kost, A. Muminov, and L. G. Yudin, Khim. Geterotsikl. Soedin., No. 2, 274 (1978).