according to TLC [benzene–2-propanol (10:1)]. The reaction mass was evaporated, and the oily residue was chromatographed with a column (25 by 300 mm) packed with silica gel by elution with chloroform–acetone (10:1). The fraction containing the N-acylaminoindoles was evaporated, and the residue was triturated in hexane. The solid material was removed by filtration and dried. The mixture of N-acylindoles IIb and IIIb obtained after chromatography was recrystallized from benzene, and the precipitated isomer IIb was separated. The filtrate, which, according to TLC, contained approximately equal amounts of isomers IIb and IIIb, was chromatographed on plates with silica gel in a benzene–ethyl acetate system (10:1). The fraction containing isomer IIIb was eluted with chloroform, the chloroform was evaporated, and the residue was recrystallized from alcohol to give N-acylaminoindole IIIb.

LITERATURE CITED

1. I. I. Grandberg, Izv. Timiryazev. Sel'skokhoz. Akad., No. 5, 188 (1972).
2. I. I. Grandberg, Zh. Org. Khim., 19, 2439 (1983).
3. N. M. Przheval'skii and I. I. Grandberg, Khim. Geterotsikl. Soedin., No. 11, 1581 (1974).
4. N. M. Przheval'skii, I. I. Grandberg, and N. A. Klyuev, Khim. Geterotsikl. Soedin., No. 8, 1065 (1976).
5. N. M. Sharkova, N. F. Kucherova, and V. A. Zagorevskii, Khim. Geterotsikl. Soedin., No. 11, 1580 (1974).
6. V. A. Zagorevskii, N. F. Kucherova, N. M. Sharkova, T. I. Ivanova, and S. M. Klyuev, Khim. Geterotsikl. Soedin., No. 10, 1353 (1975).
7. Shawali Ahmad Sami and Hassanun Hamdi Muhmoud, Bull. Chem. Soc. Jpn., 51, 512 (1978).
8. G. A. Golubeva, Yu. N. Portnov, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 4, 511 (1973).

SYNTHESIS OF BENZO(AMINOMETHYL)INDOLES

A. Muminov, L. G. Yudin, E. Ya. Zinchenko,
N. N. Romanova, and A. N. Kost

UDC 547.753:542.951.1

The benzene ring in indoles has been aminomethylated in high yield by reaction with methylolphthalimide followed by hydrazinolysis of the phthalimidomethyl derivatives. In the hydrazinolysis of one of the phthalimidomethyl compounds, an intermediate product (the amino-methylindole phthalazine) was isolated and characterized.

It has been shown previously [1, 2] that 1,2,3-trialkylindoles, on reaction with powerful amidomethylating agents such as N-hydroxy-methylphthalimide and N-hydroxymethyltrichloroacetamide in acidic solution afford 5- or 6-aminomethylindoles. These model compounds have also been chloroacetamidomethylated [3] by activating the reagent with a mixture of concentrated sulfuric acid and phosphorus pentoxide. However, the amido-methylation of indoles with N-hydroxymethylphthalimide followed by hydrazinolysis has been examined to only a limited extent, and the yields of aminomethylindoles obtained were poor.

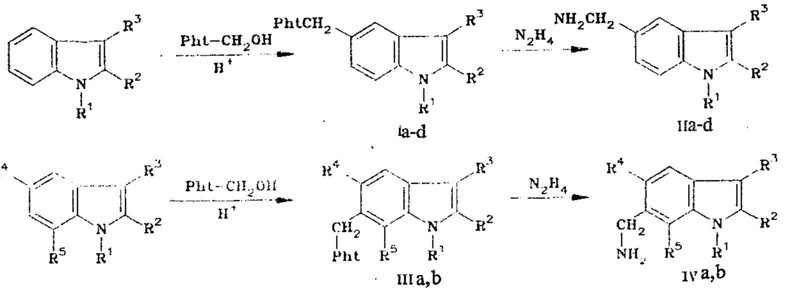
We have studied the amidomethylation of substituted indoles, varying the molar ratios of the reactants, temperature, and the concentrations of the condensing agent and acids. To avoid resinification and di-, tri-, and polymerization on dissolution in strong acids, we reduced the temperature to 0-5°C, and used freshly purified starting materials.

The amidomethylation of indoles which did not contain electron-donor substituents in the benzene ring occurred smoothly in the 5-position (Ia-d) when N-hydroxymethylphthalimide was used as the amidomethylating agent.

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, 1218-1221, September, 1985. Original article submitted March 19, 1985.

0009-3122/85/2109-1012$09.50

Indoles containing electron-donor substituents in the benzene ring underwent amidomethylation in 80–85% sulfuric acid to give (IIIa, b) in nearly quantitative yields. Evidently, the competing sulfonation of the ring which usually occurs is here avoided by the use of less concentrated sulfuric acid.

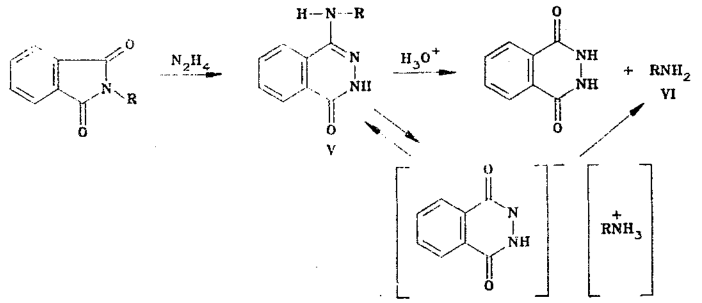


I, II a $R^1=R^3=H$; $R^2=CH_3$; b $R^1=R^2=CH_3$; $R^3=H$; c $R^1=H$; $R^2=R^3=CH_3$; d $R^1=H$; $R^2+R^3=(CH_2)_4$; $Pht=C_6H_4(CO)_2N$; III, IV a $R^1=R^5=H$; $R^2=R^3=CH_3$; $R^4=OCH_3$; b $R^1=R^4=H$; $R^2=R^3=CH_3$; $R^5=OCH_3$; $Pht=C_6H_4(CO)_2N$

The structures and compositions of (I) and (III) were confirmed by their elemental analyses and IR and NMR spectra, and by their subsequent chemical reactions.

In order to increase the yields of the aminomethylindoles (II) and (IV), the conditions for the hydrazinolysis of (I) and (III) were examined in detail.

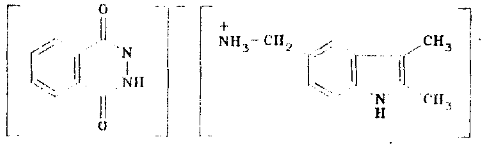
According to Ing and Manske [4], the hydrazinolysis of N-alkylphthalimides gives intermediate compounds such as (V), which on acidification undergo hydrolysis to the amine (VI).



VII

Subsequent studies [5-7] showed that the reaction proceeded via the intermediate formation of the ionic compound (VII). It is also known [6] that salts of this type can undergo autocondensation to give the original compound (V).

It has been found that the phthalimidomethylindoles obtained, which are usually insoluble in alcohol, on treatment with hydrazine rapidly dissolve therein, and after 30-40 minutes a crystalline solid separates which corresponds to the ionic structure (VII). For example, in the hydrazinolysis of (Ic) it was found possible to isolate the intermediate 2,3-dimethyl-5-aminomethylindole phthalazinate (VIII).



VIII

The IR spectrum of the salt (VIII) showed absorption at 1640 and 1580 (C=O), and 3270 and 3220 cm^{-1} (NH), together with a broad band for the NH_3^+ ion at 2600-1800 cm^{-1}.

The PMR spectrum (in conc. sulfuric acid) contained a doublet at 1.17 (3H, 3-CH_3), and singlets at 2.36 (3H, 2-CH_3) and 3.80 ppm (2H, 5-CH_2). In the aromatic region, two groups of signals were seen at 7.06 and 8.03 ppm.

The mass spectrum of (VIII) showed molecular ion peaks for both the aminomethylindole (m/z)174.50%) and phthalazinedione (m/z 162.61%), together with the indole ion fragment $[M - NH_2]^+$ (m/z 158, 100%), thus precluding the aminophthalazole structure (V) for (VIII).

Ionophoretic studies showed that (VIII) has an ionic structure incorporating the phthalazinedione anion.

Together with its elemental analysis, these physicochemical findings confirm structure (VIII).

Bearing in mind that compounds such as (V) require more severe conditions for hydrazinolysis than (VIII), the reaction mixture after hydrazinolysis was treated with an excess of 10-15% hydrochloric acid with heating, enabling high yields (79-95%) of the 5- and 6-aminomethylindoles (IIa-d) and (IVa, b) to be obtained.

EXPERIMENTAL

IR spectra were obtained on UR-20 and IKS-22 instruments in vaseline oil, and PMR spectra on a Varian T-60. Mass spectra were obtained on an MX-1303 instrument with direct introduction of the sample into the ionizing region, ionizing electron energy 50 eV.

1,2-Dimethyl-5-(phthalimidomethyl)indole (Ib). Five grams (34 mmole) of 1,2-dimethylindole was dissolved with cooling in 40 ml of conc. sulfuric acid. To the resulting solution was added dropwise a solution of 6.2 g (36 mmole) of N-hydroxymethylphthalimide in 25 ml of conc. sulfuric acid, and the mixture stirred for 30 h at ambient temperature, then poured on to crushed ice (400 g), the pH adjusted to 6-7 with aqueous ammonia, and kept for 10 h. The resulting solid was filtered off, washed with water (3-4 times) and a small amount of ether, and dried, to give 11 g of the indole (Ib) (quantitative yield), mp 229-230°C (from chloroform). PMR spectrum (CF_3COOH): 2.97 (3H, s. 2-CH_3); 3.23 (3H, s, 1-CH_3); 3.67 (1H, s, 3-H); 4.53 (2H, s, 5-CH_2); 7.33 ppm (7H, m, arom.). IR spectrum: 1710, 1690 cm^{-1} (CO). Found: C 75.2; H 5.5%. $C_{19}H_{16}N_2O_2$. Calculated: C 75.0; H 5.3%.

Phthalimidomethyl Compounds (Ia, c, and d) [1] were obtained similarly in high yields: (Ia) (96%), mp 226-227°C (from chloroform); (Ic) (98%), mp 195-196°C (from a mixture of acetone and chloroform); (Id) (quantitative yield), mp 186-187°C (from chloroform).

2,3-Dimethyl-5-methoxy-6-(phthalimidomethyl)indole (IIIa). To 80 ml of 80% sulfuric acid, previously cooled to 0°C, was added gradually with stirring 17.5 g (100 mmole) of freshly-recrystallized 2,3-dimethyl-5-methoxyindole. When the solid had dissolved completely, a solution of 17.8 g (110 mmole) of N-hydroxyphthalimide in 80 ml of 80% sulfuric acid was added dropwise with stirring over 2 h. The mixture was stirred at ambient temperature for 30 h, the reaction being followed by chromatography on Silufol UV-254 (benzene—methanol, 20:1). The mixture was then poured on to ice, and the pH of the mixture brought to 6-7 with aqueous ammonia, with cooling. After 8-10 h, the solid was filtered off, washed with water and a small amount of ether, and dried. The yield of (IIIa) was 31.2 g (93%), mp 247-249°C (from chloroform). IR spectrum: 1725, 1684 cm^{-1} (CO). PMR spectrum (CF_3COOH): 1.62 (3H, d, 3-CH_3); 2.38 (3H, s. 2-CH_3); 3.65 (3H, s, CH_3O); 4.57 (2H, s, 6-CH_2); 6.75-5.95 ppm (m. arom.). Found: C 71.6; H 5.5%. $C_{20}H_{18}N_2O_3$. Calculated: 71.8; H 5.4%.

6-Phthalimidomethylindole (IIIb) was obtained similarly in 89% yield, mp 184-186°C (from benzene). IR spectrum: 1765, 1700 cm^{-1} (CO). PMR spectrum (CF_3COOH): 1.73 (3H, d, 3-CH_3); 2.78 (3H, s. 2-CH_3); 3.80 (3H, s. OCH_3); 4.9 (2H, s. CH_2); 6.89 (1H, d, 4-H), 7.43 (1H, d, 5-H); 7.68 ppm (m. arom.). Found: C 71.5; H 5.2%. $C_{20}H_{18}N_2O_3$. Calculated: C 71.8; H 5.4%.

2,3-Dimethyl-5-aminomethylindole Phthalazinate (VIII). A mixture of 3.3 g (10 mmole) of (Ic) and 1.5 ml of hydrazine hydrate in 60 ml of methanol was boiled for 2 h. The mixture was cooled, and the solid which separated was filtered off to give 2.87 g (79%) of 2,3-dimethyl-5-aminomethylindole phthalazinate (VIII), mp 230°C (from alcohol. decomp.). Found: C 67.4; H 6.2%. $C_{19}H_{20}N_4O_2$. Calculated: C 67.9; H 6.0%.

1,2-Dimethyl-5-aminomethylindole (IIb). To a suspension of 3.3 g (10 mmole) of (Ib) in 60 ml of methanol was added 1 ml of hydrazine hydrate. The mixture was boiled for 1.5 h, completion of the reaction being checked by TLC on Silufol (benzene—methanol, 20:1). The solvent was evaporated, and to the residue was added 50 ml of 10% hydrochloric acid. The mixture was heated on the water bath for 1 h, cooled, and the solid filtered off and washed with water. The filtrate was treated with cooling with aqueous sodium hydroxide to pH 6-7. The solid which separated was extracted with ether (4 × 30 ml). The combined extracts were dried over fused sodium hydroxide, and the ether removed to give 1.45 g (83%) of the aminomethylindole (IIb), mp 81-82°C (from light petroleum). IR spectrum: 3370 cm^{-1} (NH). PMR spectrum (CCl_4): 2.26 (3H, s, 1-CH_3); 3.37 (3H, s, 2-CH_3); 3.51 (2H, s, NH_2); 5.12 (2H, s. 5-CH_2); 6.37 (1H, s, 3-H); 6.79 (1H, d, 6-H); 7.12 (1H, d, 7-H); 7.25 ppm (1H, s, 4-H). Found: C 75.6; H 8.2%. $C_{11}H_{14}N_2$. Calculated: C 75.9; H 8.0%.

Similarly obtained were (IIa), yield 92%, mp 140-142°C (from heptane) [1], (IId), 83%, mp 143-144°C (from light petroleum) [1], and (IIc), 95%, mp 152-153°C (from light petroleum) [8].

Aminomethylindoles (IVa, b), with a methoxy-group in the benzene ring, were obtained by the same method in high yields: 79% in the case of (IVa), mp 164-165°C (from ether), IR spectrum 3415-3387 cm^{-1} (NH). Found: C 70.9; H 7.7%. Calculated: C 70.6%; H 7.9%. $C_{12}H_{16}N_2O$, and 83% of (IVb), mp 177-179°C (from heptane), IR spectrum 3350-3300 cm^{-1} (NH), PMR spectrum ($CDCl_3$): 2.26 (3H, s, 3-CH_3); 2.33 (3H, s. 2-CH_3); 3.87 (3H, s. 7-OCH_3); 4.07 (2H, s. 6-CH_2); 6.46 (1H, d. 4-H), 6.78 ppm (1H, d, 5-H). Found: C 70.3; H 8.0; N 14.1%. $C_{12}H_{16}N_2O$. Calculated: C 70.6; H 7.9; H 13.7%.

LITERATURE CITED

1. L. G. Yudin, M. Abdullaev, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 8, 1066 (1978).
2. K. Freter, F. Hess, and K. Grozinger, Ann. Chem., 2, 241 (1976).
3. A. Muminov, A. N. Kost, and L. G. Yudin, Vestn. Mosk. Gos. Univ., Ser. Khim., No. 2, 158 (1979).
4. H. R. Ing and R. H. F. Manske, J. Chem. Soc., 129, 2348 (1926).
5. L. Reisch and H. Labitzke, Arch. Pharm., 9, 713 (1975).
6. E. Bergmann and Y. Migron, J. Org. Prep. Procedure, 8, 80 (1976).
7. J. McOmie, Protecting Groups in Organic Chemistry, Plenum Press (1973).
8. A. G. Terzyan and G. T. Tatevosyan, Izv. Akad. Nauk Arm. SSR, Ser. Khim., 13, 193 (1960).