amplitudes. The time interval for the observations until complete disappearance of the signal for Hβ varied from several minutes to several hours. The K_D values related solely to the pyrrole β-carbon atom; in all cases, the NH proton exchanged instantaneously.

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A NEW APPROACH TO THE SYNTHESIS OF 2-AMINOMETHYL-3-PHENYL-5-NITROINDOLE

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Bromination of 2-methyl-3-phenyl-5-nitroindoles has given previously unknown 2-bromoethyl-3-phenyl-5-nitroindoles, which were converted by the Delepine reaction into 2-aminomethyl-3-phenyl-5-nitroindoles. One of these (1-methyl-2-aminomethyl-3-phenyl-5-nitroindole) was also obtained by reductive amination of 1-methyl-2-formyl-3-phenyl-5-nitroindole by the Leuckart–Wallach reaction.

This work was carried out in view of interest in the synthesis of the tranquilizers nitrazepam [1] and hypnone [2]. The key compounds in the synthesis of these drugs are 2-aminomethyl-3-phenyl-5-nitroindoles. These compounds have hitherto been synthesized from 3-phenyl-5-nitroindole-2-carbonitriles by selective reduction of the nitro group with sodium borohydride in the presence of boron trifluoride etherate or with a mixture of diborane and sodium borohydride in tetrahydrofuran [3-7].

We here describe a new, more rational synthesis of 2-aminomethyl-3-phenyl-5-nitroindoles (see scheme on following page).

The starting material was the known 2-methyl-3-phenyl-5-nitroindole (I) [8, 9], obtained in high yield by a method improved by the authors. Methylation of (I) with dimethyl sulfate afforded 1,2-dimethyl-3-phenyl-5-nitroindole (II). Bromination of (I) and (II) gave the 2-bromomethyl derivatives (III) and (IV). The bromination was carried out with dioxane dibromide, N-bromosuccinimide, or bromine under various conditions. The highest

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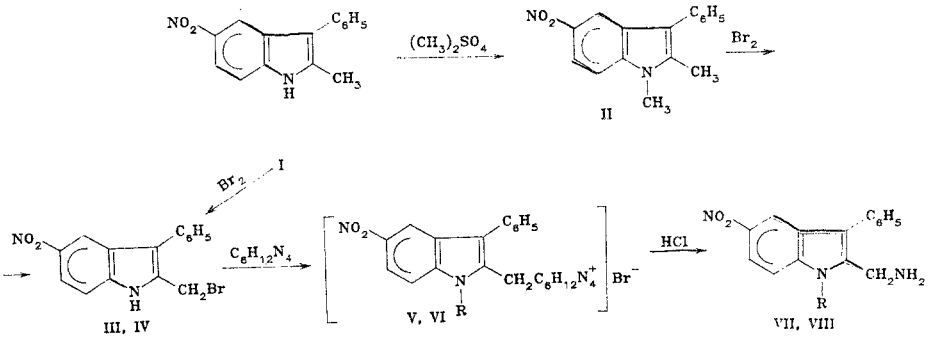


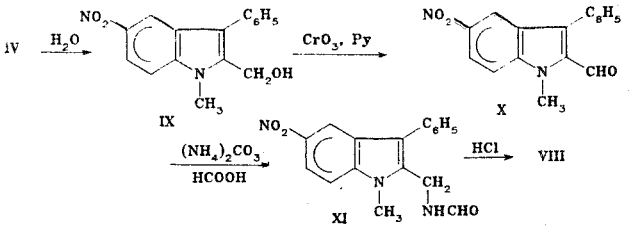
III, V, VII R=H; IV, VI, VIII R=CH_3

yields of the 2-bromomethyl compounds (III) and (IV) were obtained by bromination with bromine in glacial acetic acid or dichloroethane at 20°C under illumination.

In contrast to the PMR spectrum of the starting material (II), the spectrum of (IV) did not contain a signal for the 2-CH_3 group at 2.46 ppm, but a new singlet signal for the protons of the CH_2Br group was seen at 4.69 ppm.

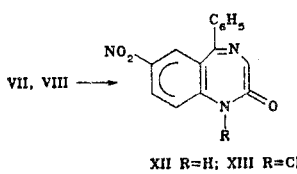
The mass spectrum of the 1-methyl-2-bromomethyl compound (IV) contained a molecular ion peak with m/z 344/346. The strongest peak corresponded to a fragment with m/z 265 (M — Br), since elimination of bromine results in the formation of a stable ion.

Reaction of (III) and (IV) with urotropin gave the urotropin complexes (V) and (VI), which on acid hydrolysis afforded 2-aminomethyl-3-phenyl-5-nitroindole (VII) and 1-methyl-2-aminomethyl-3-phenyl-5-nitroindole (VIII) [11]. The spectral characteristics of (VII) and (VIII) agreed with those given in the literature [3, 6]. Compound (VIII) was also obtained by a different method:



Hydrolysis of (IV) gave 1-methyl-2-hydroxymethyl-3-phenyl-5-nitroindole (IX). The presence in the IR spectrum of (IX) of absorption for stretching vibrations of the OH group at 3320-3480 cm^{-1} confirmed its structure. Oxidation of (IX) with chromic anhydride in pyridine yielded 1-methyl-2-formyl-3-phenyl-5-nitroindole (X), the IR spectrum of which showed strong absorption at 1670 cm^{-1} corresponding to carbonyl stretching vibrations in 2-formylindoles [12]. The Leuckart—Wallach reaction with (X) gave 1-methyl-2-formylaminomethyl-3-phenyl-5-nitroindole (XI), the structure of which was confirmed by the presence of characteristic absorption at 3220 cm^{-1} (NH) which was absent from the spectrum of the starting material (X). Acid hydrolysis of (XI) afforded the 1-methyl-2-aminomethyl compound (VIII) [13]. A mixed melting point with a sample obtained earlier in this investigation showed no depression.

On treatment with chromic acid as described in [3], the 2-aminomethyl derivatives (VII) and (VIII) were converted into the previously-described 7-nitro-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one (XII) (nitrazepam) and its N-methyl analog (hypnone).



XII R=H; XIII R=CH_3

EXPERIMENTAL

The IR spectra of the compounds prepared were obtained on Perkin-Elmer and UR-10

spectrometers in vaseline oil, UV spectra on a Hitachi ERS-3T spectrometer in methanol, and PMR spectra on Varian XL 100-A-12 and Jeol JNM-100 instruments, internal standard TMS, solvent as given in each instance. Mass spectra were obtained on an LK B-9000 chromatograph-mass spectrometer with direct introduction of the sample into the ion source, ionizing electron energy 70 eV, and source temperature 150°C. The purities of the compounds obtained and the course of the reactions were followed by TLC on Silufol-254 plates in the systems benzene, benzene–methanol (9:1), and nitromethane–ethyl acetate (85:15). Visualization was in UV light.

2-Methyl-3-phenyl-5-nitroindole (I). To a suspension of 13.4 (0.05 mole) of benzyl methyl ketone p-nitrophenylhydrazone in 20 ml of 98% acetic acid, heated to 80°C, was added with stirring 20 ml of conc. HCl. The mixture was stirred for 2 h at 80°C, cooled to 10°C, and kept for 2 h. The solid was filtered off, washed with cold acetic acid (3 × 30 ml) and water, and dried to give 8.82 g (70%), mp 197-198°C (from dichloroethane). The melting point agreed with the literature value [9].

1,2-Dimethyl-3-phenyl-5-nitroindole (II). To a solution of 2.52 g (0.01 mole) of the indole (I) in 50 ml of acetone was added at 20°C with stirring a 50% aqueous solution of KOH (2.3 g) and 1.9 g (0.017 mole) of dimethyl sulfate. The mixture was stirred for 1 h at 20°C, then poured into water, the solid filtered off, washed with water until neutral, and dried to give 2.16 g (82%), mp 169-170°C (from methanol). UV spectrum, λ_{max} (log ε): 276 (4.31), 322 nm (3.87). Found, %: C 71.9; H 5.3; N 10.5. $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.1; H 5.3; N 10.5.

2-Bromomethyl-3-phenyl-5-nitroindole (III). To a suspension of 50.4 g (0.2 mole) of (I) in 800 ml of dry dichloroethane was added with stirring under illumination by a 150-W lamp over a period of 1 h, 10.4 g (0.02 mole) of bromine in 70 ml of dichloroethane. The mixture was stirred for 1 h, and the solid which separated was filtered off and dried to give 56.3 g (85%), mp 236-237°C (from dichloroethane). Found, %: C 54.0; H 3.3; Br 24.0; N 8.3. $C_{16}H_{11}BrN_2O_2$. Calculated, %: C 54.4; H 3.3; Br 24.1; N 8.3.

1-Methyl-2-bromomethyl-3-phenyl-5-nitroindole (IV). Synthesized as for (III), (IV) was obtained in 95% yield, mp 212-213°C (from benzene), UV spectrum (in dioxane), λ_{max} (log ε): 285 (4.38), 330 nm (3.95). PMR spectrum ($CDCl_3$): 3.91 (s, 3H, N-CH_3); 4.69 (s, 2H, CH_2Br); 7.37 (1H, 7-H, J_o = 9 Hz); 7.53 (m, 5H, arom.); 8.18 (q, 1H, J_o = 9 Hz, J_m = 2 Hz, 6-H); 8.59 ppm (d, J = 2 Hz, 4-H). Found, %: C 55.8; H 3.5; Br 23.0; N 8.1. $C_{16}H_{13}BrN_2O_2$. Calculated, %: C 55.7; H 3.3; Br 23.1; N 8.1; M 345.2.

2-Aminomethyl-3-phenyl-5-nitroindole (VII). A solution of 7 g (0.05 mole) of urotropin and 16.5 g (0.05 mole) of the bromide (III) in 200 ml of chloroform was boiled for 6 h, then kept for 6 h at 20°C. The urotropin complex was treated with 100 ml of ethanol and 35 ml of conc. HCl, and the mixture was boiled for 3 h. After cooling, the solid which separated was filtered off and dried to give 14.3 g (95%) of (VII) hydrochloride, mp 283-285°C (decomp., from alcohol). Found, %: C 59.6; H 4.8; Cl 11.4; N 14.0. $C_{15}H_{14}ClN_3O_2$. Calculated, %: C 59.3; H 4.6; Cl 11.7; N 13.8.

A suspension of (VII) hydrochloride in chloroform was basified with 40% sodium hydroxide solution, and stirred at 20°C for 4 h. The chloroform layer was separated, washed with water, dried over $MgSO_4$, and evaporated to give the free base of (VII), mp 207-207.5°C (from alcohol), literature value [7], 182-184°C. IR spectrum: 3360, 3300 cm^{-1} (NH_2): UV spectrum, λ_{max} (log ε): 270 (4.4), 330 nm (3.92); PMR spectrum (DMSO + CCl_4): 4.32 (s, 2H, 2-CH_2NH_2); 7.25-7.65 (m, 6H, 5 arom. and 7-H); 8.94 (s, 2H, NH_2); 8.03 (br. d., 1H, 6-H); 8.41 (s, 1H, 4-H); 12.52 ppm (s, 1H, NH). Found, %: C 67.4; H 5.2; N 15.9. $C_{15}H_{13}N_3O_2$. Calculated, %: C 67.4; H 4.9; N 15.7.

1-Methyl-2-aminomethyl-3-phenyl-5-nitroindole (VIII). As in the preceding experiment, from 12 g (0.035 mole) of (IV), 4.9 g urotropin, 150 ml of chloroform, 25 ml of conc. HCl, and 100 ml of alcohol there was obtained 10.5 g (95%) of (VIII) hydrochloride, mp 279-282°C (from DMF) (literature value [3], 278-280°C).

The free base of (VIII) was isolated as described above, mp 159-160°C (from alcohol). IR spectrum: 3380, 3100 cm^{-1} (NH_2). UV spectrum, λ_{max} (log ε): shoulder 266 (4.35), 280 (4.45), 336 nm (3.95); PMR spectrum ($CDCl_3$): 1.34 (s, 2H, NH_2); 3.92 (s, 3H, N–CH_3); 4.06 (s, 2H, $-CH_2-$); 7.38 (d, 1H, 7-H, J_o = 9 Hz); 7.42 (s, 5H, arom.); 8.09 ppm (q, 1H, J_o = 9 Hz, 4H, J_m = 2 Hz). Found, %: C 68.5; H 5.3; N 14.9. $C_{16}H_{15}N_3O_2$. Calculated, %: C 68.3; H 5.4; N 14.9.

1-Methyl-2-hydroxymethyl-3-phenyl-5-nitroindole (IX). A mixture of 3.45 g (0.01 mole) of (II), 30 ml of dioxane, and 15 ml of water was boiled for 4 h. The mixture was poured into 100 ml of water, and the solid filtered off, washed with water, and dried to give 2.12 g (73%), mp 178-179°C (from dioxane). IR spectrum: 3330 cm^{-1} (OH). UV spectrum (in dioxane), λ_{max} (log ε): shoulder 226 (4.3), 282 (4.32), 336 nm (3.9). Found, %: C 68.0; H 4.9; N 9.9. $C_{16}H_{14}N_2O_3$. Calculated, %: C 68.2; H 4.9; N 9.9.

1-Methyl-2-formyl-3-phenyl-5-nitroindole (X). A mixture of 160 ml of pyridine and 8 g of chromic anhydride was stirred for 10 min, a solution of 10 g (0.036 mole) of (IV) in 50 ml of pyridine was added, and the mixture kept for 12 h at 20°C. The mixture was then treated with 500 ml of water, and the solid filtered off, washed with water, and dried. The solid was chromatographed on 50 g of silica gel, eluent chloroform. Yield 7 g (70%), mp 183.5-184.5°C (from acetone–alcohol). IR spectrum: 1670 cm^{-1} (CO). Found, %: C 68.4; H 4.4; N 9.8. $C_{16}H_{12}N_2O_3$. Calculated, %: C 68.5; H 4.3; N 10.0.

1-Methyl-2-formylaminomethyl-3-phenyl-5-nitroindole (XI). In a flask fitted with a reflux condenser was placed 5.5 g (0.058 mole) of ammonium carbonate, and 10 ml (0.2 mole) of 85% formic acid was added slowly through the condenser. The condenser was then set for distillation, and the mixture was slowly heated to 160°C. At this temperature, excess formic acid distilled over. To the resulting ammonium formate was added 4.2 g (0.015 mole) of the aldehyde (X), and heating was continued, whereupon the mixture became homogeneous and the temperature rose to 175-180°C. The mixture was kept at this temperature for 7 h, cooled, and diluted with twice its volume of water to dissolve unreacted ammonium formate. The solid was filtered off, washed with water, and dried to give 1.74 g (37%), mp 187-188°C (from alcohol). IR spectrum: 3220 (NH), 1660 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 260 (4.2), 270 (4.22), 3.36 nm (3.92). Found, %: C 66.0; H 4.9; N 13.6. $C_{17}H_{15}N_3O_3$. Calculated, %: C 66.3; H 4.7; N 13.4.

1-Methyl-2-aminomethyl-3-phenyl-5-nitroindole (VIII). A solution of 1.85 g (0.006 mole) of (VI) in 12 ml of conc. HCl and 12 ml of dioxane was boiled for 2 h, cooled, and the solid filtered off and dried to give 1.45 g (76%) of (VIII) hydrochloride, mp 279-180°C (decomp., from DMF). A mixed melting point with a sample obtained earlier in this work gave no depression.

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