INDOLE DERIVATIVES.
138.* SYNTHESIS OF α-(5-INDOLYL)ETHYLAMINE AND 5-(2-AMINOETHOXY)- AND 5-(AMINOETHYLTHIO)TRYPTAMINES

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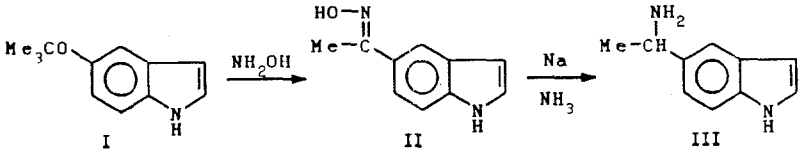
The reaction of 5-acetylindole with hydroxylamine with subsequent reduction of the resulting oxime gave α-(5-indolyl)ethylamine. Coupling of 4-(2-phthalimidoethoxy)- and 4-(2-phthalimidoethylthio)phenyldiazonium chlorides with ethyl α-acetyl-δ-phthalimidovalerate, subsequent cyclization of the resulting hydrazones, hydrolysis, decarboxylation, and removal of the phthalyl protecting group led to the formation of 5-(2-aminoethoxy)- and 5-(2-aminoethylthio)tryptamines, respectively.

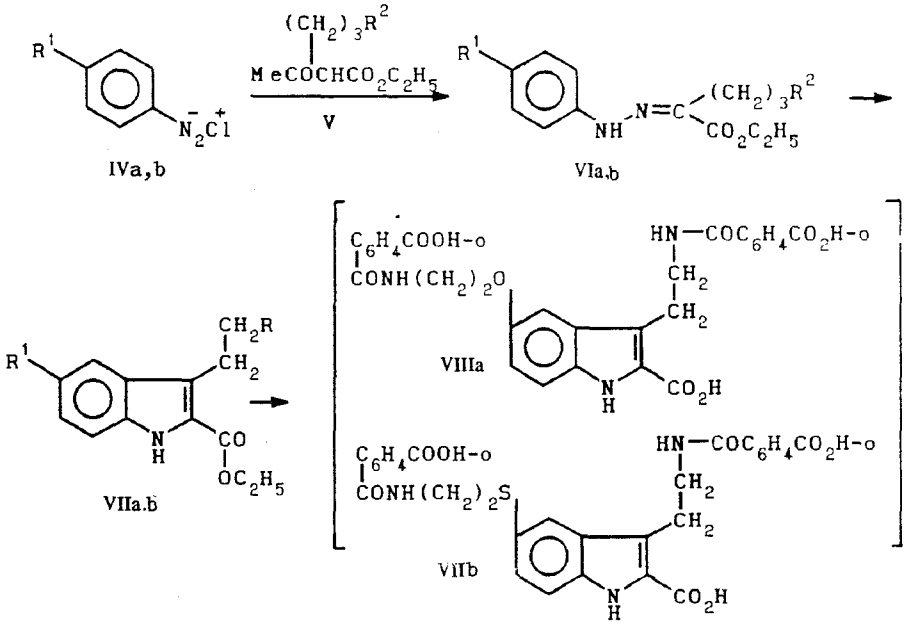
For a study of the radioprotectant activity of indole derivatives, we synthesized α-(5-indolyl)ethylamine and 5-(2-aminoethoxy)- and 5-(2-aminoethylthio)tryptamines.

The α-(5-indolyl)ethylamine (III) was obtained from 5-acetylindole (I) [2] via the corresponding oxime with subsequent reduction by sodium in liquid ammonia according to the scheme



Amine III was recovered and studied in the form of a neutral adipate.

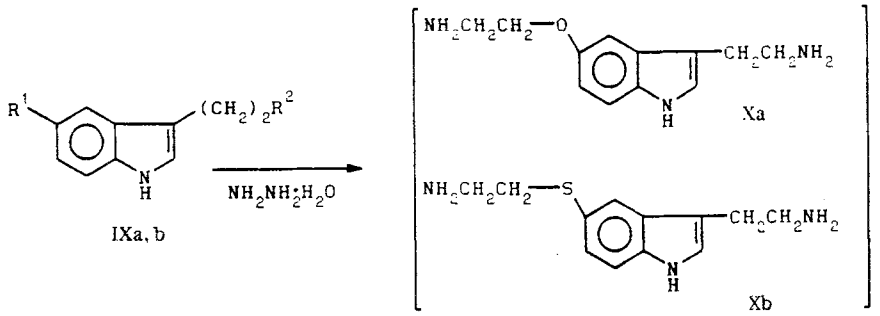
The 5-(2-aminoethoxy)- and 5-(2-aminoethylthio)tryptamines were synthesized by the Japp—Klingemann and Fischer reactions according to the scheme [3, 4]



*For Communication 137, see [1].

D. I. Mendeleev Chemical and Technological Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 46-48, January, 1992. Original article submitted March 12, 1990.

0009-3122/92/2801-0040$12.50



IV, VI, VII, IX a $R^1 = C_6H_4(CO)_2NCH_2CH_2O$-; b $R^1 = C_6H_4(CO)_2NCH_2CH_2S$-
V, VI, IX $R^2 = C_6H_4(CO)_2N$-

The starting anilines were obtained by alkylation of p-nitrophenol and p-nitrothiophenol by N-(2-bromoethyl)phthalimide [5] with subsequent hydrogenation at elevated pressure in the presence of Raney nickel.

An investigation of the obtained compounds showed that they have no radioprotectant properties.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in the form of suspensions in white mineral oil. The course of the reactions and the purity of the compounds were monitored using Silufol UV-254 plates with a fixed layer of silica gel.

The data of elemental analysis for C, H, and N corresponded to the calculated data.

5-Acetylindole Oxime (II, $C_{10}H_{10}N_2O$). A mixture of 1 g (6.3 mmoles) of 5-acetylindole [1] and 2.78 g (40 mmoles) of hydroxylamine hydrochloride in 40 ml of a 10% sodium hydroxide solution was stirred at 70-80°C for 1 h. The solution was cooled to room temperature, filtered, and acidified with 5% HCl to pH 5. The filtrate was filtered, washed with cold water, and dried. We obtained 0.81 g of oxime II (73%) with mp 147-148°C (from a mixture of ether and petroleum ether). IR spectrum: 3400 (NH), 3360-3200 (OH), 1620 cm^{-1} (C=N).

α-(5-Indolyl)ethylamine Adipate (III, $C_{26}H_{34}N_4O_4$). To 1.65 g (9 mmoles) of II, 5.9 ml (90 mmoles) of absolute alcohol, and 100 ml of liquid ammonia was added gradually, with stirring, 1.1 g (43 mmoles) of sodium. The obtained solution was stirred until complete evaporation of ammonia. The residue was worked up with 100 ml of water, extracted with methylene chloride, washed with water, and dried with $MgSO_4$, and a solution of 0.2 M adipic acid in absolute alcohol was added to the filtrate until a weakly acid reaction. The yield of the salt, with mp 216-217°C (from a mixture of absolute methanol and absolute ether), was 1.65 g (75%). IR spectrum: 3280 (NH), 1680-1600 cm^{-1} (CO).

p-(2-Phthalimidoethoxy)nitrobenzene ($C_{16}H_{12}N_2O_5$). Sodium (18 g, 750 mmoles) was dissolved in 350 ml of amyl alcohol, 105 g (750 mmoles) of p-nitrophenol was added, the whole was stirred for 30 min at 80°C, then 190 g (750 mmoles) of 2-bromoethylphthalimide was added, and the whole was heated to 130°C and stirred at that temperature for 8 h. After cooling, the resulting precipitate was filtered, washed on the filter with amyl alcohol, methanol, water, and again with methanol, and dried, and 130 g (56%) of the target substance, with mp 148-149°C (from alcohol), was obtained. IR spectrum: 1770 (CO), 1715 (CO), 1510 (NO_2), 1345 cm^{-1} (NO_2).

p-(2-Phthalimidoethylthio)nitrobenzene ($C_{16}H_{12}N_2O_4S$). This compound was similarly obtained in 68% yield, with mp 176-177°C (from methanol); the mp is 175-176°C according to the data of [6].

p-(2-Phthalimidoethoxy)aniline ($C_{16}H_{14}N_2O_3$). p-(2-Phthalimidoethoxy)nitrobenzene (74 g, 230 mmoles) was hydrogenated in 250 ml of diglyme in the presence of Raney nickel at 100°C and initial pressure 100 atm, and most of the hydrogen was absorbed in 30 min. The precipitate that formed after cooling was dissolved during heating, the catalyst was filtered, the mother liquor was evaporated under vacuum, and 63 g (94%) of p-(2-phthalimidoethoxy)aniline, with mp 155-156°C (from alcohol), was obtained. IR spectrum: 3450 (NH), 3380 (NH), 1770 (CO), 1710 cm^{-1} (CO). Its hydrochloride had mp 211-212°C.

p-(2-Phthalimidoethylthio)aniline ($C_{16}H_{14}N_2O_2S$). This compound was similarly obtained in 80% yield, with mp 145-147°C (from 2-propanol). IR spectrum: 3450 (NH), 3370 (NH), 1775 (CO), 1725 cm^{-1} (CO).

Ethyl α-Keto-δ-phthalimidovalerate p-(2-Phthalimidoethoxy)phenylhydrazine (VIa). To a solution of 28.2 g (100 mmoles) of p-(2-phthalimidoethoxy)aniline in 100 ml of acetic acid, 100 ml of water, and 40 ml of conc. HCl cooled to 0-5°C was added a solution of 7 g (100 mmoles) of sodium nitrite in 20 ml of water so that the temperature did not rise above 5°C. The reaction material was stirred at 0-5°C for 30 min, the resulting diazonium salt IVa was poured with stirring, all at once, into a solution of 32 g (100 mmoles) of ethyl α-acetyl-δ-phthalimidovalerate (V) [4] in 300 ml of acetic acid, 85 g of sodium acetate trihydrate was added in 5-10 min, with the pH of the solution being brought to 5, and the whole was stirred at 0-5°C

for 2 h and left to heat to room temperature. Then the reaction material was diluted twofold with water and extracted with chloroform (3 × 500 ml). The extract was filtered, the chloroform was evaporated under vacuum, and 54.5 g (94%) of hydrazone VIa), which was used for cyclization without additional purification, was obtained.

Ethyl α-Keto-δ-phthalimidovalerate p-(2-Phthalimidoethylthio)phenylhydrazone (VIb). This compound was similarly obtained in 84% yield.

Ethyl 5-(2-Phthalimidoethoxy)-3-(2-phthalimidoethyl)indole-2-carboxylate (VIIa, $C_{31}H_{25}N_3O_7$). To 100 ml of a 15-18% alcoholic solution of hydrogen chloride heated to 60-70°C was added, in 10-15 min, hydrazone VIa obtained from 100 mmoles of p-(2-phthalimidoethoxy)aniline, the whole was heated to boiling, and the reaction material was stirred during boiling for 2 h. After cooling, the resulting precipitate was filtered, carefully washed on the filter with methanol, water, and again with methanol, and dried, and 26.5 g (48%) of ester VIIa was obtained, with mp 214-215°C (from Methyl Cellosolve, washed with heated methanol). IR spectrum: 3340 (NH), 1775 (CO), 1720 (CO), 1695 cm^{-1} (CO).

Ethyl 5-(2-Phthalimidoethylthio)-3-(2-phthalimidoethyl)indole-3-carboxylate(Viib,$C_{31}H_{25}N_3O_6S$). This compound, with mp 219-220°C (from acetone), was similarly obtained in 52% yield, IR spectrum: 3320 (NH), 1770 (CO), 1710 (CO), 1690 cm^{-1} (CO).

Hydrolysis of Esters VIIa and VIIb. To a suspension of 10 mmoles of ester VII in 20 ml of methanol was added 75 ml of 2 N NaOH, and the whole was boiled for 3 h until complete dissolution of the precipitate. The solution was cooled to 10°C, filtered, poured onto ice, and acidified with 4 N HCl to pH 1. The resulting precipitate was filtered, washed with water, and dried. The yield was almost quantitative.

Triacids VIIIa and VIIIb were decarboxylated without additional purification.

5-(2-Phthalimidoethoxy)-3-(2-phthalimidoethyl)indole (IXa, $C_{28}H_{21}N_3O_5$). 5-[2-(o-Carboxybenzamido)ethoxy]-3-[2-(o-carboxybenzamido)ethyl]indole-2-carboxylic acid (VIIIa) was kept in an argon stream at 280-320°C for 1 h. After cooling to 70°C, the acid was extracted with acetone, the solution was filtered and stirred with activated carbon during boiling, the carbon was filtered, the acetone was evaporated under vacuum, and phthalimidoethylindole IXa, with mp 170-171°C (from a mixture of methanol and methyl ethyl ketone), was obtained in 80% yield. IR spectrum: 3450 (NH), 1790 (CO), 1740 cm^{-1} (CO).

5-(2-Phthalimidoethylthio)-3-(2-phthalimidoethyl)indole (IXb, $C_{28}H_{21}N_3O_4S$). This compound, with mp 188-189°C (from a mixture of acetone and methanol) was similarly obtained in 62% yield. IR spectrum: 3380 (NH), 1770 (CO), 1710 cm^{-1} (CO).

5-(2-Aminoethoxy)tryptamine (Xa, $C_{12}H_{17}N_3O$). A suspension of 9.6 g (20 mmoles) of indole IXa in 50 ml of methanol was heated to boiling, 3 ml (60 mmoles) of hydrazine hydrate in 10 ml of methanol was added, the whole was stirred with boiling for 2 h, the methanol was evaporated under vacuum, 100 ml of 2 N NaOH was added to the residue, the product was extracted with methylene chloride (3 × 350 ml) and filtered, the methylene chloride was evaporated under vacuum, dry benzene was added to the residue, and evaporation under vacuum was repeated. We obtained 3.1 g (70%) of tryptamine Xa. Its dihydrochloride ($C_{12}H_{17}N_3O \cdot 2HCl$), with mp 280-282°C (from a mixture of methanol and ether), was obtained in 70% yield.

5-(2-Aminoethylthio)tryptamine (Xb, $C_{12}H_{17}N_3S$). This compound was similarly obtained in 62% yield. Its dihydrochloride ($C_{12}H_{17}N_3S \cdot 2HCl$) had mp 218-220°C (from a mixture of methanol and ether).

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