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SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF N-β-[3-INDOLYL] ETHYLPROPANOLDIAMINES

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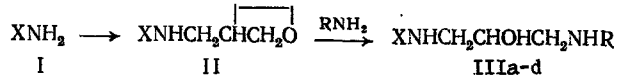
We showed earlier [3, 4] that the introduction of arylalkyl and arylalkenyl substituents into the aliphatic part of the tryptamine molecule gives compounds which act on the cardiovascular system.

In the present work, we have synthesized tryptamine derivatives substituted at the nitrogen atom with an aminopropanol group, a group found in substances acting on the adrenergic system [1].



$$\underset{\text{I}}{XNH_2} \longrightarrow \underset{\text{II}}{XNHCH_2\overline{CHCH_2O}} \xrightarrow{RNH_2} \underset{\text{IIIa-d}}{XNHCH_2CHOHCH_2NHR}$$

IIIa: R = *i*-Pr; IIIb: R = *t*-Bu; IIIc: R = $CHMeCH_2Ph$; IIId: R = $CHMe(CH_2)_2Ph$; X = 3-indolylethyl.

Epoxypropylamine (II) was obtained by the reaction of tryptamine (I) with epichlorhydrin in $CHCl_3$ in the presence of Et_3N. The latter was reacted with primary amines [6] in i-PrOH in the presence of catalytic amounts of water to give the diamines (IIIa-d), which were characterized as the dihydrochlorides.

The purity and structure of the compounds were confirmed by elemental analysis, infrared and mass spectrometry, and chromatography.

EXPERIMENTAL (CHEMISTRY)

TLC was carried out on alumina (activity II) in butanol—AcOH—water (4:1:3), using iodine vapor as a developer. IR spectra of the compounds in mineral oil were taken on a UR-20 (GDR) instrument, mass spectra on an MX-1303 with direct introduction of the sample into the ion beam. Melting points were determined on a "Boezius" micro hot stage (GDR).

N-β-(3-Indolyl)ethyl-2,3-epoxypropylamine (II). To 4.8 g (30 mmoles) of tryptamine I in 100 ml of $CHCl_3$ in the presence of 3.03 g (30 mmoles) of Et_3N at room temperature (20-25°C) was added dropwise 2.8 g (30 mmoles) of epichlorohydrin. The mixture was stirred for 2-3 hours, then heated at 50-55°C for 4-5 hours. The oily material formed was separated, heated in 100 ml of 40% NaOH at 60-65°C for 2-3 hours, filtered, washed three times with ice water and dried in a desiccator to give 5.4 g of II (77%), mp 126-127°C. Found %: C 72.32; H 7.31; N 12.62. $C_{13}H_{16}N_2O$. Calculated %: C 72.22; H 7.40; N 12.95. Rf 0.6. Mass spectrum, m/z (I rel.): 216 (12), 143 (25), 130 (75), 86 (100).

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Dihydrochloride of N-[β-(3-indolyl)ethyl]-N'-isopropyl-1,3-diamino-2-propanol (IIIa·2HCl). A mixture of 2.16 g (10 mmoles) of the epoxide II in 50 ml of i-PrOH, 1.2 g (20 mmoles) of i-$PrNH_2$, and 1 ml of water was heated in a sealed tube in an oil bath at 120°C for 7-8 hours, then filtered and the solvent and excess starting amine removed by evaporation. The residue was dissolved in anhydrous tetrahydrofuran and ethereal HCl added to give the dihydrochloride IIIa, which was reprecipitated from a mixture of ethanol and ether (1:10) to yield 1.1 g (34%) with mp 156-157°C. Found, %: C 55.03; H 7.52; Cl^- 20.09; N 12.07. $C_{16}H_{27}Cl_2N_3O$. Calculated, %: C 56.35; H 7.76; Cl^- 20.04; N 12.07. IR spectrum, ν_{max} cm^{-1}: 3600-3150 (broad band due to associated NH and OH), 3410 (NH indole), 3060 (=C–H arom.), 2850-2600 (series of bands due to $\rangle\overset{+}{N}H_2$), 1610 (C=C arom.), Rf_{OCH} 0.76, mass spectrum, m/z (I rel.): 275 (6), 257 (3), 203 (18), 173 (65), 144 (53), 102 (11), 72 (100).

Dihydrochloride of N-[β-(3-indolyl)ethyl]-N'-tert-butyl-1,3-diamino-2-propanol (IIIb·2HCl). This was obtained by the same method as IIIa·2HCl in 30% yield, mp 142-143°C. Found, %: C 56.15; H 7.81; Cl^- 19.76; N 11.59. $C_{17}H_{29}Cl_2N_3O$. Calculated, %: C 56.35; H 8.01; Cl^- 19.61; N 11.60. IR spectrum, ν_{max} cm^{-1}: 3500-3200 (broad band due to associated NH and OH), 3400 (indole NH), 3050 (=C–H arom.); 2820-2600 (series of bands due to $\rangle\overset{+}{N}H_2$), 1600 (C=C arom.), Rf_{OCH} 0.75.

Dihydrochloride of N-[β-(3-indolyl)ethyl]-N'-(methyl-3-phenyl)ethyl-1,3-diamino-2-propanol (IIIc·2HCl). To 4.32 g (20 mmoles) of the epoxide II in 100 ml of i-PrOH was added 5.4 g (40 mmoles) of phenylisopropylamine and 1 ml of water. The mixture was refluxed for 18-20 h, filtered, and the solvent evaporated off. Excess starting amine was removed by vacuum distillation. The residue was dissolved in anhydrous tetrahydrofuran, and the dihydrochloride IIIc precipitated by addition of dilute ethereal HCl. Reprecipitation from a mixture of ethanol and ether (1:10) gave 2.2 g (35%) with mp 138-139°C. Found, %: C 63.54; H 7.80; Cl^- 16.58; N 10.57. $C_{22}H_{31}Cl_2N_3O$. Calculated, %: C 63.79; H 7.49; Cl^- 16.91; N 10.14. IR spectrum, ν_{max} cm^{-1}: 3600-3100 (broad band due to associated NH and OH), 3415 (indole NH, shoulder), 3060 (=C–H, arom.), 2850-2650 (series of bands due to $\rangle\overset{+}{N}H_2$), 1595 (C=C arom.), Rf 0.75.

Dihydrochloride of N-[β-(3-indolyl)ethyl]-N'-(1-methyl-3-phenyl)propyl-1,3-diamino-2-propanol (IIId·2HCl). This was obtained in the same way as IIIc·2HCl in 50% yield with mp 123-124°C. Found, %: C 63.33; H 7.61; Cl^{-1} 15.70; N 10.00. $C_{23}H_{33}Cl_2N_3O$. Calculated, %: C 63.01; H 7.53; Cl^- 15.98; N 9.59. IR spectrum, ν_{max} cm^{-1}: 3600-3150 (broad band due to associated NH and OH) 3410 (indole NH, shoulder), 3040 (C=C–H arom.), 2800-2700 (series of bands due to $\rangle\overset{+}{N}H_2$), 1605 (C=C arom.); Rf_{OCH} 0.74.

EXPERIMENTAL (BIOLOGY)

Tests were carried out by the standard methods [7, 8] using non-pedigree white mice weighing 18-22 g and rats weighing 150-180 g of both sexes to determine the effect of compounds IIIa-d on behavior, temperature, depressant action of reserpine (ptosis, hypothermia, catalepsy, potentiation of sodium pentabarbital sleep), and also on the action of apomorphine. Amphetamine and indopan were used for comparison.

The compounds were injected subcutaneously into mice in doses of 10 and 20 mg/kg, and into rats in doses of 10, 20, and 100 mg/kg. Reserpine (1.5 and 2 mg/kg), nembutal (20 mg/kg) were injected intraperitoneally 1 h after injection of the test compounds, and apomorphine (10 mg/kg), 30 minutes after. Compounds IIIc and d were injected intraperitoneally to determine the LD_{50}.

Rats narcotized with nembutal were used to study the action of compounds IIIa, c, and d (5 mg/kg) on arterial pressure, palpitation frequency, and positive chronotropic and depressor effects of isoproterenol (0.5 mg/kg).

Experimental data were treated statistically by the methods of Student, Fisher, Litchfield, and Wilcoxon.

The test subsances IIIa-d caused excitation of the control nervous system in mice and rats: There was an increase in tactile sensitivity, agitation, and exophthalmos. The spectrum of action of these compounds is reminiscent of that of amphetamine. Unlike amphetamine, however, compounds IIIa-d caused an insignificant (0.6°C) increase in temperature, with both small and large doses. Stereotypy, characteristic of the action of small doses (5-10 mg/kg) of amphetamine, was noted in rats only after injection of 100 mg/kg of compound IIIc.

When injected into rats prior to the administration of reserpine (2 mg/kg), compounds IIIc and d (50 mg/kg), in contrast to amphetamine and indopan counteracted the development of reserpine blepharoptosis in only 3-4 h ($P < 0.05$), but did not noticeably affect hypothermia and catalepsy. Compounds IIIc and d (50 mg/kg) were injected into rats one h before the injection of reserpine (1.5 mg/kg) followed after one h by an injection of nembutal (20 mg/kg); compound IIIc completely eliminated the narcotic effect of a combination of the neuroletpic agent and nembutal, and compound IIId decreased the duration of sleep by 29 min ($P = 0.05$). Compounds IIIa and b had no significant effect on reserpine potentiation of nembutal sleep. Under the same conditions, amphetamine and indopan at a dosage of 10 mg/kg caused the destruction of the animals, and at a dosage of 1 mg/kg had no influence on the neuroleptic effect.

Compounds IIa and d had no effect on apomorphine hypothermia and stereotypy in mice.

Compound IIIa considerably decreased the frequency of heart palpitations and reduced β-adrenoblocking action, while compounds IIIc and d had no noticeable effect. Compound IIa exceeds the β-adrenoblockers propanol and atenolol.

The LD_{50}'s for compounds IIIc and d, and for indopan and amphetamine were: IIIc – 36 (22.5-57.6) mg/kg, IIId – 97(85.1-110.6) mg/kg, indopan – 137(121.2-154.8) mg/kg, and amphetamine – 80(67.2-107.2) mg/kg.

Thus, compounds IIIa-d, which are similar in structure to both tryptamine and amphetamine, caused amphetamine-like symptoms in mice and rats. However, unlike amphetamine, they did not cause hyperthermia, and stereotypy developed only after injections of large doses of compound IIIc. These compounds showed antagonism to reserpine blepharoptosis, and potentiation of neuroleptic nembutal sleep, which distinguishes them from indopan. The dihydrochloride of IIIc, which exhibits the most marked amphetamine-like activity, is more toxic than amphetamine and indopan.

The hydrochloride of IIIa possesses β-adrenoblocking activity.

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