DRUGS FROM A SERIES OF β-PHENYLISOPROPYLAMINE DERIVATIVES.

VI. BENZIMIDAZOLE ANALOGS OF β-PHENYLISOPROPYLAMINE

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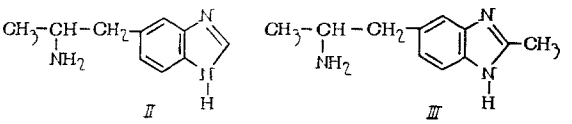
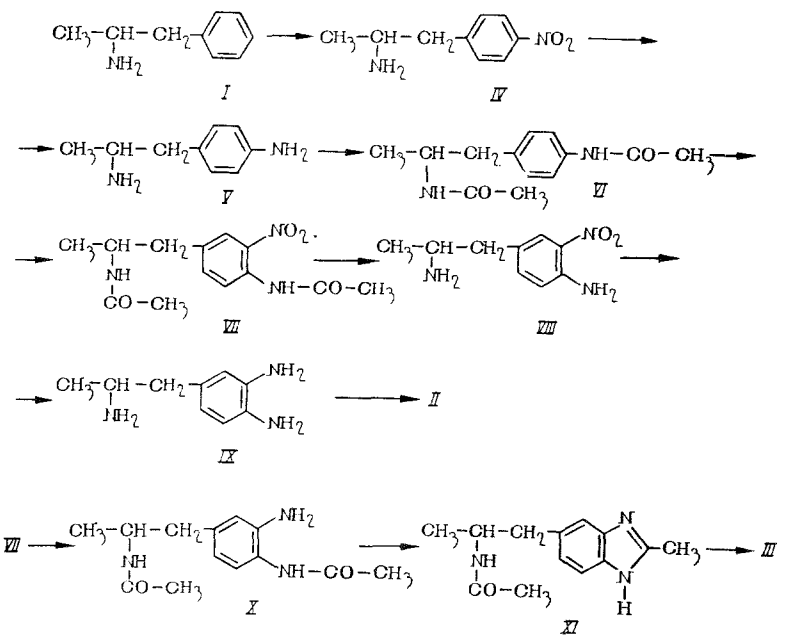
It has been shown previously that the introduction of bulky substituents into the amino group of β-phenylisopropylamine (fenamine, I) causes a change in its pharmacological action [1]. In a development of this work it seemed of interest to investigate analogs of (I) with a more complex aromatic system, in particular benzimidazole. Compounds (II) and (III), which were isolated as dihydrochlorides, have been synthesized by us.



II III

This choice is explained by the observation that the central action of (I) is coupled with the presence in the molecule of an aromatic structure [2, 3]. In addition a series of benzimidazole derivatives, which are medicinal preparations, are known [4].

The synthesis of 5-(2'-aminopropyl)benzimidazoles (II) and (III) was achieved by the following scheme:



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Selection of this synthetic route is explained by the observation that benzimidazoles which have no strong electron-donor substituent in the two position do not enter into the Friedel–Krafts reaction [5, 6].

We carried out nitration of (I) by the method of [7]. From the obtained mixture of 2- and 4-nitro-(2'aminopropyl)benzenes pure 4-nitro isomer (IV) was isolated by a single crystallization of the amine hydrochlorides from a mixture of absolute ethanol and ether. Reduction of the nitro group in compound (IV) was carried out with hydrazine hydrate over Raney nickel. For subsequent nitration compound (V) was converted into the diacetyl derivative (VI). Nitration of compound (VI) was effected with a mixture of fuming nitric and concentrated sulfuric acids at 40-43°. As was shown in [8, 9], under these conditions nitration of p-alkylacetanilides goes in the position ortho to the acetylamino group. The position of the nitro group, which had been introduced into compound (VII), was proved by the subsequent transformations.

For the synthesis of benzimidazole (II) unsubstituted in the 2 position the diacetyl nitro compound (VII) was hydrolyzed with alcoholic potassium hydroxide solution to the corresponding diamine (VIII) which was then reduced with hydrazine hydrate over Raney nickel to the triamine (IX). Compound (IX) was easily oxidized and crystallized badly. Its composition and structure were characterized by the corresponding benzimidazole (II) obtained on boiling compound (IX) with a threefold excess of formic acid in 20% hydrochloric acid. If compound (IX) was boiled in 85% formic acid in the absence of hydrochloric acid, then formylation of the aliphatic amino group occurred in addition to cyclization. For the preparation of (III) reduction of the nitro group in compound (VII) was carried out by two methods: with hydrazine hydrate over Raney nickel and with hydrogen at 50° and atmospheric pressure. In the second case the reaction proceeded considerably more cleanly and in greater yield (92% against 75%). Cyclization of compound (X) into compound (XI) was conducted by heating it in an atmosphere of dry nitrogen for 1 h at 190-200°. The acetyl residue on the aliphatic amino group of compound (XI) was removed by boiling in 25% hydrochloric acid.

A pharmacological investigation of the dihydrochlorides of benzimidazoles (II) and (III) showed that they potentiate the soporific effect of chloral hydrate and of Barbamyl. The direction of the pharmacological action was preserved in the same way as in the N-substituted derivatives of β-phenylisopropylamine [1].

EXPERIMENTAL

4-Amino-(2'-aminopropyl)benzene (V). Compound (IV) (5.8 g) was dissolved in 100 ml ethanol, approximately 1 g Raney nickel was added, and after cooling 29 ml hydrazine hydrate was gradually added. The mixture was boiled until gaseous products were no longer formed, the catalyst was filtered off, the alcohol was distilled off, and (V) was distilled in vacuum. A fraction was taken of bp 114-116° (2 mm), n_D^{20} 1.5780 [7]. Yield was 3.6 g (75%).

N,N'-Diacetyl-4-amino-(2'-aminopropyl)benzene (VI). Compound (V) (16 g) was dissolved in 100 ml dry benzene, and after cooling 20 ml acetic anhydride was added. The mixture was boiled for 1 h, cooled, and the precipitated solid was filtered off. Yield was 22 g (88%) of mp 181-182° (from ethanol). Found, %: C 66.53; 66.26; H 7.49; 7.31; N 12.36; 12.07. $C_{13}H_{18}N_2O_2$. Calculated, %: C 66.64; H 7.74; N 11.96.

3-Nitro-4-acetylamino-(2'-acetylaminopropyl)benzene (VII). To a vigorously stirred mixture of 10.8 ml fuming nitric and 6 ml concentrated sulfuric acids was added 6 g (VI) at such a rate that the temperature of the reaction mixture was within the limits of 40-43°. After the end of adding (VI) the mixture was stirred at this temperature for 1.5-2 h and poured onto ice. To the solution obtained sodium carbonate was added until an alkaline reaction was given and the crystals which had separated were filtered off. Yield was 6.4 g (89%) of mp 161-163° (from aqueous acetone). Found, %: C 55.93; 55.87; H 6.46; 6.20; N 15.13; 15.22. $C_{13}H_{17}N_3O_4$. Calculated, %: C 55.90; H 6.14; N 15.05.

3-Nitro-4-amino-(2'-aminopropyl)benzene (VIII). Compound (VII) (2.35 g) was dissolved in 15 ml ethanol, and 10 ml 10% aqueous potassium hydroxide solution was added. The reaction mixture was boiled for 30 min and the alcohol was distilled off until an oil resulted. On cooling crystals separated having mp 131-132° (from aqueous alcohol). Yield was 1.53 g (96%). Found %: C 55.04; H 6.32; 6.39. $C_9H_{13}N_3O_2$. Calculated, %: C 55.37; H 6.71.

3,4-Diamino-(2'-aminopropyl)benzene (IX). Compound (VIII) (2 g) was dissolved in 100 ml ethanol, approximately 0.5 g Raney nickel and 9 ml hydrazine hydrate were added. The mixture was boiled until gaseous products were no longer formed, then cooled, the catalyst was filtered off, and the solvent was distilled off under reduced pressure. Compound (IX) was obtained of mp 103-104° (from water with added sodium hydrosulfate). Satisfactory elemental analytical data were not obtained. The product crystallized badly and was precipitated once more as an oil.

5-(2'-Aminopropyl)benzimidazole Dihydrochloride (II). Compound (IX) (1.6 g) was dissolved in 70 ml 20% hydrochloric acid, 2 ml 80% formic acid was added, and the solution was boiled for 3 h in a stream of nitrogen. The mixture was treated with carbon and the water distilled off under reduced pressure. Yield was 1.5 g (50%) of mp 271-272° (from absolute ethanol). Found, %: C 48.33; 48.50; H 6.06; 6.01; N 16.94; 17.17; Cl 28.35; 28.05. $C_{10}H_{13}N_3 \cdot 2HCl$. Calculated, %: C 48.40; H 6.09; N 16.93; Cl 28.58.

3-Amino-4-acetylamino-(2'-acetylaminopropyl)benzene (X). A. Compound (VII) (6.3 g) was dissolved in 150 ml ethanol; then approximately 1 g Raney nickel and 18 ml hydrazine hydrate were added. The mixture was boiled until gaseous products were no longer formed, the catalyst was filtered off, and the ethanol was distilled off under reduced pressure. Yield was 4 g (75%) of mp 186-188° (from ethanol). Found, %: C 63.04; 63.05; H 8.16; 8.34; N 16.52; 16.72. $C_{13}H_{19}N_3O_2$. Calculated, %: C 62.62; H 7.68; N 16.86. B. Compound (VII) (5.4 g) was dissolved in 40 ml ethanol and was hydrogenated over Raney nickel at atmospheric pressure at 50°. The isolation and purification of the product was carried out similarly to the preceding method. Yield was 4.4 g (92%).

2-Methyl-5-(2'-acetylaminopropyl)benzimidazole Hydrochloride (XI). Compound (X) (2 g) was heated in a stream of dry nitrogen at 190-200° for 1 h. A dark-red glass-like mass was formed which was soluble in ethanol. Compound (XI) was characterized as the hydrochloride, mp 166-168° (from a mixture of ethanol with acetone). Yield was 2.1 g (95%). Found, %: C 56.73; 56.68; H 7.06; 7.09; N 14.80; 15.19; Cl 12.59; 12.59. $C_{13}H_{17}N_3O \cdot HCl \cdot 0.5H_2O$. Calculated, %: C 56.41; H 6.92; N 15.19; Cl 12.81.

2-Methyl-5-(2'-aminopropyl)benzimidazole Dihydrochloride (III). The hydrochloride (2.4 g) was boiled in 30 ml 25% hydrochloric acid for 4 h. The mixture was treated with carbon and the water was distilled off under reduced pressure. Yield was 1.5 g (60%) of mp 279-281° (from absolute ethanol). Found, %: C 47.90; 47.95; H 6.96; 7.13; N 15.47; 15.49; Cl 25.90; 26.06. $C_{11}H_{15}N_3 \cdot 2HCl \cdot 2H_2O$. Calculated, %: C 47.14; H 6.68; N 15.00; Cl 25.30.

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