SYNTHESIS AND PHARMACOLOGICAL STUDY OF 2-(QUINUCLIDYL)-SUBSTITUTED IMIDAZOLINES AND BENZIMIDAZOLES

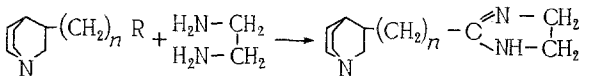
E. E. Mikhlina, V. Ya. Vorob'eva, T. K. Trubitsyna, M. D. Mashkovskii, and L. N. Yakhontov

UDC 615.217.24:547.781.1].012.1

Substances which have definite pharmacological activity are known among 2-substituted imidazolines. Some of them (naphthizine, benzoline, etc.) have found use in medicinal practice as sympatholytic and adrenolytic media. The intensity and character of pharmacological action in this series of compounds are determined by the substituent in the 2 position of the imidazoline molecule. In this connection it was of interest to synthesize and study the pharmacological properties of imidazoline derivatives containing the bicyclic quinuclidine system, on whose basis a number of effective medicinal preparations have been devised in the last decade, as a substituent in the 2 position.

With the objective of synthesizing 2-(quinuclidyl)imidazolines, we have studied the reaction of quinuclidine derivatives containing various functional groups (nitrile, carboxyl, ester, or imido ester) with ethylenediamine. It is known that imido esters are very reactive in the synthesis of 2-substituted imidazolines [1]. The reaction of ethyl 3-quinuclidylimidoacetate with ethylenediamine was performed under various conditions (temperature, solvent, and reaction time were varied). However, due to the high reactivity of this imido ester, invariably a mixture of products was formed thereupon (gas chromatographic data), from which it was not possible to isolate individual substances. Attempts to synthesize 2-(quinuclidyl)imidazolines from 2(or 3)-quinuclidinecarboxylic acids or 3-quinuclidineacetic acid also proved ineffectual. At 200-210° in the presence of hydrochloric acid, under vacuum, [2] the components did not react, and resinification was observed at higher temperatures.

2-(3'-Quinuclidyl)imidazoline (IV) and 2-[3'-(quinuclidyl)methyl]imidazoline (V) were synthesized via the reaction of 3-cyano- or 3-cyanomethylquinuclidine (I or II) with ethylenediamine in the presence of ethylenediamine dihydrochloride at 200° [3]. Compound (IV) was also prepared from ethyl 3-quinuclidinecarboxylate (III) and ethylenediamine.



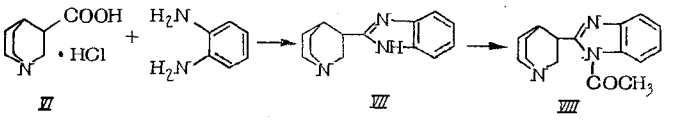
I, n = 0, R = CN
II, n = 1, R = CN
III, n = 0, R = $COOC_2H_5$
IV, n = 0
V, n = 1

It should be noted that the reactions of 3-(β-cyanoethoxy)quinuclidine and of 2-(β-cyanoethyl)-2-azaquinuclidine with ethylenediamine under the conditions indicated for the transformation of I and II into IV and V lead to splitting out acrylonitrile (a reaction inverse to cyanoethylation) and the formation of 3-hydroxyquinuclidine and 2-azaquinuclidine, respectively.

The functional derivatives of quinuclidine which were indicated above behaved somewhat differently in reaction with o-phenylenediamine. In this case, attempts to synthesize 2-(3'quinuclidyl)benzimidazole (VII) by starting with the nitrile or ethyl ester (as well as from the imido ester) of 3-quinuclidinecarboxylic

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 7, No. 12, pp. 23-26, December, 1973. Original article submitted September 29, 1972.

acid proved unsuccessful. On the contrary, the reaction of 3-quinuclidinecarboxylic acid hydrochloride (VI) with o-phenylenediamine at 220° led to VII in good yield.



VI VII VIII

Compounds IV and V were studied with respect to their effect on the adrenoreactive system. Adrenomimetic action was studied as compared with naphthizine, by their effect on arterial pressure and on the third eyelid in urethane-narcotized cats, and by their effect on isolated rabbit ear vessels. Adrenolytic activity was determined from ability to reduce the pressor action of adrenalin in narcotized cats and from the contraction of the third eyelid caused by them. Toxicity was determined on white mice, on injection into a vein; the LD_{50} was calculated by the Kerber method.

The study performed showed that, in distinction from naphthizine, compounds IV and V do not exert an adrenolytic action. While naphthizine in a dose of 0.2 mg/kg causes a strong pressor action, an intensive and prolonged contraction of the third eyelid, and constricts rabbit ear vessels by 50% in a concentration of $1 \cdot 10^{-8}$ g/ml, IV and V cause a short-term reduction in arterial pressure only in doses of 2-10 mg/kg, do not contract the third eyelid, and exert only a weak vessel-constricting action (6-8%) in a concentration of $1 \cdot 10^{-7}$ g/ml.

In distinction from the adrenolytic benzoline, which is active in a dose of 2 mg/kg, compounds IV and V in a dose of 5-10 mg/kg do not reduce the pressor action of adrenalin or the contraction of the third eyelid caused by it.

Like naphthizine and benzoline, IV and V in toxic doses cause clonic-tonic convulsions in mice. However, they are less toxic than benzoline or naphthizine. For IV, the LD_{50} on injection into the veins of white mice is 167.5 mg/kg; and for V, it is 189.5 mg/kg; while for naphthizine, the LD_{50} is 33 mg/kg, and that for benzoline is 40 mg/kg. Thus, introduction of a quinuclidine nucleus into the 2 position of imidazoline instead of a benzene or naphthalene residue leads to a loss of adrenolytic or adrenomimetic activity and to a reduction in overall toxicity.

EXPERIMENTAL

3-Cyanomethylquinuclidine (II). A solution of 11 g of 3-cyanomethylenequinuclidine [4] in 110 ml of dry ethanol was shaken with hydrogen in the presence of 0.2 g of platinum oxide. After the absorption of one equivalent of hydrogen, the platinum black was filtered off, the alcoholic solution was evaporated under vacuum, and the residue was distilled. Two fractions were collected. The first had a bp of 101-102° (1 mm); yield, 8.7 g (79%); it was compound II. Found %: C 72.11; H 9.36; N 18.84. $C_9H_{14}N_2$. Calculated %: C 71.96; H 9.39; 18.65. The second fraction had bp 138-140° (1 mm); yield, 1 g; it was bis[β-(3-quinuclidyl)ethyl]-amine. Found %: C 73.79; H 11.45; N 14.69. $C_{18}H_{33}N_3$. Calculated %: C 74.2; H 11.39; N 14.43.

Ethyl 3-Quinuclidineimidoacetate. Absolute ethanol (0.56 g) was added to a solution of 0.9 g of II in 20 ml of dry chloroform, and dry hydrogen chloride was passed through the mixture at 0° until it was saturated. The mixture was kept at 4° for 20 h, it was evaporated under vacuum, the residue was suspended in dry ether, and the resulting suspension was allowed to stand for 5 days. The ether suspension was cooled to 0° and treated with 10 ml of 50% potassium carbonate solution; the ether was separated, and the alkaline solution was additionally extracted with ether. The ether solution was dried with magnesium sulfate, it was evaporated under vacuum, and the residue was distilled. The yield was 0.75 g (64%), bp 105-106° (2 mm). Found %: C 67.45; H 10.35; N 14.55. $C_{11}H_{20}N_2O$. Calculated %: C 67.30; H 10.27; N 14.27.

2-(3'-Quinuclidyl)imidazoline (IV). A. A mixture of 2 g of I, 0.44 g of ethylenediamine, and 0.98 g of ethylenediamine dihydrochloride was heated at 200° for 6 h. The reaction mixture was dissolved in 10 ml of water, 10 ml of a 50% potassium carbonate solution was added, and the alkaline solution was extracted with chloroform. The yield of product was 0.9 g (34%), bp 146-147° (0.6 mm). The ditartrate had mp 91-92° (dec). Found %: C 44.90; H 6.34; N 8.61. $C_{10}H_{17}N_3 \cdot 2C_4H_6O_6$. Calculated %: C 45.09; H 6.10; N 8.77.
B. A mixture of 1 g of III and 1 g of ethylenediamine was boiled under reflux for 12 h. Then the reaction mixture was heated under vacuum (15 mm) for 1 h at 200° and for 1 h at 2 mm at the same temperature, after which it was distilled. The yield of product was 0.44 g (46%), bp 146-147° (0.6 mm). The ditartrate had mp 91-92° (dec.). No depression was observed when a mixed mp was taken with the sample prepared by method A.

2-[(3'-Quinuclidyl)methyl]imidazoline (V). A mixture of 3 g of II, 0.6 g of ethylenediamine, and 1.33 g of ethylenediamine dihydrochloride was heated at 200° for 6 h. The treatment of the reaction mixture was similar to that described in the synthesis of IV by method A. The yield was 1.2 g (31%), bp 153-154° (0.4 mm), mp 77-78°. Found %: C 67.80; H 9.80; N 21.94. $C_{11}H_{19}N_3$. Calculated %: C 68.27; H 9.96; N 21.74.

Condensation of 3-(β-Cyanoethoxy)quinuclidine with Ethylenediamine. A mixture of 1.8 g of 3-(β-cyanoethoxy)quinuclidine [5], 0.3 g of ethylenediamine, and 0.67 g of ethylenediamine dihydrochloride was heated at 170° for 2 h. Work-up was similar to that described in the synthesis of IV. The residue upon removal of the chloroform was sublimed under vacuum (3 mm), and then was crystallized from acetone. There was obtained 0.91 g (71%) of 3-hydroxyquinuclidine, mp 218-220° [6]. No depression was observed when a mixed mp was taken with a sample of known structure.

Condensation of 2-(β-Cyanoethyl)-2-azaquinuclidine with Ethylenediamine. The reaction of 1.65 g of 2-(β-cyanoethyl)-2-azaquinuclidine [7], 0.3 g of ethylenediamine, and 0.67 g of ethylenediamine dihydrochloride was carried out analogously to the preceding one. On analysis of the reaction products by gas chromatography, only the presence of 2-azaquinuclidine and starting nitrile was detected in them.

2-(3'-Quinuclidyl)benzimidazole (VII). A mixture of 9.6 g of VI, 5.4 g of o-phenylenediamine, and 20 ml of concentrated hydrochloric acid was slowly heated, with simultaneous distillation of water, bringing the temperature of the mass to 220°. The mixture was heated at this temperature for 5 h under atmospheric pressure and for 8 h under vacuum (70 mm); it was cooled, dissolved in 40 ml of water, made alkaline with a 50% potassium carbonate solution, and very thoroughly extracted with chloroform. After the chloroform had been distilled off, the residue was triturated with ethyl acetate. The yield was 8.9 g (79.5%), mp 238-239° (from acetone). Found %: C 73.88; H 7.64; N 18.29. $C_{14}H_{17}N_3$. Calculated %: C 74.04; H 7.48; N 18.48. The dihydrochloride forms colorless crystals, mp 269-271° (dec). Found %: C 55.91; H 6.26; Cl 23.40; N 14.26. $C_{14}H_{17}N_3 \cdot 2HCl$. Calculated %: C 55.95; H 6.38; Cl 23.61; N 14.00.

1-Acetyl-2-(3'-quinuclidyl)benzimidazole (VIII). A mixture of 1 g of VII and 10 ml of acetic anhydride was boiled for 7 h. The solution was evaporated under vacuum, the residue was made alkaline with 50% potassium carbonate solution, and it was extracted with chloroform. The yield of product was 0.9 g (76%), mp 222-224° (from acetone). C 71.29; H 7.36; N 15.3. $C_{16}H_{19}N_3O$. Calculated %: C 71.35; H 7.16; N 15.6.

LITERATURE CITED

1. G. A. Shvekhgeimer, Zh. Organ. Khim., 7, 815 (1971).
2. Swiss Patent No. 221,216; Chem. Abstracts, 43, 692 (1949).
3. P. Oxley and W. F. Short, J. Chem. Soc., 479 (1947).
4. E. E. Mikhlina and M. V. Rubtsov, Zh. Obshch. Khim., 32, 2935 (1962).
5. E. E. Mikhlina and M. V. Rubtsov, ibid., 30, 163 (1960).
6. L. Sterndach and S. Kaiser, J. Am. Chem. Soc., 74, 2215 (1952).
7. E. E. Mikhlina, N. A. Komarova, and M. V. Rubtsov, Khim. Geterotsikl. Soed., No. 2, 259 (1966).