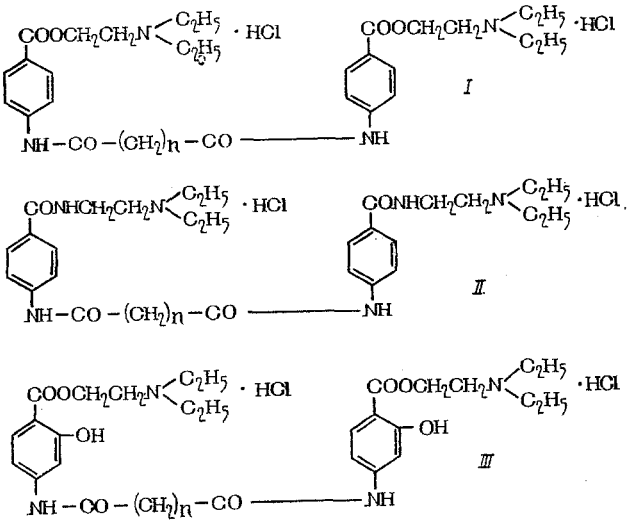
SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF N, N'-OXALYLSUCCINYL-BIS-NOVOCAINE AND ITS ANALOGS

L. B. Dashkevich, T. A. Mel'nikova, K. V. Sokolov, F. K. Sukhomlinov, A. Sh. Sagdieva, L. V. Redkova, and A. M. Sukhomlina

UDC 615.22

Earlier studies [1-2] have shown that the reaction of novocaine and its analogs with various derivatives of malonic acid leads to the formation of N, N'-bis-malonyl derivatives (Ib, IIb, IIIb).



a) n = 0, b) n = 1, c) n = 2

A study of the pharmacological action of Ib, IIb, and IIIb dihydrochlorides has shown that they exhibit antiarrythmic activity which is attributed apparently to the presence of a malonic acid residue in their molecules [3-6]. To elucidate the relation between chemical structure and pharmacological activity, the analogous compounds were synthesized in which the malonic acid residue (n=1) was replaced by residues of oxalic (n=0) and succinic (n=2) acids.

On the basis of the properties of dicarboxylic acid derivatives, we used dinonyl oxalate (IV) for the synthesis of N, N'-oxalyl-bis-derivatives and succinyl chloride (V) for the synthesis of N, N'-succinyl-bis-derivatives.

Condensation of novocaine base (VI) and novocaine amide (VII) with IV gave N, N'-oxalyl-bis-novocaine (Ia) and N, N'-oxalyl-bis-novocaine amid base (IIa). Attempts to prepare a similar product in the condensation of hydroxynovocaine base VIII with IV failed.

Condensation of VI, VII, and VIII with V gave N, N'-succinyl-bis-novocaine base (Ic); N, N'-succinyl-bis-novocaine amide base IIc; and N, N'-succinyl-bis-hydroxynovocaine base IIIc, respectively.

The composition and chemical structure of synthesized compounds were confirmed by the data on elementary analysis and molecular weight determinations.

Leningrad Pharmaceutical Chemistry Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 5, No. 7, pp. 22-24. Original article submitted July 18, 1969.

For pharmacological studies, the synthesized compounds were obtained as dihydrochlorides which were readily soluble in water. A comparative evaluation of the dihydrochlorides demonstrated the dependence of their biological activity on the chain length of the carbon atoms in the residue of the binding dicarboxylic acid. The replacement of malonic acid residue by residues of oxalic and succinic acids reduces the antiarrythmic activity and somewhat increases the toxicity of the compounds. The acute toxicity was determined in white mice of 22± 3g weight by introducing the compounds abdominally. LD_{50} was calculated in accordance with the Kerber method [7]. LD_{50} of Ib dihydrochlorides, 595 mg/kg; of Ia and Ic, 510-560 mg/kg; and of IIa and IIc, 3-6 mg/kg.

The experimental models of arrythmia used were: strophanthimic and aconitic acids and the model of acute myocardial infraction. The action of the preparations under study was compared with the action of the corresponding malonyl derivatives. Dihydrochlorides of Ia and IIa in effective doses (20-40 mg/kg) prevents strophanthin arrythmia in 20% of the cases. Dihydrochlorides of Ic, IIc, and IIIc are inactive. None of the synthesized dihydrochlorides prevents acotinic arrythmia. Dihydrochloride of Ib in a dose of 20 mg/kg exhibits the highest antiarrythmic activity in 70% of the cases [3]. A comparison of antiarrythmic activity of the synthesized compounds as a model of acute myocardial infraction has shown that dihydrochlorides of Ia and IIa display low activity (10-15%), dihydrochlorides of Ic, IIc, and IIIc are inactive, and dihydrochloride of Ib shows the highest activity (37%).

EXPERIMENTAL

N, N'-Oxalylyl-bis-Novocaine (Ia). A mixture of 47.2 g of VI and 34.2 g of IV was heated at 165° for one hour. The mixture, solidified at the completion of heating, was dissolved in boiling dimethylformamide. Upon cooling, a precipitate was formed which recrystallized from methyl alcohol. Yield 36.4 g (70%), mp 219-221°. Found, %: N 10.71. $C_{28}H_{38}N_4O_6$. Calculated, %: N 10.64.

The synthesis of IIa was carried out similarly to the condensation of VII with IV. Yield 63%, mp 214-215°. Found, %: N 16.18. $C_{28}H_4N_6O_4$. Calculated, %: N 16.09.

N, N'-Succinyl-bis-Novocaine (Ic). To a solution of 4.7 g of VI in 100 ml of absolute ether, was added while stirring 1.5 g of V in 50 ml of absolute ether. The precipitate was separated from the solvent by decantation, washed with ethyl alcohol, and dissolved in water. Sodium hydroxide was added to the aqueous solution to make it alkaline, the precipitate washed with water, filtered, dried, and recrystallized from acetone. Yield 1.7 g (34%), mp 172-174°. Found, %: N 10.18. $C_{30}H_{42}N_4O_6$. Calculated, %: N 10.10.

The synthesis of IIc was similar to the condensation of VII with V. Yield 28%, mp 250-251° (from methyl alcohol). Found, %: N 15.34. $C_{30}H_{44}N_6O_4$. Calculated, %: N 15.27.

The synthesis of IIIc was carried out similarly to the condensation of VIII with V. Yield 27%, mp 88-90° (decomp. from alcohol). Found, %: N 9.48. $C_{30}H_{42}N_4O_8$. Calculated, %: N 9.55.

LITERATURE CITED

1. L. B. Dashkevich, Investigation in the Region of the Chemistry of Suboxide Carbon [in Russian], Dissertation, Leningrad (1965).
2. L. B. Dashkevich, F. K. Sukhomlinov, and K. V. Sokolov, in: Materials of the Scientific Conference of Leningrad Pharmaceutical Chemistry Institute [in Russian], Leningrad (1967), p. 95.
3. Z. D. Tagieva, Farmakol. i Toksikol., No. 4, 428 (1967).
4. Z. D. Tagieva, Farmakol. i Toksikol., No. 6, 689 (1967).
5. T. A. Mel'nikova and A. F. Ryzhova, in: Pharmacology and Chemistry [in Russian], Moscow (1965), p. 207.
6. L. B. Dashkevich, T. A. Mel'nikova, E. G. Gromova, et al., Theses of reports on the problem of directed research of pharmacologically active substances [in Russian], Erevan' (1968), p. 51.
7. M. L. Belen'kii, Elements of Quantitative Evaluation of Pharmacological Effect [in Russian], Leningrad (1963), p. 49.