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SYNTHESIS AND INOTROPIC ACTIVITY OF N,N'-DI-[2,6-DIMETHYL-4-(2,3,5,6-TETRAHYDRO-6-PHENYLIMIDAZO[2,1-b]THIAZOLIO-7-YL)METHYL] DIPHENYLCARBODIIMIDE DIBROMIDE

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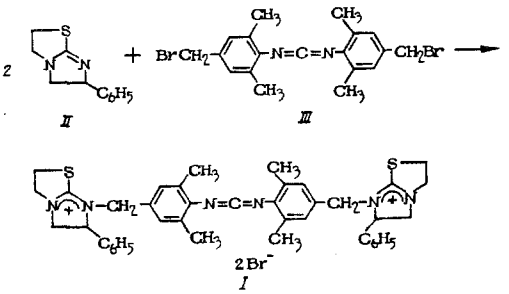
The identification and study of nontraditional cardiotonic compounds is a matter of urgency in contemporary pharmacology and pharmacy [2]. Pyrimidines, imidazoles, phthalazines, polypeptides, and arylalkylamines are known which possess positive inotropic activity [1, 3, 4]. Cardiotonic activity has also been found in some condensed imidazothiazoles [1]. High pharmacological activity has been found in bisquaternary ammonium salts, including some with hydrophobic bridging groups [1]. With this in mind, it was of interest to use bridging fragments of a fixed chain length and linear structure, such as carbodiimides, which also have physiological activity [5, 6]. It was therefore desired to synthesize novel chemical compounds containing both types of pharmacophoric fragments.

The approach which we adopted to the construction of such compounds



resulted in the formation of the salt-like carbodiimide (I), and consisted in the ready alkylation of 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]thiazole (II) with N,N'-2,2',6,6'-tetramethyl-4,4'-dibromomethyldiphenylcarbodiimide (III).

The carbodiimide (I) was a colorless, crystalline solid which was readily soluble in water and highly polar organic solvents. Its purity was confirmed by TLC, its composition by elemental analysis, and its structure by its IR spectrum, which showed strong absorption for the carbodiimide group at 2170 cm^{-1}.

EXPERIMENTAL (CHEMISTRY)

The IR spectrum was obtained on a UR-20 instrument (East Germany) in a KBr disk. TLC was carried out on Silufol UV-254 plates (Czech SSR).

N,N'-Di-[2,6-dimethyl-4-(2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]-thiazolio-7-yl)methyl]-diphenylcarbodiimide Dibromide (I). To a solution of 0.86 g (0.002 mole) of the carbodiimide (III) in 15 ml of chloroform was added 0.82 g (0.004 mole) of the thiazole (II) in 10 ml of chloroform. The mixture was kept for 48 h, then the solvent was evaporated, and the residue treated with 20 ml of diethyl ether and kept for 24 h. The crystalline product was filtered off to give 1.54 g (91%) of (I), mp 65-67°C. $C_{41}H_{46}Br_2N_6S_2$.

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TABLE 1. Comparative Myocardial Contractility Factors on Treatment with (I) (A) and the Standard Cardiotonic Drugs Dopamine (D) and Strophanthin (S) (as a % of controls)

Concn., mole/liter	Maximum tension developed			Maximum rate of contraction			Time to reaching maximum contractile force			Maximum rate of relaxation			Half-relaxation time		
	A	D	S	A	D	S	A	D	S	A	D	S	A	D	S
$1\cdot10^{-7}$	112±13	108±6	*128±6	116±11	110±7	*143±8	91±4	98±8	*92±2	115±23	120±7	130±13	86±7	99±7	88±3
$1\cdot10^{-6}$	130±13	*122±7	*139±7	75±22	*122±7	*156±9	86±6	95±7	*92±2	145±23	*129±7	*176±11	86±3	90±7	*87±3
$1\cdot10^{-5}$	114±11	*166±8	*153±5	97±35	*184±10	*179±9	*79±4	89±6	94±2	*214±38	*245±8	*182±14	78±10	82±8	*87±3
Control	100±2	100±4	100±6	100±13	100±5	100±3	100±5	100±9	100±3	100±26	100±8	100±16	100±12	100±9	100±5

Note. The mean values (M ± m) were calculated from 9-11 tests in each series. An asterisk denotes tests with $p < 0.05$.

EXPERIMENTAL (PHARMACOLOGY)

The tests were carried out on rat cardiac papillary muscle, contracted in the isometric mode by electrical stimulation. Rectangular impulses of duration 5 msec and a voltage 10-20% above the threshold value were administered via electrodes located parallel to the muscles, using an ÉS-50-1 electrical stimulator. Krebs nutrient solution was used for perfusion. The volume of the working chamber was 1 cm^3. The temperature of the bathing solution was measured directly in the chamber with a thermometer, and was maintained at 28-29°C by means of an 1TZh-0-03 thermostat. The pH of the solution was 7.4 (ÉV-74 pH meter).

Following the running-in period, the muscles were extended to the length at which the maximum contractile force was recorded. The contractile force was measured with a 6MX1C mechanotron, and recorded on a P4Ch-02 polygraph. Analysis of the contractile function of the papillary muscles gave: the maximum tension developed (T/S), the maximum rate of contraction and relaxation, the time to attainment of the maximum contraction, and the half-relaxation time. The results were expressed as a percentage of the controls.

The test compound (I) was dissolved in Krebs solution in concentrations of $1\cdot10^{-4}$ mole/liter, $1\cdot10^{-5}$ mole/liter, $1\cdot10^{-6}$ mole/liter, and $1\cdot10^{-7}$ mole/liter, and perfused for 10 min through the thermostated chamber containing the isolated muscles. The standards used were dopamine (a nonglycosidal cardiotonic), and the cardiac glycoside strophanthin, which has a positive inotropic effect.

As will be seen from Table 1, the carbodiimide (I) shows a tendency to raise the maximum muscle tension in a concentration of $1\cdot10^{-7}$ mole/liter, significant increases being seen at concentrations of $1\cdot10^{-5}$ mole/liter (44%). This value approximates to that for strophanthin, and is less than that for dopamine. The effective concentration (EC_{30}) of the test compound (I) was $9.5\cdot10^{-7}$ mole/liter, that of strophanthin $2\cdot10^{-7}$ mole/liter, and of dopamine, $2\cdot10^{-6}$ mole/liter.

Unlike the reference compounds, the test compound showed a tendency to reduce the maximum rate of contraction of isolated papillary muscles. Both the standards and the test compound increased the maximum rate of relaxation of isolated cardiac muscles, although the time to attainment of maximum contractile force of the papillary muscles on treatment with (I) was less than with strophanthin, corresponding to the duration of action of dopamine.

The standard drugs and the test compound had unidirectional effects on the half-relaxation time of the cardiac preparations. Treatment with (I) in a concentration of $1\cdot10^{-4}$ mole/liter resulted in irregular contractions of the papillary muscles, i.e., at high concentrations (I) has an arrhythmogenic effect.

Determination of the toxicity showed that the LD_{50} of (I) was 1.5 mg/kg, that of dopamine being 1120 mg/kg and strophanthin 2.45 mg/kg. The high toxicity of the test compound prevents it being recommended for further study as a cardiotonic. However, it is desirable to extend the directed synthesis and examination of salt-like heteryl-substituted diarylcarbodiimides in an attempt to reduce toxicity and obtain the optimum cardiotonic effects.

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