SYNTHESIS AND CARDIOTROPIC PROPERTIES OF AMMONIUM SALTS CONTAINING A 3,4,5-TRICHLORO-THIENYL GROUP

A. Zh. Gevorkyan, Dzh. V. Grigoryan,
A. A. Safaryan, V. M. Samvelyan,
E. G. Dzhanpoladyan, and A. T. Babayan

UDC 615.22:546.39].07

Ammonium salts with variable degrees of N-alkylation [3-6] are widely used in medical practice. An intensive search for new pharmacologically active substances of this group of drugs is continuing today.

The present study deals with the synthesis and study of cardiotropic properties of quaternary ammonium salts IV-VI. The indicated salts were synthesized by reacting 2-(chloromethyl)-3,4,5-trichlorothiophene with the following compounds which we synthesized earlier [1, 2]: N-(3,3-dimethylpentadiene-1,4-yl)morpholine (I), N-(3-phenylpentadiene-1,4-yl) piperidine (II), and N-methyl-N-furfuryl-N-(3,3-dimethylpentadiene-1,4-yl)amine (III).

$$\underset{\text{I—III}}{R_2NCH{=}CHCR^1R^2CH{=}CH_2} \xrightarrow{ClCH_2X} \underset{\text{IV—VI}}{\bar{C}l(XCH_2)R_2\dot{N}CH{=}CHCR^1R^2CH{=}CH_2}$$

R_2N = morpholino (I, IV); piperidino (II, V); methylfurfurylamine (III, VI).
R^1 = Me (I, III, IV, VI), H (II, V); R^2 = Me (I, III, IV, VI), Ph (V); X = 3,4,5-trichlorothienyl-2.

The structure of the synthesized salts was confirmed by element analysis and IR-spectroscopy, and their purity was checked by TLC. The IR-spectra of these salts had absorption bands characteristic of a thiophene ring (1055, 1500-1505, 1530-1535, 1590-1595), a terminal vinyl group (915-920, 965-975, 1635-1645, 3080-3090), and a substituted double bond on the ammonium nitrogen atom (1620-1630).

The resultant salts were stable both at room temperature and when their aq. solutions were heated on a boiling water bath (and during sterilization).

EXPERIMENTAL (CHEMISTRY)

The IR-spectra were recorded on a UR-20 (GDR) spectrometer in petroleum jelly or in the form of KBr pellets. TLC analysis was performed on Silufol UV-254 plates in a n-butanol—ethanol—AcOH—water solvent system at a 10:7:6:4 ratio; iodine vapor was used for development.

General Method for Obtaining Salts (IV—VI) in an Ether Solution (A) and in the Absence of a Solvent (B). A. An equimolar quantity of 2-(chloromethyl)-3,4,5-trichlorothiophene was added at room temperature to 0.01 mole of amine I-III in 10 ml of abs. ether. The mixture was allowed to stand for 30 h, after which the crystalline precipitate was filtered off, washed three times with abs. ether (15 ml each time), and vacuum dried. The physico-chemical characteristics of salts IV-VI are given in Table 1.

B. A mixture of equimolar amounts of amines I-III and 2-(chloromethyl)-3,4,5-trichlorophene was allowed to stand at room temperature for 20 h. The resultant salt was treated in the same manner as was done with method A.

EXPERIMENTAL (PHARMACOLOGY)

Cardiotonic activity was studied in experiments on 40 glycerinated white rat myocardial fibrils obtained by the Szent-Györgyi method [7]. These fibrils constitute an actomyosin contractile system of the heart and their amplified contraction upon exposure to ATP in the presence of the new substances was used to indicate their cardiotonic activity in vitro.

Institute of Organic Chemistry, Armenian SSR Academy of Sciences. L. A. Oganesyan Institute of Cardiology, Armenian SSR Ministry of Health, Erevan. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 22, No. 5, pp. 546-548, May, 1988. Original article submitted January 16, 1987.

 0091-150X/88/2205-0364 $12.50

TABLE 1. Physico-Chemical Characteristics of Salts IV-VI

Compound	Yield, %	mp, °C	R_f	Found, %		Empirical formula	Calculated, %		IR-spectrum, ν_{max}, cm^{-1}
				N	Cl		N	Cl	
IV	92,1	Hygroscopical	0,52	3,56	8,95	$C_{16}H_{21}Cl_4NSO$	3,36	8,56	920, 995, 1055, 1500, 1535, 1590, 1645, 3090
V	93,6	80—2	0,38	2,96	7,10	$C_{21}H_{23}Cl_4NS$	3,02	7,67	710, 760, 925, 940, 990, 1530, 1575, 1595, 1640, 3030, 3060, 3085
VI	95,8	72—4	0,46	2,94	8,25	$C_{18}H_{21}Cl_4NSO$	3,17	8,05	920, 940, 995, 1500, 1530, 1590, 1635, 3060, 3090

TABLE 2. Correlation between Cardiotonic Properties and Toxicity of Salts IV—VI and Strophanthin

Compound	Cardiotonic effect, %			Toxicity, LD_{50}, mg/kg (ip)
	on glycerinated fibrils	on isolated frog heart		
		$1 \cdot 10^{-6}$ g/ml	$1 \cdot 10^{-4}$ g/ml	
IV	25,5±0,5	20±1	40±2,1	120±5
V	24,2±0,3	19±0,5	35,7±1,2	125±3
IV	23±2	5	suppresses	105±2,3
Strophanthin	26,5±2,1	38±4,3	13±2,2	2,5±0,5

Note. Fibril contraction as affected by ATP in the control was 23.2 ± 1.2%.

The data we obtained were compared to the activity of the substances in experiments on 35 isolated frog hearts. In experiments on 8 hexenal-anesthetized cats we studied the effect of the substances on systemic arterial pressure and respiration, and found that the test substances altered the sensitivity of the choline- and adrenoreceptors of the cardiovascular system. In experiments on 150 white mice we studied acute toxicity by determining the LD_{50} upon ip administration of the new compounds.

The results of our investigations demonstrated that compounds IV and V exhibit distinct cardiotonic properties. In experiments on glycerinated myocardial fibrils we found that compound IV approximates strophanthin in ability to amplify fibril contraction whereas compound V was somewhat weaker (Table 2). Moderate cardiotonic properties of the two ammonium derivatives were confirmed on isolated frog heart. At a concentration of $1 \cdot 10^{-6}$ g/ml they increased the amplitude of cardiac contractions within the range of 20%, but less effective than strophanthin (38%). However, when the concentration of the substances was increased ($1 \cdot 10^{-4}$ g/ml) their cardiotonic activity increased and reached 40 and 35.2% respectively at a time when strophanthin was beginning to suppress contractile function significantly. This was an indication of its toxicity.

At a concentration of $1 \cdot 10^{-6}$ g/ml compound VI yielded a cardiotonic effect by increasing the amplitude of cardiac contraction within the range of 5%, and upon a greater concentration began to suppress cardiac contractile function. The toxicity indices correspond to these data (see Table 2). Strophanthin is approximately 50 times more toxic than the substances under examination.

In the experiments on the anesthetized cats the test compounds caused almost no change in systemic arterial pressure and respiration when administered at doses of 1-5 mg/kg. At doses of 1-2 mg/kg all three substances exhibited the same kind of activity, i.e., they raised cardiovascular choline receptor sensitivity within the range of 15-20% (elevated effects of acetylcholine and subecholine) and lowered the andrenoreceptor sensitivity by 38-45% (effects of epinephrine, norepinephrine, and isadrine). When the dose was raised to 3-5

mg/kg a reverse effect was observed: Choline receptor sensitivity was significantly reduced (by 70-77%) and the andrenoreceptor response was amplified by about the same degree, i.e., 70-75%.

Thus, the new ammonium chloride derivatives exhibit distinct cardiotropic properties. Compounds IV and V amplify myocardial contractile properties and exceed the effect of strophanthin with respect to cardiotonic activity and toxicity. Their modulating effect on cardiovascular chemoreceptors also indicates the potential benefit to be gained from a further synthesis of similar compounds for cardiological practice.

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SYNTHESIS, PROPERTIES, AND CARDIOVASCULAR ACTIVITY OF SUBSTITUTED 4-DIHYDROPYRIDINE-2(3H)-THIONES

A. A. Krauze, R. O. Vitolinya, M. R. Romanova, and G. Ya. Dubur

UDC 615.224:547.825].012.1

In a continuation of our research on the synthesis and study of the properties and biological activity of 1,4-dihydropyridine-2(3H)-thiones [4] we synthesized 4-substituted 6-methyl-5-acetyl-3-cyano-1,4-dihydropyridine-2(3H)-thiones and investigated their cardiovascular activity.

6-Methyl-5-acetyl-3-cyano-1,4-dihydropyridine-2-thiones III and betaines IV were synthesized by three previously described methods. Depending on the substituent in the 4 position and the reaction conditions, the following intermediates were isolated in the condensation of arylideneacetylacetone with cyanothioacetamide [2, 5] (pathway A), in the condensation of acetylacetone, an aromatic aldehyde, and cyanothioacetamide [4] (pathway B), and in the condensation of acetylacetone with 2-cyanoacrylthioamides [5, 6] (pathway C) in the presence of piperidine: piperidinium 6-hydroxy-1,4,5,6-tetrahydropyridine-2-thiolates I, piperidinium 1,4-dihydropyridine-2-thiolates II, or mixtures of them. Thiolates I are unstable compounds and undergo dehydration to give thiolates II on recrystallization. Salt I can be obtained as the principal product only in the case of a strong electron acceptor (R = p-$NO_2C_6H_4$, 4-pyridyl) in the 4 position. Thiones III and betaines IV are formed by brief refluxing of I and II or mixtures of them with an equimolar amount of hydrochloric acid in ethanol. 1,4-Dihydropyridine-2-thione sodium salts V were synthesized by the action of sodium ethoxide on thiones III and betaines IV in order to obtain water-soluble compounds (Table 1).

It was demonstrated by PMR spectroscopy that 4-aryl-substituted 3-cyano-1,4-dihydropyridine-2(3H)-thiones III are formed as mixtures of the cis and trans isomers in a ratio of 1.2:1.0 (Table 2); this differs from the data presented in [7]. The assignment of the iso-

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 22, No. 5, pp. 548-553, May, 1988. Original article submitted January 4, 1987.

0091-150X/88/2205-0366 $12.50