SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-(1-R-2,2,2-TRICHLOROETHYL)BENZENESULFONAMIDES

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Chloral hydrate is a well-known soporific, analgesic, and antispasmodic substance [1]. Its acetals also possess significant pharmacological activity, and are less toxic than chloral hydrate [2-4]. In a further search for pharmacological substances among the derivatives of chloral, we studied the biological activity and toxicity of new compounds combining in one molecule the trichloromethyl group and the benzene sulfonamide fragment: N-(1-R-2,2,2-trichloromethyl)-benzenesulfonamides of the general formula $CCl_3CH(R)NHSO_2C_6H_5$ (I-V), where R = $-NHSO_2C_6H_5$ (I), $-OCOCH_3$ (II), $-NHCOCH_3$ (III), $-ON=C(CH_3)_2$ (IV), and $-NHCOC_6H_5$ (V).

We found that I is formed by interaction of N,N-dichlorobenzenesulfonamide VI with trichloroethylene (VII) in the presence of a catalytic amount of $SnCl_4$ according to the scheme:

$$\underset{VI}{C_6H_5SO_2NCl_2} + \underset{VII}{CHCl=CCl_2} \xrightarrow{SnCl_4} \underset{VIII}{CCl_3CH=NSO_2C_6H_5} \xrightarrow{VI}$$

$$\underset{IX}{CCl_3CH(NClSO_2C_6H_5)_2} \xrightarrow{H_2O} \underset{I}{CCl_3CH(NHSO_2C_6H_5)_2}$$

In the first step of the reaction, trichloroethylidine benzenesulfonamide VIII (5) is formed by addition of the amide (VI) to (VII). Subsequent addition of another molecule of VI gives (IX). A chlorine atom of the intermediate (IX) exchanges for hydrogen with extraordinary ease in the presence of moisture to give the desired product I.

The synthesis of compounds II and V was brought about by reaction of VI with β,β-dichlorovinyl acetate (X) or β,β-dichlorovinyl benzamide (XI), respectively.

$$\underset{X}{CCl_2=CHOCOCH_3} \xrightarrow{VI} C_6H_5SO_2NClCH(OCOCH_3)CCl_3 \xrightarrow{H_2O} \underset{II}{C_6H_5SO_2NHCH(OCOCH_3)CCl_3}$$

$$\underset{XI}{CCl_2CHNHCOC_6H_5} \xrightarrow{VI} C_6H_5SO_2NClCH(NHCOC_6H_5)CCl_3 \xrightarrow{H_2O} \underset{V}{C_6H_5SO_2NHCH(NHCOC_6H_5)CCl_3}$$

The reaction of XI proceeds with a strong exotherm and gives tarry products, but V is obtained quantitatively in DMF as solvent.

The reaction of VII with amide VI by heating, followed by the addition of acetamide to the reaction mass leads to the amide III.

$$CCl_2=CHCl \xrightarrow[b)\ CH_3CONH_2]{a)\ VI} \underset{III}{C_6H_5SO_2NHCH(NHCOCH_3)CCl_3}$$

Analogously with the formation of VII, VI and acetoxime give the acetoxime ether IV.

$$CCl_2=CHCl \xrightarrow[b)\ (CH_3)_2C=NOH]{a)\ VI} \underset{IV}{C_6H_5SO_2NHCH(ON=C(CH_3)_2)CCl_3}$$

Compounds I-V are odorless, white, crystalline materials, stable to storage, and non-hygroscopic, soluble in DMSO and alcohols, and insoluble in water.

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The structures of the synthesized materials I-V were verified by elemental analysis of IR and PMR spectra. In the IR spectra, absorption bands appear for the valence oscillation of the SO_2 bonds (1180, 1350 cm^{-1}), NH (3150-3240 cm^{-1}), C_6H_5 (1580-1600 cm^{-1}), OCO for compound II (1765 cm^{-1}), NHCO for compounds III and V (1660 cm^{-1}), and C =N for compound IV (1635 cm^{-1}).

The PMR spectra show a doublet for the NH proton signal and a CH multiplet for the phenyl protons, and also signals for the protons of the radical R. The respective integral intensities corresponded to the structures of compounds I-V.

EXPERIMENTAL CHEMICAL SECTION

The IR spectra were recorded on an UR-20 spectrometer (GDR) in KBr pellets, and the PMR spectra were obtained with a Tesla Bs 487B instrument (Czechoslovakia) in $CDCl_3$ or d_6-DMSO.

2,2,2-Trichloro-1,2-bis(benzenesulfonamido)ethane (I). A solution of 0.04 mole of N,N-dichlorobenzenesulfonamide (VI) in 0.2 mole of VII was treated with 0.6 ml of $SnCl_4$ and kept at 20-25°C for 30 days. The excess VII was removed under vacuum and the residue was dissolved in chloroform and treated with petroleum ether. The precipitate was filtered off, washed with petroleum ether and dried to give 5.6 g (63%) of I, mp 181-184°C. Found, %: S 14.06; Cl 23.36; N 6.21. $C_{14}H_{13}Cl_3N_2O_4S_2$. Calculated, %: S 14.45; Cl 23.97; N 6.31. PMR spectrum in d_6-DMSO, δ, ppm: 9.28 (NH); 7.95-8.67 (C_6H_5); 5.72 (CH=, J = 9.25 Hz).

N-(1-Acetoxy-2,2,2-trichloroethyl)benzenesulfonamide (II). Compound VI (0.1 mole) was mixed with 0.2 mole of β,β-dichlorovinyl acetate (X). An exotherm developed after 10 min and the mixture was cooled in water to 8-10°C, and then stirred at 20°C for 1 h. The precipitate was filtered off, washed with petroleum ether and dried to give 34.36 g (90%) of II, mp 109-111°C. Found, %: S 9.34; Cl 30.88; N 4.07. $C_{10}H_{10}Cl_3NO_4S$. Calculated, %: S 9.25; Cl 30.69; N 4.04. PMR spectrum, in d_6-DMSO, δ, ppm: 9.81 (NH); 7.92-7.59 C_6H_5; 6.39 (CH=).

A solution of 0.005 mole of II in 10 ml of DMF was treated with 0.02 mole of water and the solution was stirred at 60°C for 1 h. The precipitate was filtered, washed with benzene and dried to give 1.3 g (95%) of N-(1-hydroxy-2,2,2-trichloroethyl)benzenesulfonamide, mp 150-151°C. Lit. mp. 150-151°C [8]. Found, %: S 10.41; Cl 35.03; N 4.58. $C_8H_8Cl_3NO_3S$. Calculated, %: S 10.52; Cl 34.92; N 4.59. PMR spectrum in d_6-DMSO, δ, ppm: 8.87 (NH); 7.89-7.52 (C_6H_5); 5.18 (C-H).

N-(1-Acetamido-2,2,2-trichloroethyl)benzenesulfonamide (III). Into a four-necked flask, previously purged with dry nitrogen or argon, and fitted with a condenser and calcium chloride tube, thermometer, and stirrer was added 0.04 mole of trichloroethylidinebenzenesulfonamide (VIII) [5] and 0.16 mole of dry benzene. The solution was purged with inert gas, and 0.04 mole of acetamide was added slowly at 20-30°C. The temperature rose to 35-40°C, where it was kept for 1 h, and then concentrated under vacuum. The solid residue was washed on a filter with petroleum ether and hexane, and dried to give 13.2 g (90%) of III, mp 201-203°C. Found, %: S 9.26; Cl 30.71; N 7.99. $C_{10}H_{11}Cl_3N_2O_3S$. Calculated, %: S 9.27; Cl 30.77; N 8.10.

O-(1-Benzenesulfonamido-2,2,2-trichloroethyl)acetoxime (IV). Into a four-necked flask, fitted with a stirrer, reflux condenser, and thermometer was added 0.04 mole of VIII [5] and 0.16 mole of dry benzene under a nitrogen atmosphere. Acetoxime (0.04 mole) was slowly added at 20°C, resulting in an exotherm to 35-40°C. The mixture was kept at this temperature for 1 h, and concentrated under vacuum, taking care that the temperature of the liquid in the flask does not exceed 50°C. The solid residue was transferred to a filter, washed many times with hexane and petroleum ether and dried to give 13.7 g (95%) of IV, mp 95-97°C. Found, %: S 8.63; Cl 29.80; N 7.91. $C_{11}H_{13}Cl_3N_2O_3S$. Calculated, %: S 8.92; Cl 29.57; N 7.99. PMR spectrum in $CDCl_3$, δ, ppm: 1.9 (CH_3); 5.90 (CH); 6.49 (NH); 7.61-8.10 (C_6H_5).

N-(1-Benzamido-2,2,2-trichloroethyl)benzenesulfonamide (V). A solution of 9.06 g VI in 20 ml of DMF was mixed with a solution of 8.64 g of β,β-dichlorovinylbenzamide (XI) in 20 ml of DMF. The temperature rose to 40°C, and the mixture was kept at 50-60°C for 2 h and then diluted with 150 ml of water. The precipitate was filtered off, washed with petroleum ether and dried over P_2O_5 to give 15.9 g (98%) of V, mp 202-203°C. Found, %: S 7.80; Cl 26.19; N 6.87. $C_{15}H_{13}Cl_3N_2O_3S$. Calculated, %: S 7.86; Cl 26.09, N 6.87. PMR spectrum in d_6-DMSO, δ, ppm: 8.63 (NH, J = 9.0 Hz); 8.46 (NH, J = 9.5 Hz); 7.70-7.45 (C_6H_5); 6.15 (CH=, J = 9.0).

EXPERIMENTAL PHARMACOLOGICAL SECTION

Biological tests were carried out on noninbred white mice of both sexes weighing 20-24 g. The acute toxicity was studied by intraperitoneal injection. The LD_{50} values are given in Table 1 and show that all the compounds studied are nontoxic. The neurotropic, antibacterial and antiinflammatory activities of the compounds were studied.

TABLE 1. Pharmacological Activity of Trichloromethyl Derivatives of Benzenesulfonamides I-V (M ± m)

Compound	LD_{50}, mg/kg	Motor activity			Rectal temperature, °C			Hot plate			Length of hexobarbital sleep
		30	60	120	30	60	120	30	60	120	
I	1340	2,2±0,3	2,9±0,6	3,4±0,4	36,0±0,1	36,0±0,1	35,2±0,2	212±13	177±16	176±16	83,4±14,2
P		>0,05	>0,05	<0,05	<0,01	<0,01	<0,01	<0,05	>0,05	>0,05	<0,05
II	896	2,3±0,4	2,5±0,6	2,3±0,3	36,6±0,5	36,8±0,2	36,4±0,3	321±48	183±32	147±42	49,5±4,7
P		>0,05	>0,05	>0,05	<0,05	>0,05	>0,05	>0,05	>0,05	>0,05	>0,05
III	500	2,4±0,2	2,3±0,3	2,5±0,3	35,9±0,3	36,1±0,2	36,1±0,3	175±30	183±16	151±12	54,3±3,8
P		<0,05	>0,05	>0,05	<0,01	>0,05	<0,001	<0,05	>0,05	>0,05	>0,05
IV	600	1,3±0,1	3,0±0,4	3,1±0,6	36,1±0,2	35,9±0,1	35,9±0,2	140±130	104±120	108±20	27,2±3,2
P		>0,05	>0,05	0,05	>0,05	>0,05	<0,05	>0,05	<0,01	<0,05	>0,05
V	3000	2,3±0,4	3,0±0,4	3,0±0,5	35,7±0,3	36,6±0,3	35,7±0,2	310±25	130±13	135±26	98,5±11,5
P		>0,05	<0,05	>0,05	>0,05	>0,05	<0,01	>0,05	<0,05	>0,05	<0,01

The neurotropic effect was evaluated by the capacity of the compounds to change spontaneous motor activity, to potentiate hexobarbital narcosis, to show hypothermic and analgesic action, to protect the animal from convulsions and death upon introduction of pentylenetetrazole, and also by their antagonism to the m-cholinolytic arecholine [8].

The studied compounds produced a lowering of the rectal temperature. The most stable hypothermal effect was shown by I. Introduction of compounds I, III-V gave a temporary lowering of motor activity, and I and IV prolonged hexobarbital narcosis and showed a weakly significant analgesic action. These compounds decreased by 40% the death of the animals from pentylenetetrazole convulsions. They prevented the tonic extension phase of spastic attacks, but did not show a marked influence on the clonic component.

The compounds studied did not prevent, and did not weaken arecholine tremors; i.e., did not possess m-cholinolytic activity.

The antibacterial activity was studied by the successive dilution method of curvatures of Staph. aureus (Strain 209P) and E. coli (Strain 675). Compound V at a concentration of 0.25% showed inhibitory activity on both cultures. Compound II at concentrations of 0.5 and 1% suppressed the growth of E. coli and Staph. aureus, respectively. The other compounds were less active.

The materials studied did not show antiinflammatory activity as measured by formalin inflammation.

This work shows that compounds I-V exhibit neurotropic activity of the disruptive type. Compounds I and V, containing the benzenesulfonamide and benzamide substituents, respectively, display the most activity and the least toxicity.

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