SYNTHESIS AND ANTICONVULSANT ACTIVITY OF N-DIBROMOACETYLBENZENESULFONAMIDE

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Extensive clinical use is made of derivatives of aromatic sulfonic acids, which are considered antimicrobial and antidiabetic agents [1-3].

There are also scattered indications that certain substituted sulfonamides, such as N-acyl o-amino- and o-nitrobenzenesulfonamides [N-(3,4-dichlorobenzoyl)-2-aminobenzenesulfonamide, N-(3,4-dichlorobenzoyl)-benzenesulfonamide, N-(3,4-dichlorobenzoyl)-2-nitrobenezenesulfonamide, etc.], also possess anticonvulsant activity [4-7].

In this context we have begun a search for aromatic sulfonamides with greater anticonvulsant efficacy.

We have used for our syntheses of N-acylarenesulfonamides the method developed earlier [8], which is based on the haloform reaction of ω-trihalomethyl aryl (alkyl) ketones with sodium arenesulfonamides when heated in solvent

$$RCOCX_3 + ArSO_2NHNa \longrightarrow ArSO_2N(Na)COR + CHX_3$$

$$ArSO_2N(Na)COR \xrightarrow{H^+} ArSO_2NHCOR + Na^+$$

$$R = C_6H_5,\ CHBr_2,\ (CH_3)_3C;$$

$$Ar = C_6H_5;\ X = Cl,\ Br.$$

During the search for a new anticonvulsant agent some of us prepared a series of substituted benzenesulfonamides differing in the acyl group [9]. Our attention was drawn to an acyl derivative containing bromine, as an element having a tranquilizing effect on the central nervous system. To raise the yield of the desired product we have developed an essentially new method for preparing N-dibromoacetylbenzenesulfonamide (DABS), involving a stepwise temperature rise and the use of chlorobenzene as solvent to ensure complete conversion of the reactants [10]. Our proposed procedure provides a 61% yield of DABS by the reaction:

$$CHBr_2COCBr_3 + C_6H_5SO_2NHNa \longrightarrow C_6H_5SO_2N(Na)COCHBr_2 + CHBr_3$$

$$C_6H_5SO_2N(Na)COCHBr + H^+ \longrightarrow C_6H_5SO_2NHCOCHBr_2 + Na^+$$

The compound is poorly soluble in water but more soluble in fats and still more so in alcohols, which we took into account when preparing solutions.

We used mice for the biological evaluation of the preparation, administering DABS as a 1% oil solution into the stomach by intubation in a dose of 187 mg/kg. The sedative action of the preparation became apparent after 40-60 min; this was accompanied by reduction in motor activity and respiratory frequency and by somnolence. Electroencephalography showed that this may be due to the development of inhibition of the cerebral hemispheres, since electrocorticograms revealed a slowing of the wave process, apparent in the reduction in the number of β waves and increase in the number of α and Δ waves,

We assessed the anticonvulsant efficacy of the preparation against corazole-induced convulsions. We administered corazole to the animals intraperitoneally in a dose of 100 mg/kg. A pattern of severe convulsions ensued, resulting in death in 94.1% of cases. If the animals had previously received DABS in a dose of 93.5 mg/kg, the same dose of corazole, administered 40 min after the preparation, caused the death of only 25% of the mice.

* Deceased.

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TABLE 1. Effect of DABS on the Survival Rate in Corazole Convulsion

Group	Survived	Died	X^2	P
Experimental	13	2	18,12	<0,001
Control	1	16		

Increase of the dose of the test compound to 187 mg/kg enhanced its protective action; the animals died only in 20% of cases. Statistical treatment of the experimental data [10] indicated high confidence limits for these results (Table 1).

We also detected the anticonvulsant effect in other animals, such as rats.

In this case we examined the effect of DABS on the threshold convulsant dose of corazole. We found that when corazole solution was slowly administered intravenously on a background of preliminary administration of the sodium salt of DABS the convulsant dose increased by 17%.

Our results demonstrate that DABS also has an anticonvulsant effect under these conditions.

We measured the toxicity of DABS to check its safety. We found that on intraperitoneal administration its LD_{100} in mica was 700 mg/kg; however, the animals died on the second and third days. Only a higher dose, 3600 mg/kg, caused death in 100% of the animals on the day of administration.

The peroral LD_{50} was 1200 mg/kg. This implies that DABS is a relatively nontoxic compound. In this respect it has several advantages over a classic anticonvulsant agent like phenobarbital.

Thus the peroral LD_{50} of phenobarbital is 180 mg/kg [11], which is 6.7 times lower than that of DABS. The anticonvulsant dose of phenobarbital that protects 50% of the animals is 75 mg/kg, whereas the dose of DABS that protects 75-80% of mice is 93.5-187 mg/kg. This indicates that DABS has a high margin of safety.

Model experiments in dogs in which blood circulation, respiration, and electrocorticograms were monitored provided further evidence for the low toxicity of DABS. Intravenous injection to dogs in moderate doses did not cause marked changes in arterial pressure, respiration, or bioelectric processes of the cardiac muscles, while producing a clear sedative effect.

EXPERIMENTAL CHEMICAL PART

The IR spectrum of DABS was recorded on a UR-20 instrument in a tablet. Thin-layer chromatography was carried out on Silufol-254 silica gel (with binder) in the system chloroform–isopropyl alcohol (3:2).

N-Dibromoacetylbenzenesulfonamide (DABS). A stirred mixture of sodium benzenesulfonamide (7.17 g, 0.04 mole) and chlorobenzene (30 ml) was heated to 50-55°C, while a solution of pentabromoacetone (18.12 g, 0.04 mole) in chlorobenzene (14 ml) was added dropwise. The temperature of the reaction mixture rose to 110°C over a period of 30 min. The reaction terminated after 15 min. Chlorobenzene and bromoform were stripped from the reaction mixture under vacuum and the solid residue was treated with saturated sodium bicarbonate solution (70 ml). After cooling to 8-10°C, residual chlorobenzene and bromoform were extracted with ether (2 × 10 ml). Activated carbon (0.5 g) was added and filtered off. The aqueous filtrate was acidified with hydrochloric acid (1:2). The oil that appeared crystallized after 10-15 min; the crystals were dried in air to give DABS (8.71 g, 61.6%), which was recrystallized from benzene (mp 161-162.5°C) and from toluene (161-162°C); Rf 0.87. In spectrum (ν, cm^{-1}): 600 (C–Br), 1710 (CO), 1350, 1180 ($SO_2N\langle$), 3240 (NH).

Sodium N-Dibromoacetylbenzenesulfonamide (NaDABS). To DABS (0.01 mole) were added sodium hydroxide (0.01 mole) in water (12 ml) and alcohol (25 ml). When the N-dibromoacetylbenzenesulfonamide had completely dissolved, the solvent was evaporated at 75°C and the residue was dried at this temperature to constant weight (roughly 8 h) to give NaDABS (0.01 mole).

Hydrolysis of DABS was carried out at room temperature (20-21°C) or under reflux (100°C) by the following procedure. The DABS (0.2 g) was mixed with water (10-14 ml) and, after a specific time, the solid product was filtered off and the filtrate was titrated with 0.1 N alkali. From the alkali used in the titration we calculated the amount of dibromoacetic acid liberated and the extent of hydrolysis of DABS (in mg-eq and then in percent).

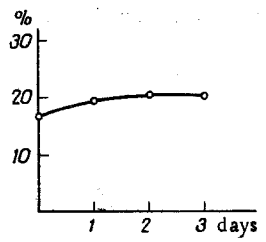

Fig. 1. Extent of hydrolysis of DABS (in %) versus time (in days) at normal temperature.

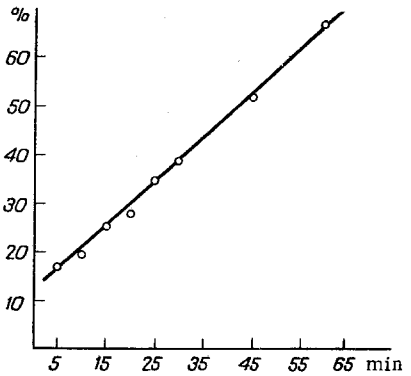

Fig. 2. Extent of hydrolysis of DABS (in %) versus time (in min) at 100°C.

Our results for the hydrolysis of DABS yielded the plots of the extent of hydrolysis against time (Figs. 1 and 2).

The figures show that the percentage hydrolysis of DABS at any time varies with temperature.

Thus the considerable efficacy of DABS relative to existing anticonvulsants and its high margin of safety suggest that it is of some promise for further study as an anticonvulsant agent.

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