THE EFFECT OF THE SULPHONE GROUP IN HYPNOTICS

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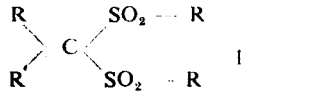
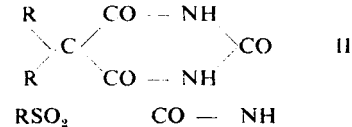
Sulphones of the type I possess remarkable narcotic properties and bear some structural resemblance to the substituted malonic acid fragment of barbituric acid derivatives II, another group of excellent hypnotics. Such resemblances has encouraged some workers to attempt the preparation of " Veronalsulphone " (III), but such attempts failed[1,2,3].

Another type of compound that would reflect both the sulphonals and the barbitones, is a barbituric acid substituted at position 5 with alkyl sulphone groups (IV).



I



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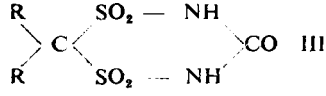

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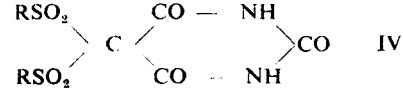
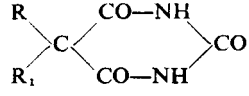


IV

By preparing such compounds the effect of introducing the sulphone groups into the barbituric acid nucleus can be tested; and as typical compounds 5-ethylsulphonylbarbituric acid (V), 5-ethyl-5-ethylsulphonylbarbituric acid (VI) and 5:5-diethylsulphonylbarbituric acid (VII) were prepared and their hypnotic potency compared with that of diethylbarbituric acid (VIII).



V : R = H, $R_1 = C_2H_5SO_2$ VII : R and $R_1 = C_2H_5SO_2$

VI : R = C_2H_5, $R_1 = C_2H_5SO_2$ VIII : R and $R_1 = C_2H_5$

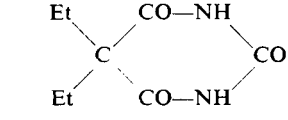
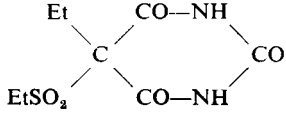
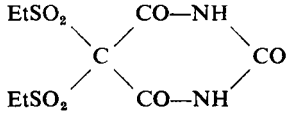
The syntheses were achieved by methods parallel to those used for substituted barbituric acids, viz.: the condensation of ethylsulphone malonic esters with urea, the substituted malonic esters being prepared by the interaction of ethylsulphonyl chloride and ethyl sodio-malonate in etheral medium. In the case of ethyl-ethylsulphonylbarbituric acid, the compound was prepared also by the interaction of sodium sulphinate and 5-ethyl-5-bromobarbituric acid[4] in order to confirm the configuration of the condensation product. This latter process also gave better yields. The physical and chemical characters of the new products are tabulated in the experimental part.

We are indebted to Professor M. Sherif of the Pharmacology Department of the Faculty for the biological investigation of the new barbiturates. The relative activities of the compounds are tabulated as follows taking the activity of veronal as a reference.

Evidently, therefore, the introduction of sulphone groups into the molecule of barbitone has decreased its activity. The toxicity of the new products is greater than that of barbitone, thus the possibility of their administration may be restricted and unsafe.

Experimental

Sodium ethanesulphonate was prepared by a modification of the method of Hemillian[5]. A clear solution of anhydrous sodium sulphite (35 g.) in water (250 ml.) and ethyl iodide (30 g.) were heated on a water-bath under a reflux condenser until all the iodide disappeared (7 hours).

COMPOUND	SO_2 GROUPS	ACTIVITY
	0	100
	1	80
	2	10

Copper sulphate solution (100 ml. of 20 per cent.) was added with stirring to the warm reaction mixture and the precipitate so formed removed by filtration. The filtrate was neutralised with sodium hydroxide solution and concentrated on a water-bath till a scum formed on the surface, then allowed to crystallise, and filtered again. The filtrate was evaporated to dryness, the residue extracted with boiling alcohol (80 per cent.) and filtered whilst hot. On cooling the alcoholic filtrate sodium ethanesulphonate crystallised in thin wide plates. Yield, 78 per cent.

Ethylsulphonyl chloride was prepared by a modification of the method of Gerhardt[6]. Sodium ethanesulphonate (13 g.), dried at 120°C. under reduced pressure for 2 hours, was finely powdered and mixed with phosphorus pentachloride (20 g.) and then heated on a water-bath for 10 minutes. The cooled mixture was decomposed by pouring into ice-cold water and the acid chloride produced extracted with ether. After drying the extract and removal of the solvent, the acid chloride was distilled at 75° to 77°C./25 mm.Hg. Yield, 68 per cent.

Ethylsulphonylmalonic Ester (I). Diethylmalonate (30 g.) was added gradually with stirring to sodium wire (2·3 g.) covered with ether (150 ml.), the whole being heated on a water-bath under a reflux condenser. Slow addition of ethanesulphonyl chloride (10 g.) dissolved in ether (50 ml.) commenced after all the sodium had disappeared (1½ hours), stirring and refluxing being continued during the addition and for a further 7 hours until the mixture became neutral to litmus. Water was then added, the mixture acidified, the ethereal layer separated and the aqueous layer repeatedly washed with ether. The mixed ethereal solutions were dried over calcium chloride, the ether removed, and the residue distilled *in vacuo*.

Ethyl-ethylsulphonylmalonic ester (II) was prepared by the same procedure as I using ethylsulphonylmalonic ester (30 g.) in place of malonic ester and ethyl iodide (20 g.) in place of ethylsulphonyl chloride.

Diethylsulphonyl-malonic ester (III) was prepared by the same procedure as I using ethylsulphonylmalonic ester (30 g.) in place of the malonic ester.

All the esters occurred in the form of pale yellow oils soluble in ether and organic solvents, insoluble in water and showing a sp. gr. greater than 1. Table I gives their constants.

TABLE I

Ester	Boiling point	Sp. Gr. at 20°C.	Sulphur found	Content required	Yield
					per cent.
I	145 to 147°C./5 mm. Hg	1·36	12·68	12·7	48
II	160 to 163°C./5 mm. Hg	1·42	11·40	11·43	42
III	172 to 174°C./5 mm. Hg	1·48	18·41	18·6	29

Condensation with Urea.

5-Ethylsulphonylbarbituric Acid (IV). Sodium (5·1 g.) was dissolved in absolute methyl alcohol (120 ml.). To the solution of 1 ml. of ethyl acetate was added followed, after 10 minutes at 60°C., by urea (12·7 g.). When the urea had dissolved, ethylsulphonylmalonic ester (15 g.) was added and the apparatus transferred to an oil-bath. A condenser for distillation and a sealed stirrer were fitted. The temperature of the reaction mixture was gradually raised to 130°C., in the course of 3½ hours, then the viscous mass was treated with ice and ice-cold water; when the bulk of the melt had dissolved, the alkaline solution was treated with 20 ml. of benzene, then rendered distinctly alkaline to congo red with hydrochloric acid, concentrated and allowed to crystallise. The crude barbituric acid was recrystallised from an acetone-benzene mixture.

5 : 5-Diethylsulphonyl-barbituric acid (V). The above procedure was

applied using diethylsulphonemalonic ester (21 g.) in place of the monoethylsulphonemalonic ester. The product was recrystallised from 95 per cent. alcohol.

5-Ethyl-5-ethylsulphonylbarbituric acid (VI). (a) The same procedure was applied using ethyl-ethylsulphonylmalonic ester; the crude product was crystallised from 85 per cent. alcohol. (b) 5-Bromo-5-ethylbarbituric acid[7] (2·7 g.) and sodium ethanesulphinate[8] (1·2 g.) were dissolved in absolute methyl alcohol (20 ml.) and the mixture refluxed for 8 hours. The precipitated sodium chloride was filtered and the filtrate concentrated and allowed to crystallise. The product was identical with that above as confirmed by a mixed melting-point.

All the barbituric acid derivatives obtained were crystalline solids soluble in ether, alcohol and dilute alkalis; some of their constants are shown in Table II.

TABLE II

Acid	Melting point	Yield per cent.	Analyses			
			Nitrogen		Sulphur	
			Found	Required	Found	Required
IV	145 to 146°C.	27	12·74	12·73	14·46	14·55
V	156 to 157°C.	41	8·96	8·97	20·28	20·26
VI	163 to 164°C.	44	11·31	11·29	12·87	12·90

REFERENCES

1. Fourneau, *Organic medicaments and their preparation*, Churchill, London, 1921, 49.
2. Bauer and Jenkins, *J. Amer. pharm. Ass.*, 1937, **26**, 486.
3. Bodendorf and Singer, *Ber. dtsch. chem. Ges.*, 1939, **72**, 571.
4. D'ouville, Myers and Conner, *J. Amer. chem. Soc.*, 1939, **61**, 2033.
5. Hemillian, *Liebig's Ann.*, 1873, **168**, 146.
6. Gerhardt and Chanal, *ibid.*, 1882, **183**, 434.
7. Fisher and Dilthey, *ibid.*, 1904, **335**, 357.
8. Liefert, *ibid.*, 1822, **114**, 142.

DISCUSSION

The paper was read by Dr. Said.

The CHAIRMAN said that the Conference would welcome this contribution on synthetic work.

DR. HARTLEY (London) asked, firstly, if the introduction of the ethylsulphone group modified in any way the dissociation of the barbiturate portion of the molecule; that is, was the sodium salt formed readily hydrolysed or comparatively neutral? Secondly, if the introduction of

the ethyl-sulphone groups modified the way in which the molecule could be broken down by acid hydrolysis?

MR. D. E. SEYMOUR (Welwyn) asked what methods were used to make compound III. The combination of sulphones with the barbiturate would be a most difficult problem, and the compound probably would not have any value in this particular field. It was a sulphonamide, and might have quite different properties. Had Dr. Said examined his compounds for biological activity other than hypnotic value?

DR. K. BULLOCK (Manchester) asked if Dr. Said could tell them a little about the method of testing hypnotics. In relating constitution to physiological action, the method of testing was important. He asked whether the decreasing activity with increasing number of sulphone groups could be related to such properties as decreasing solubility, or change of *p*H.

DR. R. E. STUCKEY (London) said he could not quite follow Mr. Seymour's remark about compound III being essentially a sulphonamide, and would like that explained. It was interesting that the compound, with free hydrogen in position 5, showed no activity; with such a compound, the molecule was more acidic, and had a considerably lower K_A value.

DR. F. SAID, in reply, said that with one ethylsulphone group the compounds were more soluble in liquids than in water, and with two ethylsulphone groups the difference was even more marked. For testing the compounds dogs had been used, the relative activities being determined from the amounts needed to produce sleep. One group of dogs was given barbitone and another the compound to be tested, but he could not give details of the method as the test was done in the Pharmacological Department. Other biological activities had not been investigated. He agreed that it was desirable to investigate the germicidal activity, but doubted whether compound III could be described as a sulphonamide.