[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KENTUCKY]

SULFONAL ANALOGS DERIVED FROM TETRAHYDROTHIAPYRAN

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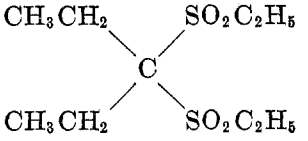
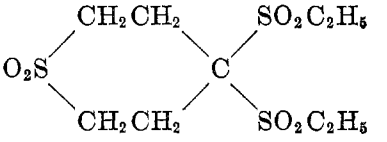
No mercaptols or their corresponding sulfones of tetrahydro-1,4-thiapyrone have been made. The close structural relationship between the sulfonal type of hypnotic (I) and these sulfones (II) can be seen from their formulas.



I



II

The sulfonal type of structure reaches its maximum hypnotic activity when all four of the alkyl groups are ethyl groups. In this series of sulfones two of the ethyl groups are attached to a tetrahydro-1,4-thiapyran-1-dioxide structure thus increasing the sulfone groups to three. Due to the possibility that sulfones of this structure might have some interesting physiological properties several sulfones of this type have been synthesized. It was found, however, that they had no hypnotic activity on rats which was probably due to their marked insolubility in appropriate solvents.[1]

The ethylmercaptols were easily made in excellent yields from all of the tetrahydro-1,4-thiapyrones used. The very stable beta-keto ester, 2,6-dimethyl-3-carbomethoxytetrahydro-1,4-thiapyrone, which is very resistant to hydrolysis (1), formed an ethylmercaptol readily. It was also found possible to prepare the ethylmercaptol of tetrahydro-1,4-thiapyrone-1-dioxide which was a very viscous liquid that distilled under diminished pressure but never solidified. The mercaptol of 3-ketothiophane was also made. The mercaptols were clear colorless stable liquids which could be purified by distillation under diminished pressure. The mercaptols made are listed in Table I.

The corresponding sulfones were made by oxidizing the mercaptols with potassium permanganate using essentially the procedure of Reitz (2). They are white crystalline solids fairly soluble in chloroform and hot acetone but practically insoluble in cold water. It was possible to prepare a sulfone from all the mercaptols made. They are listed in Table II.

EXPERIMENTAL

Preparation of 4,4-bis(ethylmercapto)tetrahydrothiapyran. In a small flask were placed 11.6 g. (0.1 mole) of tetrahydro-1,4-thiapyrone and 14.9 g. (0.24 mole) of ethylmercaptan. The mixture was cooled with ice and anhydrous hydrochloric acid was slowly passed into

[1] We are indebted to Dr. M. G. Van Campen of the Wm. S. Merrell Company for evaluating the hypnotic activity of these sulfones.

the mixture for three hours. After standing at 0° overnight, ether and water were added and the ether layer separated. The ether solution was washed well with cold 5% sodium hydroxide, then with ice-water, and dried over magnesium sulfate. After distilling off the

TABLE I

4,4-BIS(ETHYLMERCAPTO)TETRAHYDROTHIAPYRANS AND 3,3-BIS(ETHYLMERCAPTO)THIOPHANE

MERCAPTOL	YIELD, %	B.P., °C./MM.	n_D^{25}	FORMULA	SULFUR	
					Calc'd	Found
4,4 - bis(Ethylmercapto)tetrahydrothiapyran	86	112–114/2	1.5635	$C_9H_{18}S_3$	43.25	43.40
3 - Methyl - 4,4 - bis(ethylmercapto)-tetrahydrothiapyran	77	114–116/2	1.5625	$C_{10}H_{20}S_3$	40.68	41.10
2 - Methyl - 4,4 - bis(ethylmercapto)-tetrahydrothiapyran	95	112–114/2	1.5552	$C_{10}H_{20}S_3$	40.68	40.98
2,6 - Dimethyl - 4,4 - bis(ethylmercapto)tetrahydrothiapyran	63	108–110/1.5	1.5418	$C_{11}H_{22}S_3$	38.41	38.24
2,6 - Dimethyl - 3 - carbomethoxy - 4,4-bis (ethylmercapto) tetrahydrothiapyran	90	144–146/2.5[a]		$C_{13}H_{24}O_2S_3$	31.18	30.93
4,4 - bis (Ethylmercapto)tetrahydrothiapyran - 1 - dioxide	56	172–175/2	1.5505	$C_9H_{18}O_2S_3$	37.81	37.96
3,3 - bis (Ethylmercapto)thiophane	63	112–114/2.5	1.5669	$C_8H_{16}S_3$	46.16	45.91

[a] M.p. 50–52°.

TABLE II

4,4-BIS(ETHYLSULFONYL)TETRAHYDROTHIAPYRAN-1-DIOXIDES AND 3,3-BIS(ETHYLSULFONYL)THIOPHANEDIOXIDE

SULFONES	YIELD, %	M.P., °C.	FORMULA	SULFUR	
				Calc'd	Found
4,4 - bis(Ethylsulfonyl)tetrahydrothiapyran - 1 - dioxide	60.0	170.5–171.5	$C_9H_{18}O_6S_3$	30.21	30.48
3 - Methyl - 4,4 - bis(ethylsulfonyl)-tetrahydrothiapyran - 1 - dioxide	53.5	163–165	$C_{10}H_{20}O_6S_3$	28.94	29.34
2 - Methyl - 4,4 - bis(ethylsulfonyl)-tetrahydrothiapyran - 1 - dioxide	46.3	165–167	$C_{10}H_{20}O_6S_3$	28.94	29.16
2,6 - Dimethyl - 4,4 - bis(ethylsulfonyl)tetrahydrothiapyran - 1 - dioxide	57.8	199.5–200.5	$C_{11}H_{22}O_6S_3$	27.76	27.63
2,6 - Dimethyl - 3 - carbomethoxy-4,4 - bis(ethylsulfonyl)tetrahydrothiapyran - 1 - dioxide	45.8	169 –170	$C_{13}H_{24}O_8S_3$	23.78	23.65
3,3 - bis(Ethylsulfonyl)thiophanedioxide	51.4	192.5–193.5	$C_8H_{16}O_6S_3$	31.60	31.55

solvent the mercaptol was fractionally distilled under diminished pressure. The other mercaptols were made in a similar manner and the yields and physical properties are listed in Table I.

Preparation of 4,4-bis(ethylsulfonyl)tetrahydrothiapyran-1-dioxide. A mixture of 2.2 g. (0.01 mole) of 4,4-bis(ethylmercapto)tetrahydrothiapyran, 20 ml. of water, and 6.6 g. of concentrated sulfuric acid was placed in a 250-ml. separatory-funnel and heated to 70°. To this mixture was added in small portions 5 g. of potassium permanganate in 125 ml. of water heated to 70°. The reaction mixture was maintained at a temperature of 65–70° and shaken vigorously for 15 minutes. Saturated sodium acid sulfite solution was then added until the mixture was decolorized. The mixture was cooled and extracted twice with chloroform. The chloroform extract was washed well with saturated sodium acid carbonate and dried over magnesium sulfate. After distilling off the solvent the crude residue was taken up in hot acetone, either alcohol or water was added, and the solution was allowed to stand in an ice-chest overnight. The white crystals were filtered and recrystallized in the same manner. Yields and properties of the sulfones made are listed in Table II.

SUMMARY

The ethylmercaptols and corresponding sulfones of several 1,4-tetrahydrothiapyrones and 3-ketothiophane have been made for the first time. Though the sulfones are structurally somewhat similar to the sulfonal type of hypnotic they showed no hypnotic activity when tested on rats.

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REFERENCES

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(2) REITZ, FERNANDEZ, SNIDER, AND TODSON, *J. Am. Chem. Soc.*, **71**, 3433 (1949).