obtained in duplicate electron diffraction investigations. Moreover, if Rogowski actually did have spiropentane, his neglect to mention the asymmetries of the first and second minima and of the third maximum is very curious, inasmuch as these features show very clearly on our photographs. It is probably true, as would be indicated by the results of Whitmore and Williams,[13] that Rogowski's preparation was a mixture of hydrocarbons.

We are indebted to Dr. E. R. Buchman for interesting discussion, and to Dr. M. J. Murray for the sample of spiropentane.

Summary

The results of an electron diffraction investigation of the C_5H_8 hydrocarbon prepared by Murray and Stevenson[1] confirm their assignment of the spiropentane structure made on the basis of the Raman spectrum. The dimensions for this molecule are C–H = 1.08 Å. (assumed), C_1–C_3 = 1.48 ± 0.03 Å., C_1–C_2 = 1.51 ± 0.04 Å., $\angle C_2C_3C_1$ = 61.5 ± 2°, and $\angle HCH$ = 120° ± 8° ($(C-C)_{ave.}$ = 1.49 ± 0.01 Å.).

PASADENA, CALIFORNIA RECEIVED AUGUST 7, 1944

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Some Alkyl and Alkamine Esters of *p*-Fluorothiobenzoic Acid[1]

BY L. S. FOSDICK AND H. I. BARNES

In 1933 some alkyl and alkamine esters of *p*-aminothiobenzoic acid were prepared.[2] The pharmacological activity of these compounds was compared with that of their oxygen analogs, the procaine series. It was found that the substitution of sulfur for oxygen increased the anesthetic efficiency four to six times, and increased the toxicity three to four times.[3] Some clinical trials indicated that a 0.5% solution of the procaine analog, "Thiocaine," gave similar results to a 2.0% solution of procaine hydrochloride. Furthermore, unlike procaine hydrochloride, Thiocaine produced profound topical anesthesia on the cornea of the eye.

Later[4] it was found that the esters of *p*-fluorobenzoic acid possessed local anesthetic properties but were quite irritating to tissue. These esters were exceptionally non-toxic.

In view of the above, it was thought of interest to prepare the alkyl and alkamine esters of *p*-fluorothiobenzoic acid.

In the present study the alkyl and chloroalkyl esters were prepared from the potassium salt of the acid and the appropriate alkyl halide or the appropriate dihalogen substituted alkane. The alkamine esters were prepared from the halogen ester and the appropriate amine.

Preliminary pharmacological data indicate that, contrary to expectations, the substitution of sulfur for oxygen does not enhance the anesthetic efficiency, but does materially increase the toxicity of these compounds.

Experimental Part

All of the compounds were prepared from *p*-toluidine by converting it to *p*-fluorotoluene according to the method of Balz and Schiemann.[5] This was then oxidized with neutral permanganate to *p*-fluorobenzoic acid,[6,7] which was subsequently converted to the acid chloride with thionyl chloride. The *p*-fluorobenzoyl chloride was then converted to the thio acid and the various esters prepared as previously indicated.

p-Fluorothiobenzoic Acid.—A solution of 23.5 g. of potassium hydroxide and 300 cc. of ethyl alcohol was cooled in an ice-bath and saturated with hydrogen sulfide. To this was added slowly 32.5 g. of *p*-fluorobenzoyl chloride. A precipitate formed which was removed by filtration and the mother liquor was evaporated to dryness. The two solids were combined, dissolved in a minimum amount of cold water, and the free acid was precipitated by the addition of concentrated hydrochloric acid. The mixture was allowed to remain in an ice box overnight, after which the precipitate was removed by filtration. The acid was obtained as a light yellow solid; yield, 27 g., 86%; m. p. 36°; S, 21.9, 21.5; calcd., 20.5.

Alkyl Esters.—Fifteen grams of *p*-fluorothiobenzoic acid was dissolved in 10–15 cc. of alcohol mixed with a saturated alcoholic solution of 5.6 g. of potassium hydroxide. An excess of the appropriate alkyl bromide was added and the mixture was refluxed on a steam-bath for two hours. The potassium bromide which had precipitated was removed by filtration and excess alcohol and alkyl bromide was removed by distillation in a vacuum. The ester was washed with water and purified by distillation *in vacuo*.

TABLE I

p-FLUOROTHIOBENZOATES

Compound	Yield, %	M. p., b. p., °C.	S analyses, % Calcd.	Found
Ethyl	76	224–225 at 754 mm.	17.39	17.08
n-Propyl	93	106–110 at 6 mm.	16.16	16.12
n-Butyl	80	130–133 at 8 mm.	15.60	15.52
β-Chloroethyl	67	145–148 at 8 mm.	14.64	14.51
Diethylaminoethyl·HCl	60	164–170	10.98	10.91
Di-*n*-propylaminoethyl·HCl	62	200–205	10.06	9.95
Di-*n*-butylaminoethyl·HCl	65	220–224	9.21	9.20
γ-Bromopropyl	20	165 at 7 mm.	11.55	11.50
Diethylaminopropyl·HCl	61	130	10.48	10.45
Di-*n*-propylaminopropyl·HCl	65	157	9.59	9.62
Di-*n*-butylaminopropyl·HCl	60	191	8.85	8.82

(1) Presented before the Division of Medicinal Chemistry, New York meeting of the American Chemical Society, September 15, 1944.

(2) Hansen and Fosdick, THIS JOURNAL, **55**, 2872 (1933).

(3) Fosdick and Hansen, *J. Pharmacol.*, **50**, 323 (1932).

(4) Fosdick and Campaigne, THIS JOURNAL, **63**, 974 (1941).

(5) Balz and Schiemann, *Ber.*, **60**, 1186 (1927).

(6) Oliman, THIS JOURNAL, **16**, 533 (1894).

(7) Slothower, *Rec. trav. chim.*, **33**, 324 (1914).

Chloro Alkyl Esters.—These esters were prepared in the same manner as the alkyl esters with the exception that ethylene chlorobromide or propylene chlorobromide was used in place of the alkyl halide.

Dialkylaminoalkyl Ester Hydrochlorides.—To a mixture of 10 g. of the chloro ester and 15 cc. of alcohol was added 10 g. of the appropriate amine. The mixture was refluxed on a steam-bath for two hours, and poured onto a mixture of cracked ice and dilute sodium hydroxide. The free base was removed and dissolved in dry ether. The hydrochlorides were formed by passing dry hydrochloric acid into the ether solution. They were purified by recrystallization from absolute alcohol or by precipitation from an alcoholic solution by the addition of dry ether. The physical properties and analytical data are in the table.

Summary

Some alkyl and alkamine esters of *p*-fluorothiobenzoic acid were synthesized and the physical properties were determined. These compounds are rather toxic weak local anesthetics, indicating that the substitution of sulfur for an ester oxygen increases the toxicity and decreases the anesthetic efficiency of this series.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 30, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

Diaryloxyalkane Derivatives. Diphenoxypropanesulfonamides

BY JOHN A. KING AND FREEMAN H. MCMILLAN

At the same time that a series of diphenoxyethanesulfonamides was being prepared[1] and before it was learned that these substances were trypanocidally inactive, a few of the corresponding diphenoxypropanesulfonamides were prepared. This paper reports their preparation.

α,γ-Diphenoxypropane (I) was prepared by the procedure of Lohmann[2] modified according to the method of Cope[3] for diphenoxyethane. This was chlorosulfonated by a modification of the procedure of Huntress and Carten[4] to yield α,γ-diphenoxypropane - 4,4′ - disulfonyl chloride (II). This, on treatment with aqueous ammonia, gave the diamide III, and on treatment with aqueous dimethylamine yielded the corresponding N,N,-N′,N′-tetramethyl amide IV.

In order to prove the structure of IV and at the same time of the disulfonyl chloride II and all products derived from it, the tetramethyl amide was synthesized by an unequivocal method. 4-Hydroxybenzenesulfondimethylamide was condensed with trimethylene bromide, in alcoholic alkaline solution, to give the same product as had been obtained from the disulfonyl chloride II and diethylamine.

Other diphenoxypropane derivatives prepared were the di-N-ethyl derivative V, from the disulfonyl chloride II and ethylamine, the diacetamido compound VI, and its sodium salt VII.

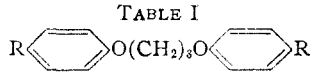
Preliminary tests carried out with these diphenoxypropane derivatives indicate that these substances are devoid of trypanocidal activity.

Experimental Part[5,6]

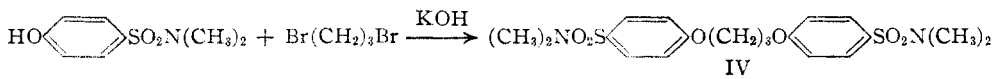
α,γ-Diphenoxypropane (I).—A mixture of phenol (94 g. 1.00 mole), trimethylene bromide (101 g., 0.50 mole), potassium hydroxide (56 g., 1.00 mole; 66 g. of 85% C. P. base), and absolute alcohol (300 cc.) was refluxed with stirring for three hours and then poured into 3.5 liters of ice-water. The solid material (m. p. 52–54°) was recrystallized from aqueous alcohol to give 87 g. (76% yield) of product, m. p. 60–61°. Lohmann[2] reported m. p. 61°.

α,γ-Diphenoxypropane-4,4′-disulfonyl Chloride (II).—This was prepared by the general procedure developed with α,β-diphenoxyethane;[1] see the following paragraph. A small sample for analysis, after recrystallization from petroleum ether, had m. p. 121°. See Table I for analysis.

TABLE I



Compound	R	% yield of pure product	M. p.,[5] °C.	Formula	Analyses, %[6] Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	—H	76	60–61							
II	—SO_2Cl	85	121	$C_{15}H_{14}O_5S_2Cl_2$	42.35	3.32		42.26	3.38	
III	—SO_2NH_2	85	194.5–195	$C_{15}H_{18}N_2O_5S_2$	46.63	4.66	7.25	46.67	4.72	7.48
IV	—$SO_2N(CH_3)_2$	...	191	$C_{19}H_{26}N_2O_5S_2$	51.59	5.88	6.33	51.69	6.02	6.68
V	—$SO_2NHC_2H_5$	69	143.5–144	$C_{19}H_{28}N_2O_5S_2$	51.59	5.88	6.33	51.65	5.89	6.36
VI	—$SO_2NHCOCH_3$	67	169–170	$C_{19}H_{22}N_2O_5S_2$	48.51	4.68	5.97	48.75	4.68	5.98
VII	—$SO_2N(Na)COCH_3$	100	dec.	$C_{19}H_{20}N_2O_5S_2Na_2$	Na,	8.95		Na,	9.06	



IV

α,γ-Diphenoxypropane-4,4′-disulfonamide (III).—The general preparative procedure is that previously described,[1] but some modification was necessary. Varying molar proportions of chlorosulfonic acid were used to determine the optimal conditions for the reaction. The crude chloroform solution of the disulfonyl chloride was stirred with excess aqueous ammonia and the resultant disulfonamide was removed by filtration, dried and weighed. The results are given in Table II.

(1) King, THIS JOURNAL, **66**, 2076 (1944).
(2) Lohmann, *Ber.*, **24**, 2632 (1891).
(3) Cope, THIS JOURNAL, **57**, 572 (1935).
(4) Huntress and Carten, *ibid.*, **62**, 603 (1940).
(5) All melting points are uncorrected.
(6) Microanalyses by Misses P. Curran and A. Rainey.