der nitrogen for 4 days, the products were carbon dioxide (44%), di-1-naphthylurea (1%), and four unidentified substances, none of which was the expected secondary amine.

Pyrolysis procedure. Thermal degradations performed in the presence of solvent were carried out in flamed ground-glass equipment. All the solvents were dried by use of Linde 5A molecular sieves. The reaction flasks were swept by a stream of Linde high purity nitrogen free from carbon dioxide and dried by passing through a tower of molecular sieves. After the reaction vessel, the gas stream was cooled to −78° to remove organic vapors and monitored for carbon dioxide with Ascarite-filled absorption tubes.

Degradations done in the absence of solvent were carried out in a 2.5 × 30 cm. Pyrex test tube that was flame dried before use. The test tube had provision for a thermometer, thermocouple, a nitrogen sweep stream, and a reflux condenser. The test tube was heated in an aluminum block,[23] a cylinder 6 in. in diameter and 12 in. high, insulated by 4 in. of rock wool. The block was heated by a 500-watt cylindrical heater operated through a relay-controlled Variac and a 120-watt heater operated through a Fenwal, bimetallic thermoregulator. Temperature fluctuations within the pyrolysis tube were held to a ±0.3° range.

In a typical pyrolysis the sample (5–20 g.) was placed in the pyrolysis tube, the system flushed with nitrogen for 15 min., the tube placed in the heating bath and allowed to equilibrate for 10–15 min. (while collecting evolved carbon dioxide which was used as a correction factor). After constant temperature had been reached by the pyrolysis mixture, reaction rates were followed by collecting carbon dioxide in Ascarite-filled weighing tubes. In the case of pyrolysis of the O^{18}-enriched carbamates, helium was used as a sweep stream and the evolved carbon dioxide was frozen out in traps cooled to −168° (liquid nitrogen). The carbon dioxide was transferred to evacuated gas sampling bulbs and analyzed for variously tagged species of tagged carbon dioxide.

Solid degradation residues were separated by solubility differences and chromatography on activated alumina. Liquid degradation residues were separated by distillation or vapor phase chromatography.

All vapor phase chromatography was carried out with an F and M Scientific Corp., Model 202 programmed gas phase chromatograph, using helium as a carrier gas and 10- to 12-ft. silicon-oil packed columns. Quantitative analyses were done by the techniques of both internal normalization of peak area and internal standardization. Qualitative work was carried out using authentic samples.[24]

Autocatalysis in the formation of carbon dioxide from 1-naphthyl isocyanate. The equation for autocatalysis $dC/dt = k(a - x)^2(b + x)$ was integrated by partial fractions to give

$$k_3't = \frac{2}{(2a + b)^2}\left[\frac{(2a + b)x}{(a - x)a} + \ln\frac{a(b + x)}{b(a - x)}\right]$$

A plot of the right-hand side of the equation *vs.* time was linear to at least 21% of reaction, when 1-naphthyl isocyanate was pyrolyzed at 268° with 0.3 mole % of added *N,N'*-di-1-naphthylcarbodiimide.

O^{18}-Enriched 1-hexadecanol. By a slight modification of the method of Boschan,[25] O^{18}-enriched 1-hexadecanol was prepared in an over-all yield of 52%.

To 5.000 g. (0.270 mole) of O^{18}-enriched water, containing 32.08% O^{18} and 0.965% O^{17} (from the Weizmann Institute, Rehovoth, Israel) and 30 ml. of dry xylene was slowly added 27.6 g. (0.270 mole) of freshly distilled acetic anhydride. The mixture stood for 1 hr. at room temperature followed by warming to 60° for 11.5 hr. The resulting mixture of xylene and O^{18}-enriched acetic acid was slowly added to 24.65 g. (0.542 mole) of a 52.7% mineral oil dispersion of sodium hydride (Metal Hydrides Corp.) in 80 ml. of dry xylene. After completion of the dropwise addition, the mixture was warmed to gentle reflux, cooled, and the O^{18}-enriched sodium acetate filtered off as 44.15 g. (0.537 mole) of white solid (dried).

Using the method of Drahowzal and Klamann[26] the new compound, 1-hexadecyl *p*-toluenesulfonate, was prepared in 83.4% yield as a white solid, m.p. 48–49° (recrystallized from ether).

Anal. Calcd. for $C_{23}H_{40}O_3S$: C, 69.65; H, 10.17; S, 8.09. Found: C, 69.71; H, 10.02; S, 8.85.

Following the procedure of Boschan,[25] the O^{18}-enriched sodium acetate was treated with 1-hexadecyl *p*-toluenesulfonate to give a 55.2% yield of O^{18}-enriched 1-hexadecyl acetate, and the acetate was reduced to O^{18}-enriched 1-hexadecanol, m.p. 49–50°, in 95% yield. The latter substance was used to prepared the O^{18}-enriched O-hexadecyl *N*-1-naphthylcarbamates.

Based on the procedure of synthesis, the O^{18} content of the alcohol should have been 8%. The data of Table III indicate that the actual content was 7.9%.

Acknowledgment. The authors are indebted to the Armstrong Cork Co. for a fellowship in support of this investigation and to Drs. L. H. Dunlap and J. A. Parker for helpful discussions.

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE AND FRENCH LABORATORIES]

Sulfolane Derivatives

BERNARD LOEV

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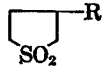
A number of 3- and 3,4-substituted sulfolanes, prepared for biological screening, are described.

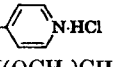
The marked chemical reactivity of sulfolene-3 made it an attractive starting material for the synthesis of sulfone-containing analogs of a variety of known biologically active compounds. A number of 3- and 3,4-substituted sulfolanes were prepared and are tabulated in Tables I and II.

The 3-substituted sulfolanes, compounds 1 through 11, were readily prepared by alkali-cat-

TABLE I

3-SUBSTITUTED SULFOLANES

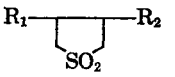


No.	R	B.P./Mm. (or M.P.)	n_D^{25}	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	—OCH_3[a]	[b]	1.4807	95	$C_5H_{10}O_3S$	39.98	6.71	40.17	6.87
2	—OC_3H_7-*i*	150–155/3	1.4688	48	$C_7H_{14}O_3S$	47.17	7.92	47.36	7.77
3	—OC_4H_9-*n*	[b]	1.4696	80	$C_8H_{16}O_3S$	49.97	8.39	50.24	8.43
4	—$OCH_2CH_2OCH_3$	[b]	1.4794	55	$C_7H_{14}O_4S$	43.28	7.26	43.59	7.47
5	—$NHCH_3$	[b]	1.5005	55	$C_5H_{11}NO_2S$				
6	—$N(CH_3)_2$	135/1.5	1.4941	60	$C_6H_{13}NO_2S$	44.15	8.03	43.86	7.90
7	—$OCH_2CH_2N(CH_3)_2 \cdot HCl$[d]	(129–131°)[e]		40	$C_8H_{17}NO_3S \cdot HCl$	39.42	7.44	39.88	7.62
8	—$SCH_2CH_2N(C_2H_5)_2 \cdot HBr$[f]	(120–121°)[g]		20	$C_{10}H_{21}NO_2S_2 \cdot HBr$	36.14	6.67	36.44	6.78
9	—$NHCH_2CH_2N(CH_3)_2 \cdot 2HCl$	(220–223°)		80	$C_8H_{19}N_2O_2S \cdot 2HCl$	34.41	7.22	34.53	7.44[h]
10	—$N(C_2H_5)CH_2CH_2OH$	[b]	1.4875	63	$C_8H_{17}NO_3S$	46.35	8.27	46.18	8.38
11	—$N(CH_3)CH_2CH_2OH$	[b] (44–45°)[i]	1.5154	62	$C_7H_{15}NO_3S$	43.50	7.82	43.58	8.03
12	—$\overset{+}{N}(CH_3)_2CH_2CH_2OH\ I^-$	(139–140.5°)		80	$C_8H_{18}INO_3$	28.66	5.41	28.92	5.62
13	—$\overset{+}{N}(CH_3)_2CH_2CH_2OAc\ I^-$	(120°)		80	$C_{10}H_{20}INO_4S$	31.84	5.34	32.00	5.56
14	—$N(CH_3)CH_2CH_2OCOC(OH)(C_6H_5)_2$	(102–103°)		25	$C_{21}H_{25}NO_5S$	62.51	6.25	62.27	6.28
15	—$NHNH_2 \cdot HCl$	(191–192°)		89	$C_4H_{10}N_2O_2S \cdot HCl$	25.74	5.94	25.81	6.01[j]
16	—NHNHCO—  ·HCl	(222–224°)		35	$C_{10}H_{13}N_3O_3S \cdot HCl$	41.16	4.84	40.74	4.99
17	—$OCH_2CH(OCH_3)CH_2HgOAc$		1.5118	91	$C_{10}H_{18}HgO_5S$	25.72	3.89	26.19	4.15

[a] Ref. 12. [b] Molecularly distilled at 1 μ. [c] *Anal.* Calcd.: N, 9.4; Found: N, 9.4. [d] The diethylaminoethyl analog has been reported (ref. 1). [e] Picrate, m.p. 137–139°. [f] Ref. 1, m.p. 122–123°. [g] Free base, n_D^{24} 1.5149; picrate, m.p. 120–123°. [h] Free base, n_D^{24} 1.5080. [i] Picrate, m.p. 158–159°; hydrochloride, m.p. 159–160°. [j] *Anal.* Calcd.: N, 15.01; Found: N, 15.10.

TABLE II

3,4-DISUBSTITUTED SULFOLANES



No.	R_1	R_2	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
18	$(CH_3)_2N$—	—OH	103–104°	83	$C_6H_{13}NO_2S$	40.20	7.31	40.06	7.43
19	$(CH_3)_2N$—	—OAc·HBr	151°	40	$C_8H_{16}NO_3S\cdot HBr$	31.79	5.34	31.80	5.58
20	$(CH_3)_2N$—	—OBz	99–100°	50	$C_{13}H_{17}NO_4S$	55.10	6.05	54.99	6.15
21a	$(CH_3)_2N$—	—$OCOC_6H_4NO_2$-*p*	151–152°	62	$C_{13}H_{16}N_2O_6S$	47.55	4.91	47.50	4.95
21b	$(CH_3)_2N$—	—$OCOC_6H_4NO_2$-*p*	216–217°	11	$C_{13}H_{16}N_2O_6S$	47.55	4.91	47.46	5.11
22a	$(CH_3)_2N$—	—$OCOC_6H_4NH_2$-*p*	145–146°	71	$C_{13}H_{18}N_2O_4S$	52.33	6.08	52.56	6.19
22b	$(CH_3)_2N$—	—$OCOC_6H_4NH_2$-*p*	190–191°	70	$C_{11}H_{18}N_2O_4S$	52.33	6.08	52.32	6.47[a]
23	$(CH_3)_2N$—	—$OCOCH(C_6H_5)_2$	100–101°	48	$C_{26}H_{27}NO_4S$	64.32	6.21	64.40	6.58
24	$I^-(CH_3)_3N^+$	—OH	197–198°	45	$C_7H_{16}INO_2S$	26.18	5.02	26.16	5.14
25	AcO—	—OAc	111–112°	30	$C_8H_{12}O_6S$	40.69	5.12	40.29	5.57
26	CH_3O—	—HgOAc	105°	63	$C_7H_{12}HgO_5S$	20.56	2.96	20.64	3.32
27	CH_3O—	—HgCl	170°	50	$C_5H_9ClHgO_3S$	15.59	2.35	15.30	2.59

[a] *Anal.* Calcd.: N, 9.39. Found: N, 9.42.

alyzed reaction of the appropriate alcohol, thiol, or amine with sulfolene. Relatively hindered amines, such as phenylisopropylamine and *N*-benzyl-*N*-(2-dimethylaminoethyl)amine, did not react under these conditions.[1] Hydrazine reacted smoothly with sulfolene to give 3-sulfolanylhydrazine (compound 15).[2]

Although both *N*- and *O*-alkylation could conceivably have occurred in the reaction of sulfolene-3 with 2-methyl- and 2-ethylaminoethanol, the sole products were the *N*-alkylated substances (compounds 10 and 11) as indicated by the presence of strong hydroxyl absorption and the absence of ether and N—H absorption in the infrared spectrum of the products. The properties of various derivatives (compounds 12, 13 and 14) were also consistent with these structures.

Sulfolene did not react with isonicotinic acid hydrazide, even in the presence of strong basic catalysis.

The desired *N*-isonicotinoyl-*N'*-(3-sulfolanyl)-hydrazine[3a] (compound 16) was prepared by treating 15, as the free base, with isonicotinic acid ester or acid chloride (Fig. 1).

Choline and acetylcholine analogs (12 and 13) and the benzilic ester (14)[3b] were prepared from 11.

Repeated attempts to prepare the benzhydryl ether of 11[3c] by condensation with benzhydryl chloride or with diphenyldiazomethane were unsuccessful. An attempt to synthesize this compound by heating together sulfolene-3 and 2-methylaminoethyl benzhydryl ether failed.

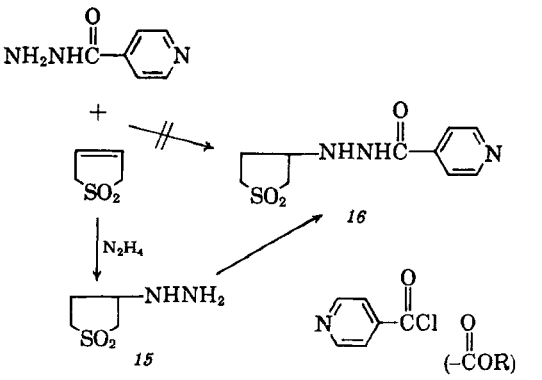


Figure 1

Most of the 3,4-disubstituted sulfolanes that were prepared were derivatives of the dimethylaminoethanol analog (18) which was synthesized in high yield by the reaction of 4-chlorosulfolanol-3 with dimethylamine.[4] 4-Dimethylamino-3-sulfolanol (18) was quaternized to give a choline analog (24).

When 24 was heated with acetic anhydride in an attempt to synthesize the acetylcholine analog there was obtained, instead, *trans*-sulfolane-3,4-diol diacetate 25.

The *p*-nitrobenzoate of 24 separated into two isomeric substances (21a and 21b) in a 15:1 ratio, undoubtedly the *trans* and *cis* isomers respectively.[4] Each of these was then reduced to the corresponding *p*-aminobenzoate (22a and 22b).[3d]

The diphenylacetate[3e] (23) and benzoate[3b] (20) were readily synthesized, but the benzilate[3b] could not be prepared.

(1) M. T. Leffler and W. D. Krueger, *J. Am. Chem. Soc.*, 71, 370 (1949), had also observed that highly hindered substances do not add to sulfolene.

(2) It was hoped that compound 15 might serve as a useful derivative for aldehydes and ketones, but the reaction products were all oils.

(3) An analog of (a) iproniazid, (b) benactyzine, (c) diphenylhydramine, (d) procaine, (e) Trasentine (Ciba), (f) amylocaine.

(4) The structures of all of the 3,4-disubstituted compounds are believed to be *trans* on the basis of the known stereochemical course of the reactions involved. In one instance, compounds 21a and b, a small amount of an isomeric substance (*cis*) was obtained, suggesting that a small amount of *cis*-4-chlorosulfolanol-3 was probably present in the starting material.

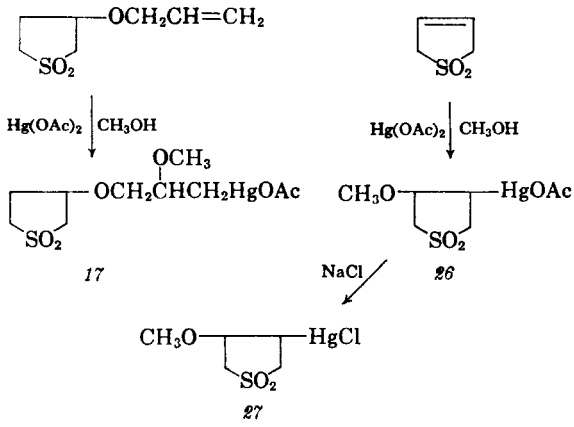


Figure 2

Several sulfolane mercurials were prepared as indicated in Fig. 2. The very insoluble mercury chloride derivative was stable, but the mercury acetates gradually decomposed on standing.

During the course of this work we also prepared the known *cis*- and *trans*-sulfolane-3,4-diols.[5] The literature dealing with the identity of the sulfolene 3,4-epoxide intermediate used for the synthesis of the *trans*-glycol is in a rather confused state. The melting point of the epoxide was initially reported as being 130°[6] then 159–160°[7], and once again 124.5–126.°[8] We have found that both the high and low melting points are correct—*i.e.*, we have isolated two epoxides (m.p. 123–125° and 157–159°) from the same reaction mixture and found that both are converted to the same *trans*-glycol (see Fig. 3).

Although the high- and low-melting forms of the epoxide could not be interconverted, they must correspond to two different crystalline modifications of the same substance.[9]

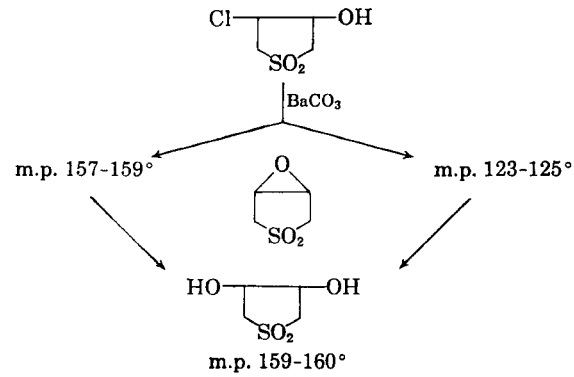


Figure 3

(5) E. de Roy van Zuydewijn, *Rec. trav. chim.*, **57**, 445 (1938).

(6) O. E. van Lohuizen and H. J. Backer, *Rec. trav. chim.*, **68**, 1137 (1949).

(7) W. R. Sorenson, *J. Org. Chem.*, **24**, 1796 (1959).

(8) M. Prochazka and V. Horak, *Coll. Czech. Chem. Comm.*, **24**, 1509 (1959).

(9) The only other possibility, that one of these substances is the isomeric 4-hydroxy-2-sulfolene, is ruled out, as this compound is known and is a liquid.[4]

As the melting point of the high-melting form of the epoxide is almost identical to the melting point of the *trans*-glycol product, it is possible that the two groups reporting only the low-melting oxide did, in fact, have some of the high-melting material also, but assumed it to be the glycol.

Pharmacology. The mercurial compounds were found to be devoid of diuretic activity; the other compounds described in this paper were given a mouse dose range and were tested for hypotensive activity, and were found to be essentially inactive in both screens.

EXPERIMENTAL[10]

Sulfolene-3, 4-chlorosulfolanol-3, and 3-allyloxysulfolane were kindly supplied by the Shell Development Co. and used as received.

3-Alkoxysulfolanes (Compounds 1 to 4). Powdered sulfolene-3 (1 mole) was added to a solution of 0.1 mole of potassium hydroxide dissolved in 2 moles of the appropriate alcohol. On warming to about 35° a slow spontaneous exothermic reaction resulted. The temperature was kept below 50° by gentle cooling when necessary. The solution was maintained at 40–50° for 48 hr.; then the base was exactly neutralized with hydrochloric acid, and the solution was concentrated on the steam bath *in vacuo* to constant weight. The resulting oil was then taken up in benzene, washed with saturated salt solution, dried, concentrated, and distilled. As sulfolanes have a tendency to decompose at high temperatures, most of the products were molecularly distilled. The products were colorless to pale yellow oils. Compounds 1 and 4 were completely miscible with water, 2 was moderately soluble, and 3 was only slightly soluble. They were all soluble in all of the common organic solvents except hexane.

3-(N-Mono- and N,N-dimethyl)aminosulfolane (Compounds 5 and 6). 3-Sulfolene (100 g.) was added to 315 g. of a 25% aqueous methylamine or 286 g. of 40% dimethylamine solution containing 4.74 g. of potassium hydroxide. The solution was heated at 35–45° for 10 hr.; then the volatile material was removed *in vacuo*, and the resulting oil was taken up in benzene, dried, concentrated, and molecularly distilled. The products were colorless oils completely miscible with water.

Dimethylaminoethyl 3-sulfolanyl ether, hydrochloride (Compound 7). Dimethylaminoethanol (26.7 g., 0.3 mole), 21 g. (0.19 mole) of sulfolene, and 0.5 g. of powdered potassium hydroxide were placed in a pressure bottle and heated at 65°. After 1 hr., 10 g. of the dark mixture was removed, but no recognizable reaction product could be isolated. The balance of the reaction mixture was heated in a sealed bottle at 60–70° for 5 days. At the end of this time the orange solution was taken up in benzene, filtered, and concentrated, giving 20.5 g. of a viscous orange oil. The oil was dissolved in ethanol and treated with ether previously saturated with hydrogen chloride. An oil formed that was converted to a solid after vigorous stirring. The extremely hygroscopic salt was recrystallized from a hot mixture of ethanol and isopropyl alcohol to which isopropyl ether was added to cloudiness. The white solid was recrystallized again from ethanol.

Diethylaminoethyl 3-sulfolanyl sulfide, hydrobromide (Compound 8). An aqueous solution of 21 g. (0.123 mole) of diethylaminoethanethiol hydrochloride was treated with the theoretical amount of sodium hydroxide in water containing a little sodium hydrosulfite. The resulting free base was extracted with ether, dried, and the ether was evaporated giving 13 g. (79%) of the pale yellow aminoethyl mercaptan.

The mercaptan, 14.8 g. of sulfolene, and 0.3 g. of powdered potassium hydroxide were heated in a pressure bottle for 3

(10) All melting points are corrected.

days at 60°. The solution rapidly turned dark, and then slowly became lighter. The resulting orange oil was dissolved in benzene and filtered from some flocculant material present, and then the volatile materials were removed by heating in vacuum. The residual viscous orange liquid, 24 g., could not be induced to crystallize, nor could solid derivatives other than the picrate be formed.

The entire quantity was converted to the picrate which was then recrystallized from ethanol-acrylonitrile (29 g.). Fifteen grams of this salt was dissolved in 100 cc. of warm acetonitrile and passed through an alumina column to decomposed the picrate. The column, of ordinary (alkaline) Fisher alumina, was 2 in. high and 3.5 in. in diameter, and acetone was used as the eluent. Four reactions of approximately 150 cc. each were collected, then individually evaporated to pale yellow, water-miscible oils. The first two fractions readily gave solids with ethereal hydrogen bromide (the hydrochlorides were too hygroscopic to handle conveniently). The hydrobromide recrystallized nicely from alcohol.

N-Dimethylaminoethyl-3-sulfolanylamine dihydrochloride (Compound 9). 3-Sulfolene (20 g.) and 15.4 g. of dimethylaminoethylamine were placed in a pressure bottle and heated at 60° for 2 days. The resulting oil was taken up in benzene, treated with charcoal, and concentrated, giving a water-miscible orange oil. The oil was dissolved in ethanol and treated with ethereal hydrogen chloride giving a curdy precipitate, which was recrystallized from acetic acid–ethanol-hexane mixture.

N-Alkyl-N-(2-hydroxyethyl)-3-sulfolanylamine (Compounds 10 and 11). Sulfolene-3 (3.8 moles) and 4.55 moles of methyl- or ethylaminoethanol were mixed and heated at 80–85° for 2 hr., then at 75° for 15 hr.[11] The excess amine was removed by heating on a steam bath at 5 mm. for 2 hr. The resulting orange oils were molecularly distilled, giving colorless or very pale yellow oils miscible with water and most organic solvents in all proportions. The *N*-methyl compound (10) crystallized after several months.

2-Hydroxyethyldimethyl-3-sulfolanylammonium iodide (Compound 12). To a solution of 15 g. of 11 in 60 cc. of absolute alcohol was added with vigorous stirring a solution of 22 g. of methyl iodide in 40 cc. of ethanol. After 35 min. the solution, which was originally completely homogeneous, started to turn cloudy and gradually an oil settled out which soon crystallized. After an additional 3 hr. of standing, the mixture was placed in an ice bath overnight. The white crystalline product was recrystallized from methanol.

2-Acetoxyethyldimethyl-3-sulfolanylammonium iodide (Compound 13). Acetic anhydride (10 cc.) and 10 g. of 11 were heated on the steam bath for 2 hr.; then the excess anhydride and acetic acid were removed *in vacuo* leaving 12.5 g. of reddish oil. This acetate was heated with toluene, and 1.5 g. of starting material separated and was discarded. The remaining 11 g. of oil was treated with 7 g. of methyl iodide. An oil slowly formed. On stirring and chilling the oil gradually solidified. The product was treated with a mixture of isopropyl alcohol–isopropyl ether and filtered, then recrystallized from methanol.

N-Methyl-N-(3-sulfolanyl)aminoethyl benzilate (Compound 14). A mixture of 10 g. of 11 and 17 g. of methyl benzilate was dried by azeotroping with benzene; the benzene was then removed, and 0.5 g. of sodium was added. The mixture was put in a bath at 100°, and put under 20–30 mm. vacuum for 24 hr. The resulting tacky brown oil (25 g.) was dissolved in ethanol and treated with ethereal hydrochloric acid. The resulting gum was dissolved in water and the solution was extracted with benzene; then the aqueous layer was made basic, and the resulting oil was extracted with ethyl acetate. Evaporation left a viscous oil which on treatment with a small volume of ethyl acetate crystallized. The product was recrystallized from alcohol.

(11) The addition of a small amount of base appeared to accelerate the reaction somewhat.

3-Sulfolanylhydrazine hydrochloride (Compound 15). 3-Sulfolene (25 g., 0.212 mole) and 14.3 g. of 95% hydrazine were placed in a pressure bottle and heated for 17 hr. at 70°. The reaction mixture was diluted with ethanol and concentrated under reduced pressure, giving a gray oil, 30.5 g. (96%). A solution of 4.0 g. of this oil in 50 ml. of ethanol was treated with ethanolic hydrogen chloride; a white crystalline solid formed immediately and was filtered and washed with ethanol. It was recrystallized from methanol with addition of just a trace of water and then addition of ether.

N-(3-Sulfolanyl)-N'-isonicotinoylhydrazine hydrcchloride (Compound 16). (a) Three grams of 3-hydrazinosulfolane and 2.5 g. of methyl isonicotinate were heated at 100° for 20 hr. at 50 mm. The pressure was then reduced to remove unchanged ester, leaving 5.5 g. of black amorphous solid. This was dissolved in ethanol, treated with charcoal, and then with ethanolic hydrogen chloride. The resulting solid was recrystallized from ethanol The yield was 1.65 g.

(b) 3-Hydrazinosulfolane (3 g.) was dissolved in benzene containing a small quantity of ethanol. To this was added 5 g. of isonicotinoyl chloride hydrochloride and 2 cc. of pyridine. A gum formed. The mixture was refluxed for 1 hr. and concentrated; then the residue was extracted with hot alcohol, leaving 0.5 g. of tan crystals identical to the previous product.

3-Acetoxymercuri-2-methoxypropyl 3-sulfolanyl ether (Compound 17). To a solution of 30 g. (0.170 mole) of 3-allyloxysulfolane in methanol was added a hot methanolic slurry containing 54 g. (0.170 mole) of mercuric acetate and 12.2 ml. (0.204 mole) of glacial acetic acid over a period of 30 min. The mixture was stirred and refluxed overnight; the cloudy reaction was cooled, filtered, and the filtrate evaporated to dryness under reduced pressure at a temperature not above 60°, to give an oil. The oil was dissolved in the minimum amount of cold chloroform and then reprecipitated with ether. The supernatant liquid was poured off and the product dried in a vacuum desiccator.

4-Dimethylamino-3-sulfolanol (Compound 18). To a slurry of 50 g. (0.294 mole) of 4-chloro-3-sulfolanol and 200 ml. of tetrahydrofuran was added with vigorous stirring 45.8 g. of dimethylamine dissolved in 300 ml. of tetrahydrofuran. After 3 days at room temperature the suspension was filtered and the solid rinsed with tetrahydrofuran. The filtrate was concentrated to dryness leaving a red solid which was dissolved in the minimum amount of acetonitrile and then cooled. The resulting solid was rinsed with ether, then recrystallized from ethanol-ether. It was very soluble in water and most organic solvents other than hexane.

4-Dimethylamino-3-sulfolanol acetate hydrobromide (Compound 19). Acetyl bromide (0.067 mole) was cautiously added with vigorous stirring to a solution of 10 g. (18) in 50 ml. of pyridine. The resulting slurry was rapidly heated to reflux, then cooled and poured into 200 ml. of water. No oil separated, so the solution was taken to dryness by heating *in vacuo*, giving a red-brown oil which slowly crystallized. It was recrystallized from ethanol.

4-Dimethylamino-3-sulfolanol benzoate (Compound 20). To a solution of 5 g. (0.028 mole) of 18 in 15 ml. of pyridine was added 4.7 g. (0.0336 mole) of benzoyl chloride. The solution was quickly heated to boiling, boiled for a short while, cooled, and then poured into 100 ml. of water. An oil separated which crystallized on stirring. The product was recrystallized from ethanol water.

4-Dimethylamino-3'-sulfolanol p-nitrobenzoate (Compounds 21a and b). *p*-Nitrobenzoyl chloride (10.4 g.) was added to a solution of 10 g. of 18 in 50 cc. of pyridine. The solution was refluxed for 5 min., cooled, and poured into water and the resulting solid was extracted with 200 cc. of boiling ethanol. The insoluble isomer (21b) amounted to 2 g. The filtrate or cooling deposited the other isomer (21a), 11.4 g.

4-Dimethylamino-3-sulfolanol p-aminobenzoate (Compounds 22a and b). Compounds *21a* and *b* were each reduced at 50 p.s.i.g. in acetic acid solution using a 10% palladium

on carbon catalyst. The product, isolated by removing the acetic acid, was recrystallized from isopropyl alcohol.

4-Dimethylamino-3-sulfolanyl diphenylacetate (Compound 23). To a warm solution of 11 g. (0.0615 mole) of 18 in 50 ml. of pyridine was rapidly added 17 g. (0.074 mole) of diphenylacetyl chloride. After the solid had dissolved, the solution was boiled briefly and poured into 200 ml. of water; an oil separated immediately which thickened but would not solidify. The oil was extracted with ether, the ethereal solution dried, filtered, and concentrated, and then the oily residue crystallized on standing (25.0 g.). It was recrystallized from alcohol-ether. The product was insoluble in water and dilute base, was soluble in dilute acid and partially soluble in ether.

4-Trimethylammonium-3-sulfolanol iodide (Compound 24). To a solution of 3 g. of 18 in ethanol was added 4.7 g. (0.034 mole) of methyl iodide in 10 ml. of ethanol; the solution was stoppered and allowed to stand overnight. The resulting white solid was recrystallized from ethanol-water.

trans-3,4-Sulfolanediol diacetate (Compound 25). A solution of 5 g. of 18 in 50 ml. of acetic anhydride was heated on a steam bath for 17 hr.; then the solution was taken to dryness leaving a black solid which was recrystallized from alcohol to give a white crystalline solid.

3-Acetoxymercuri-2-methoxysulfolane (Compound 26). To a solution of 11.8 g. of sulfolene-3 in absolute methanol was added 2.42 g. of benzoyl peroxide, then a solution of 31.9 g. of mercuric acetate and 7.2 cc. of acetic acid in hot methanol. The solution was refluxed overnight, then concentrated at 50–60°. The resulting oil was stirred with acetone and the insoluble white solid was discarded. The solvent was removed at room temperature, the oil was dissolved in chloroform, treated with charcoal, and thrown back out with ether, giving a colorless oil. After several weeks the oil crystallized, m.p. 105°.

3-Chloromercuri-4-methoxysulfolane (Compound 27). To a concentrated aqueous solution of the acetate (26) was added 0.85 g. of sodium chloride. A white precipitate formed rapidly. After being stirred for 0.5 hr., the solid was filtered and rinsed thoroughly with water. It could not be recrystallized without decomposition.

Sulfolene-3 epoxide. Barium carbonate (9.8 g., 0.05 mole) was added to a solution of 17.1 g. (0.1 mole) of 4-chlorosulfolanol-3 dissolved in 200 ml. of hot water. The mixture was stirred and maintained at 85° until all the carbonate went into solution (2 hr.). On chilling, 6 g. of a solid formed and was filtered, m.p. 120–125°. On recrystallization from acetone this material separated into two substances, (*a*) m.p. 123–125°, and (*b*) m.p. 157–159°. The infrared spectra of (a) and (b) in Nujol mulls were identical.

Anal. Calcd. for $C_4H_8SO_4$ (for substance *a*): C, 35.81; H, 4.58. Found: C, 36.23; H, 4.87.

Anal. Calcd. for $C_4H_8SO_4$ (for substance *b*): C, 35,81; H, 4.58. Found: C, 35.92; H, 4.72.

When the dehydrohalogenation was carried out in more dilute solution (500 cc. of water), the only substance isolated was (b).

Substance (b), 5.5 g., was suspended in 25 ml. of water and heated in an autoclave for 2 days at 210°, the autogeneous pressure reaching 200 psig. The resulting brown solution was concentrated to give 5.5 g. of an oil that soon crystallized. It was recrystallized several times from an alcohol-acetone-benzene mixture to give 1 g. of *trans*-3,4-sulfolanediol, m.p. 159–160°. A mixed melting point with the starting epoxide [substance (*b*)] melted at 125–130°. By the same procedure, substance *a* was converted to the identical *trans*-3,4-sulfolanediol.[12]

Anal. Calcd. for $C_4H_8SO_4$: C, 31.57; H, 5.30. Found: C, 31.64; H, 5.40.

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(12) D. Delfs, Ger. Patent 682079 (1939), b.p. 164° (12.5 mm.).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, LOUISIANA STATE UNIVERSITY]

A New Approach to Polycyclic Bases. II. 1-Azabicyclo[4.3.0]nonanes, 1-Azabicyclo[3.3.0]octanes, and Related Systems[1,2]

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The acid-catalyzed condensation of a ditertiary glycol and several ω-chloronitriles has led to a convenient synthesis of 1-azabicycloalkanes. The three-step method involves the formation of an ω-chloroalkyl-1-pyrroline which is reduced with aqueous sodium borohydride to the ω-chloroalkylpyrrolidine and then to the bicyclic base *via* intramolecular alkylation. None of the intermediate products is isolated. The final product is obtained in 60–65% yield based on the glycol.

The chemistry of 1-azabicycloalkanes has received considerable attention in the last decade and several comprehensive reviews[4] have appeared during this period. Particular significance has been attributed to the 1-azabicyclo[3.3.0]octanes, more commonly referred to as the pyrrolizidines, because

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(2) Presented before the 16th Annual Southwest Regional Meeting of the American Chemical Society, Oklahoma City, Okla., December 1–3, 1960.

(3) American Cancer Society Summer Research Fellow, 1960.

(4) H. R. Ing, *Heterocyclic Compounds*, Vol. 3, R. C. Elderfield, ed., Wiley, New York, 1952, p. 396; Houben-Weyl, *Methoden der Organischen Chemie*, Band XI 2, G. T. Verlag, Stuttgart, 1958, p. 582; T. S. Stevens, *Chemistry of Carbon Compounds*, Vol. 4, E. H. Rodd, ed., Elsevier, New York, 1957, p. 117.