yield of II was obtained, the aqueous layer was acidic and the chloroform layer remained red in color. In addition, a nicely crystalline product melting at 104° consistently appeared by fractional recrystallization of the crude II. This was identified as tetramethylthiuram monosulfide (III) and in one experiment (Table I) it became the major product. Tetramethylthiourea was also isolated in this instance. Billiter and Rivier[4] fail to mention the formation of any by-products in their reaction.

TABLE I

THIOPHOSGENATION OF DIMETHYLAMMONIUM CHLORIDE[a]

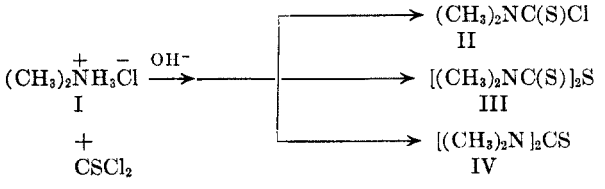
Temp. °	Ratio NaOH/ $Me_2\overset{+}{N}H_3\overset{-}{Cl}$	% Yield of Dimethylthiocarbamyl Chloride
28	1	2
28	2	7
28	2.5	None[b]
20	2.7	25[c]
10	2	15
−5[d]	2	38
−20[e]	2	46–50

[a] In all experiments a one to one molar ratio of thiophosgene to dimethylammonium chloride was maintained. [b] Tetramethylthiuram monosulfide was isolated in 1.6% yield, the major product being an unworkable oil. [c] The major product (47%) was III; 5% of IV was also obtained. [d] The temperature varied from 0° to −5°. [e] The temperature varied from −10° to −20°.

An investigation of this reaction was conducted. The results are summarized in Table I. Increasing the quantity of sodium hydroxide until the aqueous layer became alkaline was without effect, in fact no yield of II was obtained and only 1.6% of III and an intractable oil were the major products. The most important variable was the temperature of the reaction regardless of whether the aqueous phase ended up in an acidic or alkaline condition. The lowest practical temperature with the set of reagents used was found to be −10 to −20° in which case consistent yields of II of 46 to 50% were obtained. At lower temperatures increase in sodium hydroxide reduces the yield of II while favoring the formation of III. This suggests that the formation of III can be accounted for by a nucleophilic displacement of chloride ion by sulfide ion: the sulfide ion arising from the alkaline

$$2\ \mathrm{II} + S^{=} \longrightarrow \mathrm{III} + 2\ Cl^{-}$$

hydrolysis of the thiophosgene.



EXPERIMENTAL[6,7]

Dimethylthiocarbamyl chloride (II). Into a three necked round-bottom flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel and surrounded by acetone-Dry Ice bath was placed 8.3 g. (0.1 mole) of dimethylammonium chloride dissolved in 10 ml. of water. The temperature was adjusted to −10°. Thiophosgene (12 g., 0.1 mole) dissolved in 30 ml. of alcohol-free chloroform was added to the reaction flask with stirring over a period of 30 min. An aqueous solution of sodium hydroxide (100 ml. of a 2*M* solution) was then added over a period of 1 hr., not allowing the temperature to rise above −10°. The mixture was finally stirred for an additional 30 min., the chloroform layer separated and immediately dried over calcium chloride. The chloroform was then removed at reduced pressure at steam bath temperature. The residue (which is semisolid when cooled in an ice bath) was recrystallized from petroleum ether yielding a product melting at 41° in agreement with that reported.[4] The yield varied from about 5 to 5.5 g. (45 to 50% based on I).

Tetramethylthiuram monosulfide (III). This arises (Table I) from the fraction-crystallization of crude II. It was identified by mixture melting point with an authentic specimen of tetramethylthiuram monosulfide prepared according to the procedure of von Braun and Stechele.[8] When using anhydrous ether (as solvent for the thiophosgene) II is recovered as the ether soluble fraction, while recrystallization of the ether-insoluble residue yields III.

Tetramethylthiourea (IV). This was found in several instances as a by-product of the fractional crystallization of II. It was identified by its melting point[9] of 75–76°.

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(6) Melting points are uncorrected.

(7) The thiophosgene was supplied by the Rapter Chemical Company, Chicago, Illinois. Vapor phase chromatography showed this to be 99% plus in thiophosgene content.

(8) J. von Braun and F. Stechele, *Ber.*, **36**, 2274 (1903).

(9) O. Billiter, *Ber.*, **43**, 1856 (1910).

Cyclic Sulfites and the Bissinger Rearrangement

RICHARD G. GILLIS

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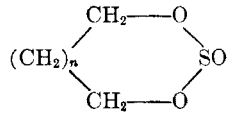
The "Bissinger rearrangement" is a convenient name for the reaction first described by Bissinger, Kung, and Hamilton,[1] in which a dialkyl sulfite gives an alkyl alkanesulfonate on heating with a tertiary base. Dimethyl sulfite gave a 49–56% yield of methyl methanesulfonate after 24 hr. with 1 mol. per cent of tributylamine; the yield decreased with increasing size of alkyl groups. The rearrangement of dimethyl sulfite gave dimethyl ether as by-product, and a mechanism was suggested which accounted for both the rearrangement and the ether formation. We have found triethylamine is also a

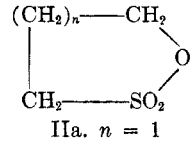
(1) W. E. Bissinger, F. E. Kung, and C. W. Hamilton, *J. Am. Chem. Soc.*, **70**, 3940 (1948).

satisfactory catalyst, but not quinoline or dimethylaniline.

If the Bissinger rearrangement of trimethylene sulfite (Ia) were successful, it would provide a convenient route to



Ia. $n = 1$
Ib. $n = 2$



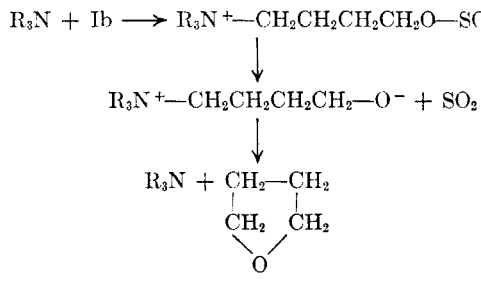
IIa. $n = 1$
IIb. $n = 2$

3-hydroxy-1-propanesulfonic acid sultone (IIa) whose preparation from allyl alcohol has been described.[2] Similarly, a successful rearrangement of tetramethylene sulfite (Ib) would provide a route to 4-hydroxy-1-butanesulfonic acid sultone (IIb) which has been prepared from 4-chlorobutyl acetate.[3]

In an attempt to prepare Ia, Majima and Simanuki[4] obtained mainly trimethylene chloride. Myles and Prichard[5] state that 1,4-butanediol and longer chain glycols give only chain polymers when treated with thionyl chloride and pyridine below 35°. However, successful preparations have been reported by de la Mare and co-workers,[6] and also by Szmant and Emerson.[7] We have prepared both Ia and Ib in reasonable yield from the corresponding glycol and thionyl chloride by the method of Kyrides.[8]

The attempted rearrangement of Ib gave only tetrahydrofuran as an identifiable organic product in 76% yield. It was substantially pure; in one experiment traces of two carbonyl containing impurities were detected by paper chromatography. The attempted rearrangement of Ia gave a mixture of six organic products including acrolein and propionaldehyde, together with water and sulfur dioxide. The same reaction of ethylene sulfite gave seven organic products including acetaldehyde.

The formation of tetrahydrofuran from tetramethylene sulfite is compatible with the mechanism advanced by Bissinger *et al.* for the formation of dimethyl ether as a by-product from dimethyl sulfite. The reaction may be formulated as shown:



The formation of a five-membered ring is favored for steric reasons; trimethylene and ethylene sulfites would lead to four- and three-membered rings, and the decomposition of the zwitterionic intermediate to aldehyde products is understandable.

EXPERIMENTAL[9]

Preparation of cyclic sulfites. Tetramethylene sulfite was prepared from tetramethylene glycol and thionyl chloride by the method of Kyrides[8] in 45% yield. The product had b.p. 119° at 15 mm., n_D^{20} 1.4650; d_4^{20} 1.2537; R_D. Calcd.: 29.90. Found: 30.02 (lit.,[7] n_D^{25} 1.4631).

Trimethylene sulfite was prepared from trimethylene glycol and thionyl chloride by the same method in 42% yield. The product had b.p. 76° at 15 mm., n_D^{20} 1.4567; d_D^{20} 1.3225; R_D. Calcd. 25.25. Found 25.14 (lit., n_D^{25} 1.4509,[6] n_D^{20} 1.4530[7]).

Ethylene sulfite was prepared similarly in 79% yield and had b.p. 70° at 20 mm., n_D^{20} 1.4461 (lit.,[6] n_D^{25} 1.4450).

Analytical methods. Gas chromatography of the products was carried out using a McWilliam-Dewar detector[10] and dioctyl phthalate as stationary phase supported on 30–50 mesh crushed "Insulox"[11]; nitrogen was the carrier gas and the column temperature was 100°. The retention times, q, are given relative to benzene (1.00) under the same conditions.[12] Peak heights relative to the largest peak are shown in parentheses. The organic products were also treated with dinitrophenylhydrazine in methanol, and the mixed dinitrophenylhydrazones were separated by descending paper chromatography in a heptane-methanol system.[13–15] Finally, the products were examined by infrared spectroscopy in a Perkin Elmer Model 12C instrument using sodium chloride optics.

Rearrangement products. The rearrangement was attempted by heating the sulfite (0.2 mol.) with triethylamine (0.01 mol.) at a pot temperature of 180° for 9 hr. The reaction mixture was distilled and the distillate examined. In each case the residue was an intractable tar.

Tetramethylene sulfite gave tetrahydrofuran in 76% yield. The distillate had b.p. 64–70°; n_D^{20} 1.4030 (lit.,[16] b.p. 64–66°; n_D^{20} 1.4070). Gas chromatography showed no trace of contaminants, and the product had retention time identical with an authentic specimen. In one experiment, the paper chromatograph showed very faint traces of two carbonyl components which ran slower than crotonaldehyde; in a second experiment, not even these trace impurities were found. Tetrahydrofuran was characterized as tetramethylene

(2) J. H. Helberger, *Ann.*, **588**, 71 (1954).
(3) W. E. Truce and F. D. Hoerger, *J. Am. Chem. Soc.*, **76**, 5357 (1954).
(4) R. Majima and H. Simanuki, *Proc. Imp. Acad. Japan*, **2**, 544 (1926); *Chem. Abstr.*, **21**, 1796 (1927).
(5) W. J. Myles and J. H. Prichard, U. S. Patent **2,465,915**; *Chem. Abstr.*, **43**, 4835 (1949).
(6) C. A. Bunton, P. B. D. de la Mare, P. M. Greaseley, D. R. Llewellyn, N. H. Pratt, and J. G. Tillett, *J. Chem. Soc.*, 4751 (1958).
(7) H. H. Szmant and W. Emerson, *J. Am. Chem. Soc.*, **78**, 454 (1956).
(8) L. Kyrides, *J. Am. Chem. Soc.*, **66**, 1006 (1944).
(9) Melting points and boiling points are uncorrected.
(10) I. G. Williams and R. A. Dewar, "*Second Symposium on Gas Chromatography*," (ed. D. H. Desty), Butterworths Scientific Publications, London, 1958, p. 174.
(11) "Insulox" is the registered trade name for an insulating firebrick manufactured by Nonporite Pty. Ltd., Hawthorn, Victoria.
(12) R. J. Cvetanovic and K. O. Kutschke, "*Vapor Phase Chromatography*" (ed. D. H. Desty), Butterworths Scientific Publications, London, 1957, p. 87.
(13) F. E. Huelin, *Australian J. Sci. Res.*, **5B**, 328 (1952).
(14) D. F. Meigh, *Nature (London)*, **170**, 579 (1952).
(15) D. A. Forss, E. A. Dunstone, and W. Stark, *Chem. & Ind.*, **42**, 1292 (1954); **45**, 521 (1957).
(16) T. H. Durrans, "*Solvents*," Chapman & Hall Ltd., London, 7th ed., 1957, p. 185.

bis(2-thiopseudourea)dipicrate, prepared from 1,4-diiodobutane made by a modification of the method of Stone and Schechter.[17] To 5 g. of potassium iodide was added 5 ml. of sirupy phosphoric acid (85%) and 1 ml. of rearrangement product. The mixture was refluxed gently for 1.5 hr., then 10 ml. of water was added, and the whole was extracted with 15 ml. of ether. The ether solution was washed with water, sodium thiosulfate solution and again with water; then the ether was removed and replaced by 10 ml. of ethanol. A 1-g. sample of thiourea was added, and after 10 min. refluxing, 0.5 g. of picric acid. The precipitated tetramethylene bis(2-thiopseudourea)dipicrate was filtered, washed with ethanol, and dried, m.p. 240° dec. (lit.[18] 240–242° dec.). A specimen prepared in the same way from authentic tetrahydrofuran also had m.p. 240° dec., and the mixed melting point of the two was the same.

Trimethylene sulfite gave a product which showed five peaks on the gas chromatograph, at q = 0.17 (26), 0.32 (100), 0.42 (48), 0.86 (48), 2.22 (7). The second peak was an unresolved mixture of acrolein (q = 0.29) and propionaldehyde (q = 0.32). In check experiments, these were not resolved on a squalane column at 100° or 64°. Three aldehydes were detected by paper chromatography, acrolein (R_f = 0.21), propionaldehyde (R_f = 0.26) and a third (R_f = 0.35) which is thought to be an aldol condensation product. Infrared spectroscopy of the mixture confirmed the presence of acrolein and propionaldehyde by the C=C and C=O stretching bands in the 6μ region. There were no indications at any time of the presence of acetone.

Ethylene sulfite gave a product which showed seven peaks on the gas chromatograph at q = 0.14 (100), 0.54 (6), 0.60 (6), 0.90 (35), 1.14 (12), 1.64 (94), and 3.18 (6). Two of these were identified as acetaldehyde (q = 0.16) and paraldehyde (q = 0.56). Paper chromatography of the dinitrophenylhydrazone from the product showed only one spot due to acetaldehyde (R_f = 0.12), and the 6μ region of the infrared spectrum confirmed this.

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(17) H. Stone and H. Schechter, *Org. Syntheses*, **30**, 33 (1950).

(18) A. W. Nineham, *J. Chem. Soc.*, 2601 (1953).

Synthesis of Certain Sulfonium Analogs of Meperidine and of the Methadone Class of Analgesics

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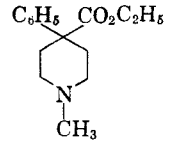
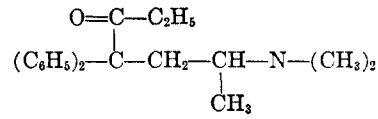
In continuation of our investigations[1] dealing with the preparation of sulfonium analogs of pharmacologically active tertiary and quaternary amines, we wish to report the synthesis of sulfonium analogs of meperidine[3] and also of the methadone class. Both meperidine and methadone are important analgesic agents.



Meperidine



Methadone

The meperidine sulfonium analog VI was prepared from the known 4-cyano-4-phenyltetrahydrothiapyran (III).[7] This nitrile (III) was converted to the 4-carbethoxy intermediate (V) by direct ethanolysis in the presence of sulfuric acid or, more satisfactorily, in two steps by hydrolysis with 70% aqueous sulfuric acid to the corresponding acid[7] (IV) followed by esterification with ethanolic hydrogen chloride. Treatment of V with excess methyl iodide then gave the desired analog (VI); reaction of V with excess ethyl iodide afforded the corresponding ethiodide.

The intermediate nitrile (III) was obtained directly by the sodium amide-catalyzed condensation of phenylacetonitrile (I) with bis(2-chloroethyl) sulfide, a synthesis originally described by Eisleb[7] and which in our hands afforded a 40% yield of III. This nitrile (III) was also prepared from 1,5-dichloro-3-cyano-3-phenylpentane (II)[8] on treatment with sodium sulfide. Although the latter procedure avoids the use of the dangerous mustard gas, the preparation of the 1,5-dichloride (II) requires three steps, and in our experience proceeded in relatively poor over-all yield (11%).[9] It was also possible to prepare the more advanced intermediate, 4-carbethoxy-4-phenyltetrahydrothiapyran (V), by direct condensation of bis(2-chloro-

(1) M. J. Weiss and M. B. O'Donoghue, *J. Am. Chem. Soc.*, **79**, 4771 (1957). This paper contains a review of sulfonium analog work in the pharmaceutical field. The preparation of sulfonium derivatives in the phenazine series has been reported recently.[2]

(2) S. O. Winthrop and M. A. Davis, *J. Am. Chem. Soc.*, **80**, 4331 (1958).

(3) There are two reports in the literature concerning unsuccessful attempts to prepare sulfonium analogs of the 1-methyl-4-acyloxy-4-phenylpiperidine class.[4,5] These piperidines are closely related to meperidine and are active analgesics.[6]

(4) H. M. E. Cardwell, *J. Chem. Soc.*, 1059 (1950).

(5) V. Mychajlyszn and J. O. Jilek, *Chem. Listy*, **50**, 1479 (1956); *Chem. Abstr.*, **51**, 2666 (1957).

(6) A. Ziering, L. Berger, S. D. Heineman and J. Lee, *J. Org. Chem.*, **12**, 894 (1947).

(7) O. Eisleb, *Ber.*, **74B**, 1433 (1941).

(8) F. Bergel, A. L. Morrison, and H. Rinderknecht, *J. Chem. Soc.*, 265 (1944).

(9) Dichloride II was obtained by condensation (sodium amide) of phenylacetonitrile (I) with 2-vinyloxyethyl chloride, acid hydrolysis of the vinyloxy groups and treatment of the resulting 1,5-diol with thionyl chloride.[8]