Dithiotosylates as Reagents in Organic Synthesis[1]

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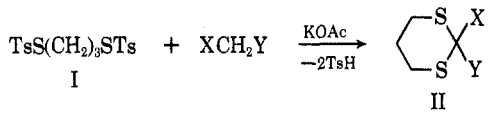
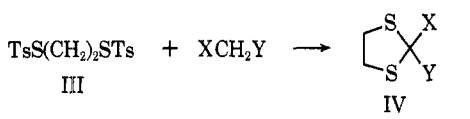
Reliable procedures for the preparation of trimethylene and ethylene dithiotosylates are reported. Techniques for the formation of dithianes and dithiolanes by reaction of these reagents with activated methylene groups are described; these include prior activation of methylene groups adjacent to carbonyl by conversion to either hydroxymethylene or enamine derivatives. Applications of dithiotosylate reactions to various aspects of organic synthesis are discussed.

Trimethylene dithiotosylate or trimethylene di-*p*-toluenethiosulfonate (I)[3] reacts with malonic, benzoylacetic, or acetonedicarboxylic esters or with deoxybenzoin in the presence of acetate ion to form the corresponding 2,2-substituted 1,3-dithiane (II). The reaction presumably occurs with elimination of 2 equiv of the unstable *p*-toluenesulfinic acid. In like manner ethylene dithiotosylate or ethylene di-*p*-toluenethiolsulfonate (III) forms the corresponding 2,2-substituted



I II



III IV

1,3-dithiolane. The dithioketal groups of the dithianes or dithiolanes obtained in this manner, unlike the acetal groups of the analogous oxygen compounds, are remarkably acid stable; even prolonged boiling in hydrochloric acid does not affect the thioacetal group in these substances. Dithianes and dithiolanes can be readily converted back to methylene compounds by reduction with Raney nickel or hydrazine.[4] The dithioketal group can also be removed by hydrolysis to the carbonyl compound in the presence of suitable catalysts, such as salts of Hg^{II}.[5]

The properties of dithianes and dithiolanes suggest that I and III could serve as reagents in organic synthesis for blocking active methylene groups. A compound containing a reactive methylene group could be converted to the corresponding dithiane or dithiolane, and alkylation or some other chemical operation might be applied to some less active site on the molecule. A sequence of transformations could be carried out even in acidic media with the dithioketal group remaining intact. A methylene group would be regenerated by Raney nickel reduction or a carbonyl formed by mercuric ion catalyzed hydrolysis at a desired stage in the synthetic sequence. However, the potential of these reagents in organic synthesis was limited by the lack of a reliable method of preparation and purification of I and by the failure of I and III to form dithioketals with relatively less activated methylene groups, such as those in cyclohexanone.

A reproducible preparation for trimethylene dithiotosylate has been developed in these laboratories based on the reaction of trimethylene dibromide with potassium thiotosylate. Difficulties associated with the synthesis of I are to a considerable extent related to the mode of preparation and resultant purity of the thiotosylate salt obtained by the reaction of potassium hydrosulfide with tosyl chloride. The potassium thiotosylate must be free of tosylate and *p*-toluenesulfinate. The latter can be formed from desulfurization of thiotosylate by the hydrogen sulfide generated in the reaction. Attention should be directed toward control of the reaction temperature so that hydrogen sulfide is rapidly removed, thereby ensuring survival of the S–S bond of the thiotosylate. *p*-Toluenesulfinate ion can displace bromide to form stable sulfones, such as tosyltrimethylene thiotosylate (V), which is poorer in solubility than I and difficult to separate by fractional crystallization when contaminating samples of I.

$$2KHS + TsCl \longrightarrow TsSK + H_2S + KCl$$

$$2TsSK + Br(CH_2)_3Br \longrightarrow I + 2KBr$$

$$KSTs + H_2S \longrightarrow KTs + H_2S_2$$

$$Br(CH_2)_3STs + KTs \longrightarrow Ts(CH_2)_3STs$$

V

Techniques have been devised for extending the dithiotosylate reaction to carbonyl compounds containing less reactive methylene groups. These methods involve activation of the methylene group prior to reaction with I, either by conversion to an enamine or a hydroxymethylene derivative. Cyclohexanone and cholestan-3-one are converted to 2,2-trimethylenedithiocyclohexanone[6] and 2,2-trimethylenedithiocholestan-3-one, respectively, *via* the intermediacy of the pyrrolidine enamines. Correspondingly, the hydroxymethylene derivative of cyclohexanone is converted to 2,2-ethylenedithiocyclohexanone on reaction with III in the presence of acetate. An unambiguous synthesis of lanosterol from cholesterol involves formation of 2,2-trimethylenedithio-(4)-cholesten-3-one by reaction of I with the hydroxymethylene derivative of (4)-cholesten-3-one. The dithiane is alkylated at the 4 position, and reduced with Raney nickel to 4,4-dimethyl-(4)-cholesten-3-one, which can be converted in several steps to lanosterol.[7] Dithiane formation with

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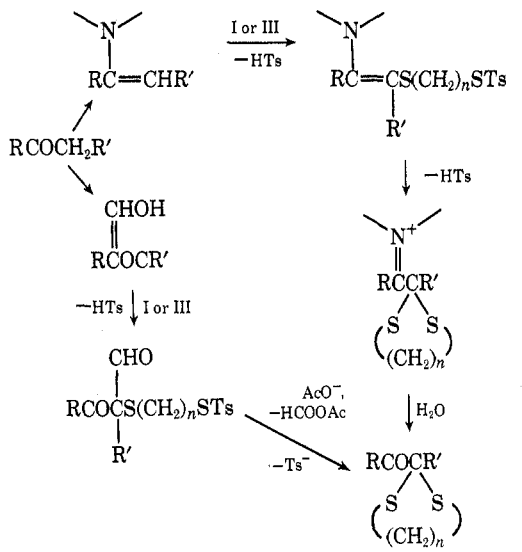
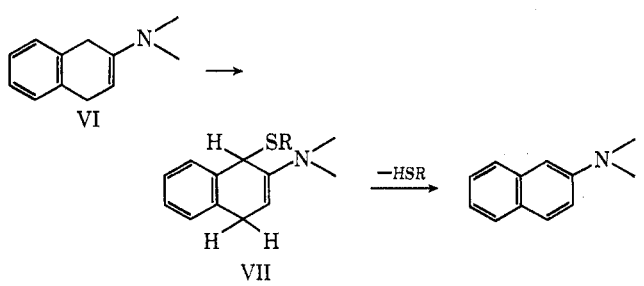
I has also been employed in a total synthesis of colchicine;[8] in this case, the dithioketal group is removed by mercuric acetate catalyzed hydrolysis to an α-diketone. Marshall and Roebke[9] have recently devised a technique for effecting transmigration of carbonyl and methylene groups, $RCH_2COR' \rightarrow RCOCH_2R'$, involving formation of the dithiane with I, selective reduction of the carbonyl, and subsequent hydrolysis of the dithiane group. These same authors have also developed a new method of carbon–carbon bond cleavage such that a ketone can be degraded to an aldehyde and an ester, $RCH_2COR' \rightarrow RCHO + R'COOR''$, using the dithiane derivative of the ketone as intermediate.[10]

The formation of dithianes and dithiolanes by these methods involves displacement of *p*-toluenesulfinate ion, followed by triethylamine induced removal of a proton in the case of enamines and displacement of a formyl group by acetate ion in the hydroxymethylene case. A second, internal displacement occurs in either case to give the dithiane or dithiolane.

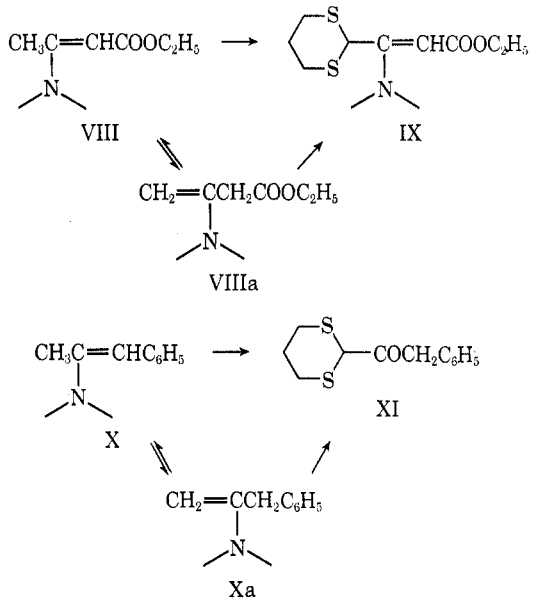


$n = 2$ or 3

Unexpected results are obtained in certain cases with the enamine method. The pyrrolidine enamine derived from β-tetralone (VI) is converted to β-pyrrolidinonaphthalene even in an inert atmosphere. The tendency of the system toward aromatization favors loss of thiol in intermediate VII rather than dithiane



formation. Reaction of enamines derived from acetoacetic ester and phenylacetone with I results in dithiane formation at the methyl groups rather than the methylenes; thus, ethyl 3-pyrrolidinobut-2-enoate (VIII) yields ethyl 4,4-trimethylenedithio-3-pyrrolidinobut-2-enoate (IX), and β-pyrrolidino-β-methylstyrene (X) affords trimethylenedithiomethyl benzyl ketone (XI) on hydrolytic work-up. These results may be rationalized by postulating a tautomerization of the poorly reactive enamines VIII and X to the less stable isomers VIIIa and Xa which react preferentially with trimethylene dithiotosylate.



Experimental Section

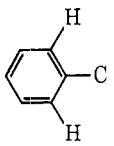
Melting points are uncorrected; infrared spectra were taken with a Perkin-Elmer infrared spectrophotometer and nmr spectra with a Varian A-60 spectrophotometer using TMS as internal reference; elemental analyses were performed by the Scandinavian Microanalytical Laboratory and by Galbraith Laboratories.

I. Preparation of Thiotosylates. Potassium Thiotosylate.—A solution of 56.1 g of potassium hydroxide in 28 ml of water was cooled in an ice bath, saturated with hydrogen sulfide, and flushed with nitrogen to ensure removal of excess H_2S. The freshly prepared potassium hydrosulfide solution was diluted with 117 ml of water and stirred under nitrogen at 55–60°. Finely ground tosyl chloride (Matheson Coleman and Bell, mp 69–71°, free of *p*-toluenesulfonic acid) was introduced in small portions at a uniform rate so that the reaction temperature was maintained at 55–60°. The mild exothermic reaction that ensued was accompanied by an intense yellow coloring. After 90 g of tosyl chloride had been introduced, the yellow color disappeared and the dissolution of the chloride ceased. The reaction mixture was rapidly suction filtered with a warmed funnel, and the filtrate was cooled several hours at 0–5°. The crystals were filtered, dissolved in 200 ml of hot 80% ethanol, filtered hot to remove traces of sulfur, and cooled several hours at 0–5°. The recrystallized salt was filtered and dried, affording 48.1 g of white crystals.

Trimethylene Dithiotosylate (I).—A mixture of 40 g of potassium thiotosylate, 20 g of trimethylene dibromide (Eastman White Label, distilled), 150 ml of 95% ethanol, and 10–20 mg of potassium iodide was refluxed in the dark 8 hr under nitrogen with stirring. The mixture was cooled to ambient temperature, diluted with an equal volume of cold water, and agitated. The supernatant liquid was decanted, leaving a honey-like layer of product, which was washed three timse with 200-ml portions of water, once with 100 ml of 95% ethanol, and once with 100 ml of absolute ethanol. The crude product was dissolved in 15 ml of acetone, diluted with 80 ml of hot absolute ethanol, and stirred under nitrogen at 0–5°. Whenever the oil had failed to crystallize, seed crystals were introduced and the mixture was stirred several hours in the cold. The microcrystalline product (21 g) was collected by filtration. The crude solid or, if crystals were not obtained, the water and alcohol-washed oil were best purified by column chromatography, using 40 parts by weight neutral

(8) R. B. Woodward, *Harvey Lect.*, **59**, 31 (1965).
(9) J. A. Marshall and H. Roebke, *J. Org. Chem.*, **34**, 4188 (1969).
(10) J. A. Marshall and H. Roebke, *Tetrahedron Lett.*, **18**, 1555 (1970).

Woelm alumina, activity grade I, and benzene elution. The center cuts (mp 65°) were combined and recrystallized from nine parts of ethanol to give white needles, mp 67°. Material melting lower than 65° had a tendency to oil out of hot ethanol; in such cases the supernatant solution was decanted, seeded, and cooled, the oil being purified separately. Two recrystallizations of chromatographed product gave material with mp 67.5°; ir ($CHCl_3$) 3030 (w), 3240 (w), 1600 (w), 1490 (w), 1440 (w), 1410 (w), 1330 (s), 1310 (m), 1180 (w), 1150 (s), 1080 (s), 1020 (w), and 815 cm^{-1} (s); nmr ($COCl_3$) δ 1.98 (p, 2, $CH_2CH_2CH_2$, J = 12 Hz), 2.43 (s, 3, CH_3), 2.97 (t, 4, $CH_2CH_2CH_2$, J = 12 Hz), 7.30 (d, 4, fragment 1, J = 14 Hz), and 7.75 ppm (d, 4, fragment 2, J = 14 Hz). *Anal.* Calcd for $C_{17}H_{20}O_4S_4$: C, 49.00; H, 4.84; S, 30.79. Found: C, 49.13; H, 4.81; S, 30.51.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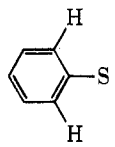
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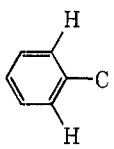
Tosyltrimethylene Thiotosylate (V).—The sulfone, mp 92° (benzene), could be isolated from contaminated samples of I by virtue of the poor solubility of III in cold benzene: ir ($CHCl_3$) is almost identical with that of I; nmr δ 2.06 (p, 2, $CH_2CH_2CH_2$, J = 12 Hz), 2.43 (s, 3, CH_3), 3.08 (t, 4, $CH_2CH_2CH_2$, J = 12 Hz), 7.29 (overlapping doublets, 4, fragment 3, J = 12 Hz), and 7.72 ppm (overlapping doublets, 4, fragment 4, J = 12 Hz). *Anal.* Calcd for $C_{17}H_{20}O_4S_3$: C, 53.09; H, 5.24; S, 25.01. Found: C, 53.04; H, 5.23; S, 25.0.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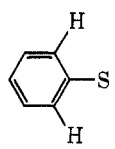
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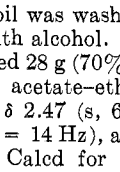
Ethylene Dithiotosylate (III).—A mixture of 46 g (0.2 mol) of potassium thiotosylate, 18 g of ethylene dibromide, 200 ml of ethanol, and 10–20 mg of potassium iodide was refluxed 8 hr in the dark under a nitrogen atmosphere. The mixture was concentrated to abuut 80 ml and diluted with 150 ml of water. An oil was formed and was separated by decanting the supernatant liquid. The oil was washed several times with water and then crystallized with alcohol. Recrystallization from ethyl acetate–ethanol afforded 28 g (70%) of III, mp 72–75°. Three recrystallizations (ethyl acetate–ethanol) gave white crystals: mp 76°; nmr ($CDCl_3$) δ 2.47 (s, 6, CH_3), 3.31 (s, 4, CH_2), 7.48 (c, 4, fragment 5, J = 14 Hz), and 7.97 ppm (d, 4, fragment 6, J = 14 Hz). *Anal.* Calcd for $C_{16}H_{18}S_4O_4$: C, 47.73; H, 4.51; S, 31.86. Found: C, 47.89; H, 4.44; S, 32.22.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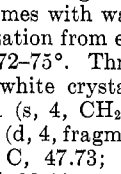
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II. Reaction with Hydroxymethylene Derivatives. 2,2-Ethylenedithiocyclohexanone.—A mixture of 3.85 g (30 mmol) of 2-hydroxymethylenecyclohexanone,[11] 10 g (25 mmol) of ethylene dithiotosylate (III), and 10 g of potassium acetate in 150 ml of methanol was refluxed 3 hr under nitrogen. The solution was evaporated and the residue extracted with ether. The ethereal extract was washed with cold aqueous 2 N NaOH and with NaCl solution, dried ($MgSO_4$), and evaporated. The crude product was dissolved in benzene, filtered through alumina, and evaporated to give 2.9 g (68%) of a white solid. Recrystallization from methanol afforded needles, mp 56–57°. *Anal.* Calcd for $C_8H_{12}OS_2$: C, 51.02; H, 6.42; S, 34.01. Found: C, 51.11; H, 6.53; S, 34.12.

III. Reaction with Enamines.—Petroleum ether refers to Fischer reagent petroleum ether, bp 38.7–57.9°; acetonitrile (Fischer reagent) was distilled over P_2O_5; triethylamine (Eastman White Label) was distilled over sodium hydroxide; enamines were prepared and purified by conventional techniques.[12]

2,2-Trimethylenedithiocholestan-3-one.—A solution of 2.5 mmol (1.04 g) of I, 2.5 mmol (1.10 g) of 3-pyrrolidinocholest-2-ene, 100 ml of acetonitrile, and 10 ml of triethylamine was refluxed under nitrogen 12 hr, after which 1 ml of water was introduced. The mixture was cooled to 0–5° and filtered to give 1.19 g (90%) white solid: mp 179–180° (ethyl acetate); ir ($CHCl_3$) 1695 (s) and 913 cm^{-1} (w). *Anal.* Calcd for $C_{30}H_{50}OS_2$ C, 73.41; H, 10.27; S, 13.07. Found: C, 73.41; H, 10.27; S, 13.25.

Ethyl 3-Pyrrolidino-4,4-trimethylenedithiobut-2-enoate (IX).—A solution of 20 mmol (3.66 g) of enamine VI, 20 mmol (8.32 g) of I, 130 ml of acetonitrile, and 10 ml of triethylamine was refluxed under nitrogen 10 hr. The solvent was evaporated and the residue extracted several times with hot petroleum ether. Evaporation of the extracts afforded 1.59 g (28%) VII: white needles; mp 109–110° (petroleum ether); ir ($CHCl_3$) 1680 (s), 1570 (broad), and 908 cm^{-1} (w); uv (95% EtOH) λ_{max} 296 mμ (log ϵ 3.62); nmr ($CDCl_3$) δ 1.20 (t, 3, CH_3), 1.92 (m, 6, CH_2), 2.92 (m, 4, CH_2S), 3.58 (t, 4, CH_2NCH_2), 4.08 (q, 2, OCH_2), 4.30 (s, 1, SCHS), and 7.52 ppm (s, 1, C=CH). *Anal.* Calcd for $C_{13}H_{21}NO_2S_2$: C, 54.31; H, 7.36; N, 4.87; S, 22.31. Found: C, 54.26; H, 7.40; N, 4.83; S, 22.20.

1-Phenyl-3,3-trimethylenedithiopropan-2-one (XI).—A solution of 10 mmol (1.87 g) of enamine VIII, 10 mmol (4.16 g) of I, 5 ml of triethylamine, and 150 ml of acetonitrile was refluxed 24 hr under nitrogen. The solvent was evaporated and the residue treated with a mixture of 15 g of sodium acetate, 10 ml of acetic acid, and 15 ml of water for 12 hr at ambient temperature with stirring. The mixture was extracted with ether, and the extract was washed (NaCl, 10% $KHCO_3$, and NaCl), dried (Na_2SO_4), and evaporated. The residue is extracted for 2 hr in a Soxhlet extractor with petroleum ether. Evaporation of the extract and trituration with 95% ethanol afforded 1.62 g (68%) IX: white crystals; mp 94° (petroleum ether); ir ($CHCl_3$) 1710 (s) and 914 cm^{-1} (w); nmr ($CDCl_3$) δ 2.0 (m, 2, $CH_2CH_2CH_2$), 3.0 (m, 4, $CH_2CH_2CH_2$), 3.95 (s, 2, CH_2CO), 4.27 (s, 1, SCHS), and 7.30 ppm (s, 5, C_6H_5). *Anal.* Calcd for $C_{12}H_{14}OS_2$: C, 60.46; H, 5.92; S, 26.90. Found: C, 60.37; H, 5.94; S, 26.94.

2-Pyrrolidinonaphthalene.—A solution of 5 mmol (0.99 g) of enamine IV, 5 mmol (2.08 g) of I, 35 ml of acetonitrile, and 5 ml of triethylamine was refluxed 10 hr under nitrogen. The solvent was evaporated, the residue extracted several times with hot petroleum ether, and the extract evaporated to afford a residue which on trituration with 95% ethanol gave 0.91 g (92%) of 2-pyrrolidinonaphthalene: white plates; mp 86–87° (isopropyl alcohol); uv identical with that of 2-N,N-dimethylaminonaphthalene in neutral alcohol and in dilute acid; ir ($CHCl_3$) 1630 and 1370 cm^{-1}; nmr ($CDCl_3$) 7 aromatic and 8 aliphatic protons. *Anal.* Calcd for $C_{14}H_{15}N$: C, 85.23; H, 7.66; N, 7.10. Found: C, 85.15, H, 7.76; N, 7.03.

Registry No.—I, 3866-79-3; III, 2225-23-2; V, 27694-05-9; IX, 27694-06-0; XI, 27694-07-1; 2,2-ethylenedithiocyclohexanone, 27694-08-2; 2,2-trimethylenedithiocholestan-3-one, 3885-11-8; 2-pyrrolidinonaphthalene, 13672-14-5.

Acknowledgment.—The authors are indebted to R. Speake and G. Seld for experimental assistance and to the National Institutes of Health for a predoctoral fellowship for M. L. S.

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