

## A Facile Synthesis of 6,7-Dihydro-1,4-dithiepins (1)

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Received November 13, 1978

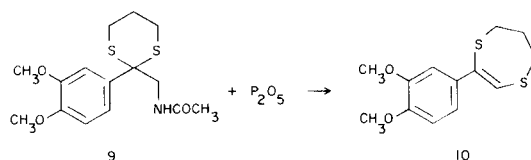
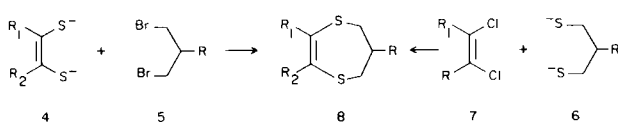
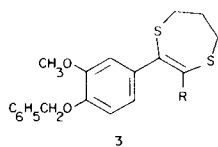
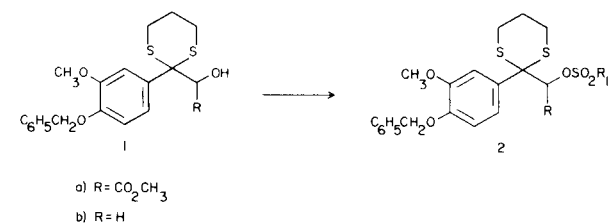
Ring expansion by dehydration of 1,3-dithian-2-ylmethanols gives 6,7-dihydro-5H-1,4-dithiepins.

*J. Heterocyclic Chem.*, 16, 1081 (1979).

Attempts to prepare tosylate **2a** ( $R_1 = 4$ -tolyl) for use in some displacement reactions, did not produce the desired product. Rather, we obtained a crystalline compound which analyzed for  $C_{21}H_{22}O_4S_2$  (calcd. molecular weight 402) and had a parent ion at  $m/e$  402. The pmr spectrum showed no incorporation of a 4-tolyl unit. These data are consistent for structure **3a**. The same compound was obtained when methanesulfonyl chloride was used in the reaction. We found, further, that alcohol **1b** reacted with methanesulfonyl chloride in pyridine to give **3b**.

Two syntheses of 5,6-dihydro-1,4-dithiepins are known (2,3) involving condensation of a dimercaptide such as **4** or **6** with a dihalide **5** or **7**, respectively to give **8**. Another synthesis (3), somewhat analogous to the above rearrangement, is the reaction of amide **9** with phosphorus pentoxide in pyridine to give **10**.

Several syntheses of dihydro-1,4-dithiens are known in which the position *alpha* to a 1,3-dithiolane may develop electrophilic character leading to migration of a sulfur atom and ring enlargement (3,4). Most recently, an acid catalyzed rearrangement of a hydroxyalkyl-1,3-benzodithiolane to a 1,4-benzodithiin was reported (5).



Additional work on the scope of this reaction and possible utility of the 5,6-dihydro-1,4-dithiepins is in progress.

## EXPERIMENTAL

All melting points were determined in open capillary tubes on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 521 grating spectrophotometer using potassium bromide pellets for solids and neat film for liquids. Ultraviolet spectra were recorded on a Perkin-Elmer 350 spectrophotometer in ethanol. Proton magnetic resonance spectra were run on a Varian A-60A with tetramethylsilane as an internal standard and were run in deuteriochloroform. The standard drying agent used was magnesium sulfate and the solvents were removed *in vacuo* on a rotary evaporator. Silica gel was used for chromatography.

Methyl 2-[3-Methoxy-4-(benzyloxy)phenyl]-1,3-dithian-2-(2-oxoacetate).

A stirred solution of 2-[3-methoxy-4-(benzyloxy)phenyl]-1,3-dithiane (**6**) (20.0 g., 60.2 mmoles) in THF (250 ml.) under nitrogen was cooled to  $-35^\circ$  and treated with 1.67M butyl lithium in hexane (43 ml.). After 0.25 hour, the deep purple solution was treated rapidly with dimethyl oxalate (14.2 g., 120 mmoles) in THF (30 ml.). After 2 hours, the yellow solution was treated with saturated aqueous ammonium chloride and the organic layer was concentrated. The residue was partitioned between ether and water. The organic layer was dried, treated with charcoal, filtered and concentrated to a yellow solid which was chromatographed (520 g. silica eluting with benzene-60% hexane to 100% benzene). The fractions containing product were combined and concentrated. The residue crystallized from acetone-hexane to give the title compound (11.4 g., 45.2%), m.p.  $117-118^\circ$ ; ir:  $\nu$  1750, 1710, 1510, 1250, 1135, 1090  $cm^{-1}$ ; uv:  $\lambda$  238 (log  $\epsilon$  4.086) 284 (log  $\epsilon$  3.661); pmr:  $\delta$  1.65-2.18 (2H, m,  $CH_2$ ), 2.54-3.42 (4.4H, m, 2 x  $CH_2S$ ), 3.67 (3H, s,  $CH_3O$ ), 3.89 (3H, s,  $CH_3$ , s,  $CH_3O$ ), 5.17 (2H, s,  $CH_2O$ ), 6.82-7.17 (3H, m, Ar-H), 7.23-7.58 (5H, m, Ar-H).

*Anal.* Calcd. for  $C_{21}H_{22}O_5S_2$ : C, 60.27; H, 5.30; S, 15.32. Found: C, 60.67; H, 5.35; S, 15.29.

Methyl 2-[3-Methoxy-4-(benzyloxy)phenyl]-1,3-dithiane-2-(2-hydroxyacetate) (**1a**).

A stirred solution of the above ketone (21.5 g., 51.4 mmoles) in methanol (150 ml.)-THF (150 ml.) was treated with sodium borohydride (1.88 g., 49.5 mmoles). After 10 minutes, acetic acid was carefully added, then the mixture was poured into cold water and extracted with diethyl ether (3 x 150 ml.). The combined organic extract was washed with saturated brine, dried, filtered and concentrated to a liquid which was purified by chromatography (7) (500 g. silica, benzene-4% acetone) to give a white solid **1a** (11.1 g., 51.1%); ir:  $\nu$  3480, 1735, 1590, 1580, 1500, 1205, 1130  $\text{cm}^{-1}$ ; uv:  $\lambda$  240 (log  $\epsilon$  4.998), 281 (log  $\epsilon$  3.548); pmr:  $\delta$  1.63-2.13 (2H, m,  $\text{CH}_2$ ), 2.53-2.83 (4H, m, 2 x  $\text{CH}_2\text{S}$ ), 3.03 (1H, d,  $J = 9.5$  Hz, OH), 3.55 (3H, s,  $\text{CH}_3\text{O}$ ), 3.88 (3H, s,  $\text{CH}_3\text{O}$ ), 4.45 (1H, d,  $J = 9.5$  Hz, CHO), 5.13 (2H, s,  $\text{CH}_2\text{O}$ ), 6.85 (1H, d,  $J = 8$  Hz, Ar-H), 7.13-7.60 (7H, m, Ar-H).

Anal. Calcd. for  $\text{C}_{21}\text{H}_{24}\text{O}_5\text{S}_2$ : C, 59.98; H, 5.75; S, 15.25. Found: C, 60.17; H, 5.76; S, 15.25.

Methyl 6,7-Dihydro-3-[3-methoxy-4-(benzyloxy)phenyl]-5H-1,4-dithiepin-2-carboxylate (**3a**).

A solution of **1a** (9.7 g., 23.1 mmoles) in dry pyridine (10 ml.) was treated with methanesulfonyl chloride (3.20 g., 23.1 mmoles) and allowed to stand overnight at room temperature. The mixture was poured onto ice-20% hydrochloric acid and extracted with chloroform. The organic layer was washed with 10% aqueous hydrochloric acid, dried, treated with charcoal, filtered and concentrated to a yellow solid which crystallized from dichloromethane-acetone to give, in two crops, **3a** (5.9 g., 63.2%), m.p. 152-153°; ir:  $\nu$  1700, 1590 (w), 1575 (w), 1260, 1220, 1130  $\text{cm}^{-1}$ ; uv:  $\lambda$  231 sh (log  $\epsilon$  4.165), 333 (log  $\epsilon$  3.839); pmr:  $\delta$  2.14 (2H, quint,  $J = 6$  Hz,  $\text{CH}_2$ ), 3.38 + 3.56 (7H, s + t,  $J = 6$  Hz,  $\text{CH}_3\text{O} + 2$  x  $\text{CH}_2\text{S}$ ), 3.88 (3H, s,  $\text{CH}_3\text{O}$ ), 5.14 (2H, s,  $\text{CH}_2\text{O}$ ), 6.83-7.03 (3H, m, Ar-H), 7.22-7.58 (5H, m, Ar-H); ms: 402 (P), 371 (P-O $\text{CH}_3$ ), 343 (P-CO $_2$ CH $_3$ ), 311 (P-C $_6$ H $_5$ CH $_2$ ).

Anal. Calcd. for  $\text{C}_{21}\text{H}_{22}\text{O}_4\text{S}_2$ : C, 62.66; H, 5.51; S, 15.93. Found: C, 62.57; H, 5.56; S, 15.88.

2-[3-Methoxy-4-(benzyloxy)phenyl]-1,3-dithiane-2-carboxaldehyde.

A stirred solution of 2-[3-methoxy-4-(benzyloxy)phenyl]-1,3-dithiane (33.25 g., 0.10 mole) in THF (400 ml.) under nitrogen was cooled to -30° and treated with 1.67N butyl lithium in hexane (71.5 ml.). After 10 minutes, ethyl formate (16.5 g., 0.22 mole) was added. The reaction mixture was treated with 50% hydrochloric acid (10 ml.), diluted with water and extracted with dichloromethane (twice). The combined organic layer was washed with saturated brine, dried, treated with charcoal, filtered and concentrated. The residue was crystallized from benzene (200 ml.)-hexane (400 ml.) to give the title compound (31.9 g., 88.6%), m.p. 131-132°; ir:  $\nu$  1710, 1595 (w), 1580, 1510, 1255, 1140  $\text{cm}^{-1}$ ; uv:  $\lambda$  238 (log  $\epsilon$  4.084), 283 (log  $\epsilon$  3.665); pmr:  $\delta$  1.53-1.70 (2H, m,  $\text{CH}_2$ ), 2.43-3.45 (4H, m, 2 x  $\text{CH}_2\text{S}$ ), 3.89 (3H, s,  $\text{CH}_3\text{O}$ ), 5.15 (2H, s,  $\text{CH}_2\text{O}$ ), 6.90-7.15 (3H, m, Ar-H), 7.40 (5H, s, Ar-H), 9.15 (1H, s, OCH).

Anal. Calcd. for  $\text{C}_{19}\text{H}_{20}\text{O}_3\text{S}_2$ : C, 63.30; H, 5.59; S, 17.79. Found: C, 63.22; H, 5.66; S, 17.82.

2-Hydroxymethyl-2-[3-methoxy-4-(benzyloxy)phenyl]-1,3-dithiane (**1b**).

A stirred suspension of the above aldehyde (4.47 g., 12.7 mmoles) in ethanol (100 ml.)-toluene (50 ml.) was treated with sodium borohydride (1.0 g.) and stirred 4 hours. Acetic acid was

cautiously added and the mixture concentrated to ca 50 ml., diluted with diethyl ether and washed with water. The organic layer was dried, filtered and concentrated to an oil which solidified on standing. It crystallized from methanol to give **1b** (2.90 g., 64.5%), m.p. 90.5-91.5°; ir:  $\nu$  3500, 1595 (w), 1580 (w), 1510, 1255, 1150  $\text{cm}^{-1}$ ; uv:  $\lambda$  (log  $\epsilon$ ) 237 (3.799), 281 (3.314); pmr:  $\delta$  1.72-2.35 (3H, m, one exchangeable,  $\text{CH}_2 + \text{OH}$ ), 2.57-3.02 (4H, m, 2 x  $\text{CH}_2\text{S}$ ), 3.83 (3H, s,  $\text{CH}_3\text{O}$ ), 3.95 (2H, s,  $\text{CH}_2\text{O}$ ), 5.82 (2H, s,  $\text{CH}_2\text{O}$ ), 6.82 (1H, d,  $J = 8$  Hz, Ar-H), 7.13-7.52 (7H, m, Ar-H).

Anal. Calcd. for  $\text{C}_{19}\text{H}_{22}\text{O}_3\text{S}_2$ : C, 62.95; H, 6.12; S, 17.69. Found: C, 63.22; H, 6.19; S, 17.84.

6,7-Dihydro-2-[3-methoxy-4-(benzyloxy)phenyl]-5H-1,4-dithiepin (**3b**).

A solution of **1b** (1.07 g., 2.95 mmoles) in pyridine (10 ml.) was treated with methanesulfonyl chloride (0.43 g., 3.75 mmoles) and allowed to stand overnight at room temperature. The reaction mixture was poured onto cold 10% aqueous hydrochloric acid (25 ml.) and extracted with diethyl ether (75 ml.). The ether was backwashed with 50% aqueous hydrochloric acid (40 ml.), 10% aqueous hydrochloric acid (25 ml.), water (25 ml.), saturated aqueous sodium bicarbonate (40 ml.), dried, filtered and concentrated. The resulting solid crystallized diethyl ether-methanol to give, in two crops, **3b** (0.70 g., 68.6%), m.p. 99.5-100°; ir:  $\nu$  1590, 1505, 1255, 1130  $\text{cm}^{-1}$ ; uv:  $\lambda$  (log  $\epsilon$ ) 250 sh (4.015), 3.9 (4.077); pmr:  $\delta$  2.13 (2H, quint,  $J = 6$  Hz,  $\text{CH}_2$ ), 3.35-3.72 (4H, m, 2 x  $\text{CH}_2\text{S}$ ), 3.87 (3H, s,  $\text{CH}_3\text{O}$ ), 5.12 (2H, s,  $\text{CH}_2\text{O}$ ), 6.06 (1H, s, C=CH), 6.68-7.12 (3H, m, Ar-H), 7.38 (5H, br s,  $\text{C}_6\text{H}_5$ ).

Anal. Calcd. for  $\text{C}_{19}\text{H}_{20}\text{O}_2\text{S}_2$ : C, 66.24; H, 5.81; S, 18.61. Found: C, 66.28; H, 5.95; S, 18.60.

## REFERENCES AND NOTES

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- (7) Also isolated off the column was 1.4 g. (8.2%) of 2-[3-methoxy-4-(benzyloxy)phenyl]-1,3-dithiane (*ii*) which presumably arose from *i* as shown.

