

While stirring a solution of 5.1 g iodine (and some potassium iodide) in 100 ml of 50 % ethanol was added in portions until the colour persisted. Almost the theoretical amount of iodine was consumed. On cooling with a dry ice-alcohol bath, 2.4 g (70 %) of 1,2-dithiolane-4-one semicarbazone were obtained as a precipitate, m.p. 174–176° (decomp.).

2,2-Bis-(mercaptomethyl)-1,3-dithiacyclohexane-5-one semicarbazone. (a) Directly from dimercaptoacetone: To a solution of 18.4 g (0.15 mole) of dimercaptoacetone in 500 ml of ethanol, was added, while stirring, a solution of 8.4 g (0.075 mole) of semicarbazide hydrochloride in 150 ml of water. The mixture was kept, while stirring, at room temperature for about 1 h. The solution was neutralized to about pH 6 with a solution of sodium bicarbonate as described above. On cooling the semicarbazone precipitated. Yield 14.5 g (69 %), m.p. 161–164° (decomp.). Recrystallisation improved the m.p. to 167–169° (decomp.). (Found: C 29.67; H 4.61; N 14.48; S 44.65. Calc. for $C_8H_{13}N_3OS_4$ (283.44): C 29.66; H 4.62; N 14.83; S 45.24).

(b) From dimercaptoacetone semicarbazone: 11.8 g (0.06 mole) of dimercaptoacetone semicarbazone were dissolved in 100 ml of ethanol. While stirring a solution of 7.4 g (0.06 mole) of dimercaptoacetone in 150 ml of ethanol was added rapidly. The temperature was kept at 60–70° for about 1 h. During this time some precipitate was formed. The mixture was diluted with 100 ml of water and was then cooled with an ice-salt mixture. The precipitate was collected and yielded 15.3 g (65 %), m.p. 171–172° (decomp.). The m.p. of a mixture with the compound prepared according to (a) showed no depression.

Dimercaptoacetone thiosemicarbazone. 5.0 g (0.042 mole) of freshly prepared dimercaptoacetone were dissolved in 200 ml of ethanol. To this solution was added a solution of 4.0 g (3.83 g = 0.042 mole) of thiosemicarbazide in 20 ml of 2 N hydrochloric acid. Water was added to a total volume of 250 ml and the solution was neutralized to pH 6 with a solution of potassium carbonate. After cooling in an ice bath, 7.1 g (86 %) were collected as white crystals, m.p. 127–130° (decomp.). Recrystallisations from acetone and ethanol raised the m.p. to 145–146° (decomp.). (Found: C 24.46; H 4.67; S 48.15. Calc. for $C_4H_9N_3S_2$ (195.31): C 24.60; H 4.64; S 49.24). Iodometric titration showed a purity of about 97 %.

Oxidation with iodine in ethanol yielded a product with m.p. 167–169°. Mixed melting point with 1,2-dithiolane-4-one thiosemicarbazone showed no depression.

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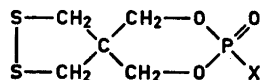
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Some 8-Substituted Derivatives of 2,3-Dithia-7,9-dioxa-8-phosphaspiro [4,5] decane-8-oxide

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The compounds which have been prepared for pharmacological purposes have the general formula:



and are phosphoric acid derivatives of 4,4-bis-hydroxymethyl-1,2-dithiolane. By treating this last compound with phosphorus oxychloride, the 8-chloro derivative is easily obtained. This has been converted to the acid ($X = OH$) and the morpholide ($X = N \begin{array}{c} \diagup \\ \diagdown \end{array} O$). The compounds in which X is an ester group ($X = OR$) or amide group ($X = NR_1R_2$) may also be prepared directly from the bishydroxymethyldithiolane and esters of phosphorodichloridic acid, $Cl_2PO(OR)$, and N,N-disubstituted phosphoramidic dichloride, $(R_1R_2N)POCl_2$. The bis-(β -chloroethyl)-amide ($X = N(CH_2CH_2Cl)_2$) has been synthesized in this way from N,N-bis-(β -chloroethyl)-phosphoramidic dichloride.

2,3-Dithia-7,9-dioxa-8-chloro-8-phosphaspiro [4,5]decane-8-oxide. 230 ml of freshly distilled phosphorus oxychloride were heated to about 40° in a flask equipped with a mechanical stirrer and an inlet fitted with a calcium

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chloride tube. 25.0 g (0.15 mole) of 4,4-bis-hydroxymethyl-1,2-dithiolane were added *via* the inlet tube by means of a small spoon and dissolved while stirring and keeping the temperature at 40–45°. This procedure took about 45 min. The solution was kept at about 40° while stirring for about 2.5 h. The excess of phosphorus oxychloride was distilled off *in vacuo*. The residue was dissolved in 225 ml of chloroform, the solution treated with Norite and filtered. 450 ml of petrol ether was added while stirring. The precipitate formed was filtered off and washed with petrol ether. Yield 31.3 g (85.5 %), m.p. 142–145°. This product was dissolved in 400 ml of boiling benzene, minor amounts of undissolved impurities were filtered off, and some petrol ether was added. After cooling, 25.3 g (69 %) of white crystals with m.p. 146–148° were collected. By recrystallisation of substance obtained from the mother liquors, another crop of 2.3 g (6.2 %) and m.p. 143–145° could be obtained.

Since the compound is an acid chloride, it should be stored under exclusion of moisture. An earlier prepared sample had m.p. 142–145°. (Found: C 24.28; H 3.43; Cl 14.42; S 26.13. Calc. for $C_5H_9ClO_3S_2P$ (246.68): C 24.34; H 3.27; Cl 14.38; S 25.99).

2,3-Dithia-7,9-dioxa-8-hydroxy-8-phosphaspiro[4,5]decane-8-oxide and its sodium salt. A mixture of 29.6 g (0.12 mole) of the acid chloride (X = Cl) from the preceding step, 120 ml (0.24 mole) of 2 N sodium hydroxide and 300 ml of water was heated on a water bath for about 10 min. The warm solution was filtered and cooled to about 10°. The acid (X = OH) was precipitated by adding 120 ml of 5 N hydrochloric acid and the precipitate filtered off. Yield 22.5 g (82 %). The compound decomposes at about 200°. (Found: C 26.19; H 4.00; S 26.38. Calc. for $C_5H_9O_4S_2P$ (228.22): C 26.31; H 3.97; Cl 26.31; H 3.97; S 28.10).

8.0 g (0.035 mole) of the acid were dissolved in 150 ml of warm 99.5 % ethanol and the solution poured, while stirring, into a solution of sodium ethoxide in ethanol (from 0.81 g of sodium and 25 ml of 99.5 % ethanol).

The sodium salt precipitated immediately. After cooling, the precipitated sodium salt was collected and washed with cold ethanol. Yield 8.0 g (91.5 %).

2,3-Dithia-7,9-dioxa-8-morpholino-8-phosphaspiro[4,5]decane-8-oxide. A mixture of 7.4 g (0.03 mole) of the acid chloride (X = Cl), 6.0 g (0.07 mole) of morpholine, and 100 ml of benzene was refluxed, while stirring, for about 1 h. After cooling, water and petrol ether were added and the precipitate formed was collected. Yield 8.0 g (90 %), m.p. 221–229°. Two recrystallisations from benzene + petrol ether gave 4.0 g (45 %) with m.p. 231–233.5°. (Found: C 36.81; H 5.48; N 4.77; S 21.43. Calc. for $C_9H_{16}NO_4S_2P$ (297.33): C 36.35; H 5.48; N 4.71; S 21.57).

2,3-Dithia-8-bis-(β-chloroethyl)-amino-7,9-dioxa-8-phosphaspiro[4,5]decane-8-oxide. 8.3 g (0.05 mole) of 4,4-bis-hydroxymethyldithiolane were dissolved in 75 ml of dry pyridine, and 15.0 g (theor. 13.0 g) of N,N-bis-(β-chloroethyl)phosphoramidic dichloride¹ were added in portions while stirring. During this procedure the temperature was kept below 25°. The mixture was then kept at room temperature. After about half an hour pyridine hydrochloride began to precipitate. Next day pyridine was distilled off *in vacuo* until the volume had decreased to about 25 ml. 100 ml of cold water was added while stirring. The impure precipitate was filtered off and washed with water, giving 18 g of crude product. Recrystallisation from benzene + petrol ether yielded 14.5 g with m.p. 100–112°. Recrystallisation from benzene + cyclohexane gave 11.5 g with m.p. 109–114°. A final crystallisation from carbon tetrachloride raised the m.p. to 113–115°. Yield 6.0 g (34 %). (Found: C 30.50; H 4.57; Cl 21.49; S 17.86. Calc. for $C_9H_{16}Cl_2NO_4S_2P$ (352.24): C 30.69; H 4.58; Cl 20.13; S 18.20).

1. Friedman, O. M. and Seligman, A. M. *J. Am. Chem. Soc.* **76** (1954) 657.

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