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Synthesis of Possible Cancer Chemotherapeutic Compounds Based on Enzyme Approach. III. 1,2,3-Oxadithiolane 2-Oxide[1]

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Received May 15, 1961

1,2,3-Oxadithiolane 2-oxide (II) was prepared from mercaptoethanol and thionyl chloride in chloroform. The 5-methyl homolog (X) was also prepared by this method. Attempted preparation of the 5-phenyl homolog under the same conditions leads to only 2,5-diphenyl-*p*-dithiane (XII). Treatment of II with potassium carbonate gave carbon dioxide, sulfur dioxide, and ethylene sulfide. Bromination of II with elemental bromine yields bis(2-bromoethyl) disulfide, with *N*-bromosuccinimide, yields *N*-(2-bromoethylthio)succinimide. Other reactions of II under various conditions have also been investigated.

The preparation of 2-chloro-2′-mercaptodiethyl sulfide (IV) (MSM) and its derivatives as possible cancer chemotherapeutic agents has been reported.[2b] In searching for an alternate synthetic route of IV, 2-chloroethyl mercaptan (III) was needed. While III has been prepared by heating mercaptoethanol or ethylene sulfide with concentrated hydrochloric acid,[3-5] attempts to prepare III by the reaction of mercaptoethanol and thionyl chloride in chloroform were not successful. Instead, 1,2,3-oxadithiolane 2-oxide (II) was obtained as the main product together with only a small amount of IV, *p*-dithiane (V) and a polymeric sulfide (VI).

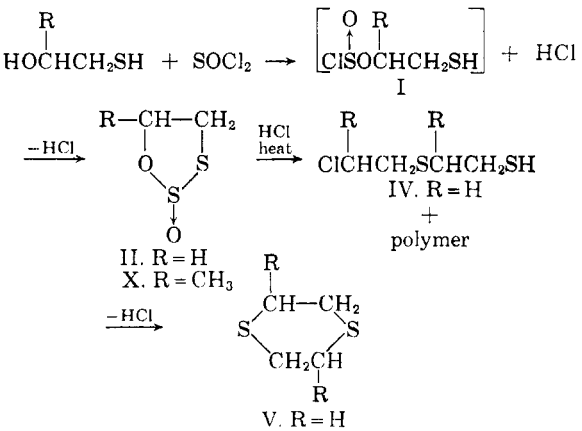

Figure 1

The interaction of mercaptoethanol and thionyl chloride gave the unstable intermediate *O*-chlorosulfinyl-2-mercaptoethanol (I), which proceeded in two possible routes by either elimination of sulfur dioxide to give III or by intramolecular dehydrochlorination to give II. When solvents (chloroform, benzene, *etc.*) were used, II was the main product. When II was treated at elevated temperature with hydrogen chloride, I was again formed. Under such conditions, the reaction proceeded further to give IV. By intramolecular dehydrochlorination of IV, the dithane (V)[6] was isolated.

The undistillable paste VI that remained from the preparation of III was examined; it was insoluble in organic solvents. The thermoplasticity and qualitative test suggests its structure as a linear polysulfide, $-(C_2H_4S_2)n-$(VI). When VI was treated with a hot concentrated sulfuric acid–nitric acid mixture, oxidation took place. A dark spongy, rubbery substance (VII) was obtained.

The yields of II and IV decreased when benzene was used as the reaction medium with increase in the yield of polymeric materials. In the absence of solvent, the reaction of mercaptoethanol and thionyl chloride failed to give II and IV, the desired products. Distillation of this reaction mixture led only to severe decomposition.

In order to compare the biological properties of II with other structural modifications, we proceeded to prepare 5-methyl-1,2,3-oxadithiolane 2-oxide X. 1-Acetylthio-isopropyl acetate (VIII) was prepared from isopropenyl acetate and thiolacetic acid, by a procedure similar to the method used for 1-acetoxy-1-butene by Behringer and Kley.[7] The hydrolysis of VII was carried out in the usual manner[8] by refluxing the diacetyl compound in methanol with 5% hydrochloric acid to give 2-hydroxypropyl mercaptan (IX). When IX was treated with thionyl chloride in chloroform, 5-methyl-1,2,3-oxadithiolane 2-oxide (X) was obtained as colorless long needles.

Using a modified procedure of Martynov and

(1) This research was supported by research grant C-2530 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare, Bethesda 14, Md.

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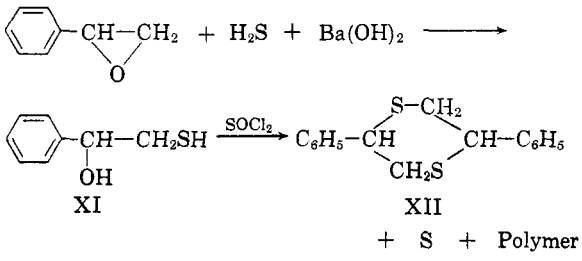

Figure 2

Romanov[9] styrene oxide was added to barium hydroxide in ethanol saturated with hydrogen sulfide to give 1-phenyl-2-mercaptoethanol[10] (XI). However, the reaction of XI with thionyl chloride in chloroform (or other solvents) failed to give 5-phenyl-1,2,3-oxidithiolane 2-oxide. Only 2,5-diphenyl-1,4-dithiane (XII) and sulfur were isolated. Since the phenyl group probably facilitates the S_Ni reaction of the intermediate sulfinyl chloride before cyclic elimination of hydrogen chloride could take place.

When alkylating potency was determined on II by 4-(*p*-nitrobenzyl)-pyridine (NBP) method,[2a] it was found to be negative. Since II does show activity against S-180 and L-1210 in mouse tumor screening, it was highly of interest to us to understand more of its chemical behavior.

Treatment of II with potassium carbonate at about 100° gave carbon dioxide, sulfur dioxide, and ethylene sulfide. Thermal decomposition at higher temperature (270°) under reduced pressure yielded sulfur dioxide and water, together with a yellow, soft, rubbery substance and a carbonized residue.

Bromination of II in carbon tetrachloride at 0°, gave bis(2-bromoethyl) disulfide (XV). This reaction probably took place *via* a free radical mechanism with the formation of 2-bromoethylthio radical as an intermediate. When *N*-bromosuccinimide was used as the brominating agent, only a small amount of XV was obtained and interestingly, *N*-(2-bromoethylthio)succinimide (XVI) was obtained as the major product. Chlorination of II with chlorine in carbon tetrachloride and benzoyl peroxide as catalyst gave bis(2-chloroethyl) disulfide[11] (XIV) in good yield. When *N*-chlorosuccinimide was used as chlorinating agent, there was obtained only a low yield of XIV. Under all conditions, no halogenated cyclic derivatives of II were isolated.

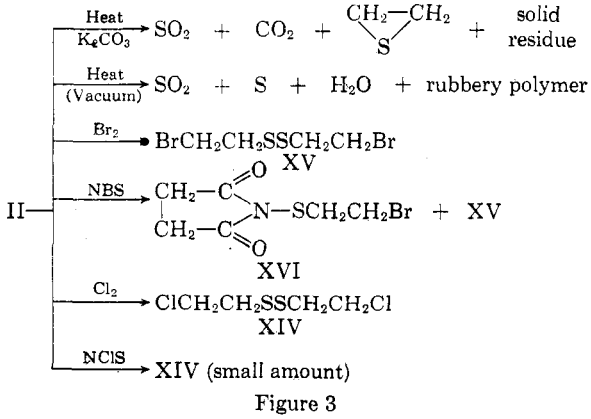

Figure 3

When II was heated with acetic acid, hydrogen sulfide, methanol, or phenol in the presence of catalytic amount of anhydrous potassium carbonate, no reaction took place. It was also recovered unchanged when heated with thiophenol and amyl mercaptan.

At present we have attributed the biological activity of II to a free radical type intermediate and in its ability to interfere with SH enzymes. *In vivo* study of its reaction with enzymes is now in progress.

EXPERIMENTAL[12,13]

1,2,3-Oxadithiolane 2-oxide (II). Mercaptoethanol (156 g., 2 moles) in 150 ml. of chloroform and thionyl chloride (262 g., 2.2 moles) in 150 ml. of chloroform were added dropwise simultaneously into 200 ml. of chloroform with stirring at room temperature. The solution was then stirred for 5 hr. The solvent and volatile materials were removed *in vacuo*. The residual liquid was distilled to obtain 1,2,3-oxadithiolane 2-oxide (II) in 71% (176 g.) yield with b.p. 77–79° (3 mm.) or 56–57° (0.5–0.6 mm.), n_D^{20} 1.5771 and n_D^{24} 1.5782 λ_{max} 3.40, 6.88, 7.00, 7.92, 8.50–8.60 (b), 10.18, 11.00, 11.75, 14.35–14.45 (b) μ.

Anal. Calcd. for $C_2H_4S_2O_2$: C, 19.34; H, 3.25; S, 51.64. Found: C, 19.61; H, 3.74; S, 51.43.

Further distillation gave a yellow oil and white solids with some decomposition. After separation by filtration, the oil was redistilled to obtain 2-chloro-2′-mercaptodiethyl sulfide (IV) in 22.3% yield, with b.p. 91–94° (4 mm.) and n_D^{20} 1.5653. Its infrared spectrum was identical to IV obtained by another method.[2b]

Anal. Calcd. for $C_4H_9ClS_2$: C, 30.66; H, 5.79. Found: C, 30.57; H, 5.45.

The solid was recrystallized from ether–light petroleum (b.p. 30–60°) to give *p*-dithiane[6] (V) in white glistening flakes of m.p. 111–112° (with sublimation) in 1.5% yield; λ_{max} (Nujol): 7.15, 7.72, 7.85, 8.62, 8.72, 11.10, 15.08 μ.

Anal. Calcd. for $C_4H_8S_2$: C, 39.96; H, 6.71. Found: C, 39.93; N, 7.02.

The residual paste (VI) was treated by hot mixture of concd. sulfuric acid and nitric acid. The product was washed thoroughly with water. A dark gray sponge (VII) was obtained.

Anal. VII Calcd. for $-[(C_2H_4S_2)_4O]n-$: C, 24.98; H, 4.19; S, 66.68. Found: C, 24.13; H, 3.66; S, 67.02.

1-Acetoxythioisopropyl acetate (VIII) *and 1-methyl-2-mercaptoethanol* (IX). To isopropenyl acetate (20 g., 0.2 mole) was added thiolacetic acid (16.7 g., 0.22 mole) dropwise with stirring and cooling. The mixture was heated over a water bath for 2 hr. The product VIII was obtained at b.p. 56.5–58° (0.65–0.70 mm.) in 74% (35.2 g.) yield, n_D^{33} 1.4635; λ_{max} 3.35, 3.40 (Spl.); 5.75–5.90 (b), 7.00, 7.30, 7.90–8.20 (b), 8.75–9.08 (b), 9.50–9.70 (b), 10.45 μ. The product obtained

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(12) All melting points and boiling points are corrected.

(13) All analyses were done by Dr. Stephen Nagy, Microchemical Laboratory, Massachusetts Institute of Technology.

by Davies and Savige[8] from propylene sulfide and acetyl chloride boiled at 119–121° (19 mm.), n_D^{18} 1.467.

VIII was refluxed with 1% methanolic hydrogen chloride (90 ml.) for 7 hr. After removal of solvent *in vacuo*, IX was collected at b.p 75–79° (46–47 mm.) with $n_D^{30.8}$ 1.4818 in 62% yield; λ_{max} 2.90–3.00, 3.35, 3.41 (spl.), 3.92 (w), 6.88, 7.08, 7.30 (triple), 8.35, 8.85–8.95, 9.30–9.50 (b), 10.65, 11.75 μ. Davies and Savige[8] reported b.p. 70–71°. (20 mm.) n_D^{18} 1.4815.

5-Methyl-1,2,3-oxadithiolane 2-oxide (X). The procedure used in preparing II was adapted. After stirred at 28–30° for 3 hr., low volatile materials and solvent were removed *in vacuo*. The viscous liquid was distilled to yield 74% of X at b.p. 72–85° (1.7–2.1 mm.). The distillate soon solidified into long colorless needles, m.p. 39–39.5°, λ_{max} (potassium bromide) 3.40, 6.85, 6.90 (Spl.), 7.00, 7.22, 8.18, 8.60–8.78 (b), 8.95, 9.30, 9.95, 11.05, 11.25, 12.20–12.30 (b), 13.70–14.00 (b) μ.

Anal. Calcd. for $C_3H_6S_2O_2$: C, 26.07; H, 4.38. Found: C, 26.20, H, 4.38.

Further distillation of the residue gave a dark liquid with b.p. 82–120° (1.6–2.1 mm.). Attempted redistillation of this product only led to severe decomposition. The major fraction was collected at 96–120° (2 mm.) with n_D^{24} 1.5468.

1-Phenyl-2-mercaptoethanol (XI). Styrene oxide (36 g., 0.3 mole) was added slowly over a period of 5 hr. to barium hydroxide (30 g., hydrate) in 75% ethanol previously saturated with hydrogen sulfide at the temperature below 30°. Again the hydrogen sulfide stream was maintained for 1 hr., then followed by saturation with carbon dioxide. The gelatinous mass was extracted with ethanol. After removal of the solvent, the residue was distilled to yield 76.8% (35.5 g.) of XI, b.p. 124.5–127° (3.7–4.1 mm.), n_D^{27} 1.5803.

Anal. Calcd. for $C_8H_{10}OS$: C, 62.30; H, 6.54. Found: C, 62.22; H, 6.55.

This compound was also prepared by Djerassi, *et al.*[10] from reduction of phenacyl benzyl xanthate, b.p. 93–95° (3 mm.), or 125–126° (5 mm.), n_D^{20} 1.5816.

Attempted preparation of 5-phenyl-1,2,3-oxadithiolane 2-oxide. XI (31.5 g., 0.2 mole) and thionyl chloride (35.7 g., 0.3 mole) were dissolved separately and added simultaneously into chloroform at 25–30°. After stirring for 5 hr., a green solution resulted. The solvent was removed *in vacuo*, but the residue was not distillable.

The viscous liquid was then decolorized with charcoal in chloroform. The solution was concentrated to its smallest volume, then triturated with ether. The solid obtained was recrystallized from chloroform-ether to yield white flakes (1 g.), m.p. 212–214°, of 2,5-diphenyl-1,4-dithiane (XII); λ_{max} (potassium bromide) 6.72, 6.90, 7.12, 7.80, 8.10, 8.20, 8.67, 9.33, 9.68, 10.05, 11.21, 12.88, 13.66, 14.28 μ.

Anal. Calcd. for $C_{16}H_{16}S_2$: C, 70.54; H, 5.92. Found: C, 70.34; H, 5.85.

The chloroform-ether filtrate was further concentrated *in vacuo*. The residue was distilled to give a yellow liquid. There was some decomposition and evolution of sulfur dioxide at 150–190° (1–2 mm.). The distillate solidified and was recrystallized from ether–light petroleum to bright yellow rhombic crystals of sulfur, m.p. 113–115°.

Thermal decomposition of II *in presence of potassium carbonate.* Equimolar amounts of II and potassium carbonate were mixed and heated to the temperature when evolution of gases started. Almost theoretical quantities of carbon dioxide and sulfur dioxide were collected. In the cold trap about 2.3 ml. of ethylene sulfide (b.p. 55–56°) was obtained, n_D^{20} 1.4821 (lit.,[14] n_D^{18} 1.4900).

Thermal decomposition of II *at high temperature under reduced pressure.* Into a preheated flask at 270° and 130–135 mm. was added II (12.4 g., 0.1 mole) dropwise. The products were distilled into three receivers successively. The first receiver (room temperature) contained yellowish brown crystals (sulfur) with m.p. 113–115° together with unchanged II as pale yellow liquid of b.p. 62–62.5° (0.9 mm.) with n_D^{20} 1.5785. The second receiver (ice bath temperature) contained a small amount of water (b.p. 99.5°, n_D^{20} 1.3386) and a pale yellow, rubbery substance. The last receiver (Dry Ice–acetone bath temperature) contained sulfur dioxide (liquid), water, and more pale yellow, rubbery, soft mass. A carbonized residue remained in the flask.

Bromination of II. *A. With bromine.* A dry carbon tetrachloride solution (100 ml.) of II (12.4 g., 0.1 mole) was cooled to −5°. Bromine (16 g., 0.1 mole) in 20 ml. of dry carbon tetrachloride was added while the temperature was kept below 0°. After the reaction mixture was stirred at room temperature for 5 hr., the solvent and volatile materials were removed. Distillation of the residue yielded 4.5 g. (64.3%) of bis(2-bromoethyl) disulfide (XV) at b.p. 103–106° (0.5–0.55 mm.) with n_D^{18} 1.6190; λ_{max} 3.35, 6.95, 7.05, 7.15 (sh), 8.00, 8.42, 9.12, 11.98–12.08 (b), 12.90, 13.50, 14.30 μ.

Anal. Calcd. for $C_4H_8Br_2S_2$: C, 17.15; H, 2.88; Br, 57.18; S, 22.90. Found: C, 17.12; H, 2.81; Br, 57.08; S, 22.80.

B. With N-bromosuccinimide. N-Bromosuccinimide (17.8 g., 0.1 mole) was added in portions to II (12.4 g., 0.1 mole) in 100 ml. of dry carbon tetrachloride at 15–20°. The reaction mixture was heated cautiously until initial vigorous reaction started (32–37°), then cooled rapidly and maintained at 25–30° for 6 hr. After standing overnight, the solid and liquid were separated. The solid was recrystallized from ethanol to give 8 g. of *N*-(2-bromoethylthio)succinimide (XVI) with m.p. 89–90.5; λ_{max} (Nujol) 3.42, 5.78, 7.05, 7.70, 8.05, 8.33, 8.80, 9.00 (sh), 9.93 (w), 12.28, 14.50 (w), 15.40 μ.

Anal. Calcd. for $C_6H_8BrNO_2S$: C, 30.25; H, 3.39; N, 5.88. Found: C, 30.78; H, 3.60; N, 5.87.

The liquid was evaporated to remove solvent and volatile materials. A small amount of yellow liquid of XV was obtained at b.p. 122–124° (0.9–1.0 mm.). The infrared spectrum of this sample was identical to that prepared by the previous method.

Chlorination of II. *A. With chlorine.* A 28.3-g. sample (0.228 mole) of II containing benzoyl peroxide (0.1 g.) was cooled to −5° and saturated with chlorine until the gain of weight reached 7.6 g. After stirring at 0° for 3 hr. and then at room temperature overnight, the orange-yellow liquid was distilled. Bis (2-chloroethyl) disulfide[11] (XIV) was obtained at b.p. 96–98° (1.1–1.2 mm.) with n_D^{25} 1.5644 in 63% yield; λ_{max} 3.35, 6.92, 7.05, 7.13 (triple), 7.75, 7.90 (Spl.), 8.30, 8.92, 9.60, 10.85, 11.72, 13.65–13.75 (b), 14.50–14.60 (b), 15.10 μ.

Anal. Calcd. for $C_4H_8Cl_2S_2$: C, 25.13; H, 4.22; Cl, 37.10; S, 33.55. Found: C, 24.68; H, 4.16; Cl, 37.11; S, 33.65.

B. With N-chlorosuccinimide. II (12.4 g., 0.1 mole) and *N*-chlorosuccinimide (13.4 g., 0.1 mole) in 100 ml. of carbon tetrachloride were refluxed gently for 8 hr. The soft mass settled and was recrystallized to give white crystals, m.p. 122–124°. It did not change the melting point of an authentic sample of succinimide.

The carbon tetrachloride solution was concentrated *in vacuo*, and the residue was distilled. After the forerun of II (2–3 g.) at 60–68° (0.4–0.6 mm.), about 1.5 g. of XIV was collected at b.p. 80–87° (0.8 mm.) with some decomposition, n_D^{20} 1.5634.

Bromination of X. X was treated with bromine in carbon tetrachloride according to the procedure described previously for II. Bis(2-bromo-*n*-propyl) disulfide was obtained as a yellow oil at b.p. 113–114° (0.8 mm. with n_D^{22} 1.5805, λ_{max} 3.37, 3.42 (spl.), 6.90, 7.00 (sh), 7.10 (sh), 7.28, 8.08, 8.20 (sh), 8.62, 9.58, 10.00, 11.18, 11.85, 12.05, 13.80, 14.65, 15.05 μ.

Anal. Calcd. for $C_6H_{12}Br_2S_2$: C, 23.39; H, 3.93; Br, 51.87; S, 20.81. Found: C, 23.69; H, 3.91; Br, 52.00; S, 20.79.

Acknowledgment. Acknowledgment is due to Dr. B. D. Halpern for his helpful interest in this project.

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