Anal. Calcd. for $C_8H_{19}ClN_2O_4$: C, 39.59; H, 7.89; N, 11.54. Found: C, 39.38; H, 7.97; N, 11.31.

2-(2-Diethylaminoethylamino)methyl-2-nitro-1,3-propanediol (V. R″ = H, R‴ = $CH_2CH_2N(C_2H_5)_2$) *dihydrochloride.* The preceding procedure was applied to 10 g. of II [R and R′ = —$(CH_2)_5$—, R″ = H, R‴ = $CH_2CH_2N(C_2H_5)_2$]. Yield, 6.6 g. (67%); m.p. 146–147°, after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{10}H_{25}Cl_2N_3O_4$: C, 37.27; H, 7.82; N, 13.04. Found: C, 37.43; H, 7.67, N, 12.95.

4-Diethylaminomethyl-4-hydroxymethyloxazolidone-2 (VI. X = O). A mixture of 3.5 g. of IV, 10 ml. of dry ethyl carbonate, and 0.01 g. of sodium methoxide was stirred and heated at 120° for 0.5 hr., while ethanol was removed by distillation through a short column. The excess ethyl carbonate was removed *in vacuo* and the residue was distilled: b.p. 205–210°/0.08 mm.; yield, 2.4 g. (54%); m.p. 51–54°, after recrystallization from pentane.

Anal. Calcd. for $C_9H_{18}N_2O_3$: C, 53.44; H, 8.97; N, 13.85. Found: C, 53.68; H, 8.80; N, 13.75.

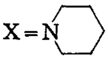
4-Diethylaminomethyl-4-hydroxymethyloxazolidine-2-thione (VI. X = S). In accordance with the procedure of Skulski *et al.*[13] there was added dropwise 7.1 g. of carbon disulfide and 10 ml. of ethanol to a stirred and cooled solution of 17.6 g. of IV in 75 ml. of ethanol. During the addition the temperature was maintained at 2–5°. The reaction mixture was refluxed for 16 hr., another portion of 3.5 g. of carbon disulfide was added, and refluxing was continued for 10 hr. The excess ethanol was evaporated and the residue was recrystallized from ether: m.p. 93–94°; yield, 19 g. (87%).

Anal. Calcd. for $C_9H_{18}N_2O_2S$: C, 49.52; H, 8.31; N, 12.84. Found: C, 49.80; H, 8.30; N, 12.72.

4,4-Bis(chloromethyl)oxazolidone-2 (VII. X = Cl). To a cooled and stirred solution of 14.7 g. of 4,4-bis(hydroxymethyl)oxazolidone-2[6] in 17 ml. of dry pyridine was added dropwise 24 g. of thionyl chloride. The mixture was stirred at room temperature for 48 hr. The solid mass was washed well with water, dried, and recrystallized from chloroform: m.p. 156–157°; yield, 11 g. (60%).

Anal. Calcd. for $C_5H_7Cl_2NO_2$: C, 32.63; H, 3.83; N, 7.61; Cl, 38.53; mol. wt., 184. Found: C, 32.88; H, 3.80; N, 7.69; Cl, 38.21; mol. wt., 182.

4,4-Bis(piperidinomethyl)oxazolidone-2

(VII. X= ).

A solution of 20 g. of VII (X = Cl) and 100 ml. of piperidine was heated on a steam bath for 24 hr. The semisolid reaction product was acidified with 3*N* hydrochloric acid and the insoluble portion was filtered off. The filtrate was made basic with 10% potassium hydroxide and extracted with 100 ml. of ether. The extract was dried and diluted with three volumes of pentane. The solid was collected by filtration and recrystallized from 50% ethanol; m.p. 180–181°; yield, 17.4 g. (58%).

Anal. Calcd. for $C_{15}H_{27}N_3O_2$: C, 64.02; H, 9.67; N, 14.93. Found: C, 64.10; H, 9.44; N, 14.85.

2,2-Dimethyl-5-p-aminobenzyl-5-nitro-m-dioxane (VIII. R = NO_2, R′ = NH_2). A suspension of 3 g. of 2,2-dimethyl-5-*p*-nitrobenzyl-5-nitro-*m*-dioxane[7] (VIII, R = R′ = NO_2), 0.5 g. of 5% palladium on charcoal catalyst, and 100 ml. of 95% ethanol was subjected to hydrogenation at an initial pressure of 60 lb. After completed hydrogen consumption the catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was triturated with ether and the ether-insoluble portion was recrystallized from ethanol; m.p. 195–196°; yield, 1.8 g. (67%).

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.70; H, 6.77; N, 10.54. Found: C, 58.72; H, 6.97; N, 10.30.

2,2-Dimethyl-5-amino-5-p-aminobenzyl-m-dioxane (VIII. R = R′ = NH_2). A suspension consisting of 41 g. of VIII (R = R′ = NO_2), 300 ml. of ethanol, and 10 g. of Raney nickel catalyst[12] was subjected to hydrogenation at an initial pressure of 1700 lb. and at a temperature of 180°. After completed reaction the catalyst was filtered off and the solvent evaporated. The residue was recrystallized from hexane; m.p. 96–97°; yield, 24 g. (74%).

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.17; H, 8.52; N, 11.62.

2,2-Dimethyl-5-hydroxymethyl-5-ureido-m-dioxane (IX). A solution of 5 g. of 2,2-dimethyl-5-amino-5-hydroxymethyl-*m*-dioxane,[8] 3.3 g. of nitrourea, 30 ml. of ethanol, and 60 ml. of water was heated and stirred at 70° for 1 hr. The volume was reduced by evaporation to 10 ml. and the solid was allowed to crystallize. Yield, 4.6 g. (73%), m.p. 173–174° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.90; N, 13.72. Found: C, 47.07; H, 7.90; N, 13.55.

8,8-Dimethyl-1-aza-3,7,9-trioxaspiro[4.5]decanone-2 (X. R = R′ = CH_3). A mixture consisting of 5 g. of 2,2-dimethyl-5-amino-5-hydroxymethyl-*m*-dioxane[8] and 30 ml. of ethyl carbonate was heated at 120° while the ethanol formed in the reaction was allowed to distil slowly through a 1-ft. Vigreux column. The excess ethyl carbonate was removed *in vacuo* and the residue was recrystallized from ethyl acetate; m.p. 164–165°, yield, 3.6 g. (62%).

Anal. Calcd. for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.47. Found: C, 51.45; H, 7.03; N, 7.42.

1-Aza-3,7,14-trioxadispiro[4.2.5.2]pentadecanone-2 [X. R and R′ = —$(CH_2)_5$—]. A suspension of 14.7 g. of 4,4-bis(hydroxymethyl)oxazolidone-2[6] and 35 ml. of cyclohexanone was heated and stirred on a steam bath for 15 min. The mixture was cooled to 20° and 13 ml. of boron trifluoride etherate was added to the manually stirred paste. The temperature rose to 50° and the reaction mixture was allowed to stand for 0.5 hr. The solid mass was poured onto 120 ml. of saturated bicarbonate and the paste was stirred for 1 hr. The solid was filtered, washed with water and dried. Yield, 21 g. (92%), m.p. 201–202° after recrystallization from acetone.

Anal. Calcd. for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6 16. Found: C, 58.35; H, 7.72; N, 6.35.

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Chloroethylation of Sulfuric Acid

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The formation of bis(2-chloroethyl)sulfate by the simultaneous addition of chlorine and ethylene to sulfuric acid has been reported by Titov and Maklyaev.[1,2] In connection with another problem in this laboratory, we found it desirable to study the factors affecting the yield of bis (2-chloroethyl) sulfate from this reaction.

$$CH_2{=}CH_2 + Cl_2 + H_2SO_4 \longrightarrow ClCH_2CH_2OSO_3H + HCl$$

$$CH_2{=}CH_2 + Cl_2 + ClCH_2CH_2OSO_3H \longrightarrow (ClCH_2CH_2)_2SO_4 + HCl$$

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(13) M. Skulski, D. L. Garmaise, and A. F. McKay, *Can. J. Chem.*, **34**, 815 (1956).

(1) A. I. Titov and F. L. Maklyaev, *Doklady Akad. Nauk S.S.S.R.*, **98**, No. 5, 795–8 (1954).

(2) A. I. Titov and F. L. Maklyaev, *Zhur. Obshchei Khim.*, **24**, 1631–5 (1954).

Chlorine and ethylene were added to 98% sulfuric acid at equal and constant rates at room temperature and atmospheric pressure to form bis(2-chloroethyl)sulfate, 2-chloroethyl hydrogen sulfate, and ethylene dichloride. The formation of ethylene dichloride was the major side reaction. When small amounts of sulfuric acid were converted, the yield of ethylene dichloride, based on chlorine and ethylene consumed, was low. However, when the reaction mixture was mostly 2-chloroethyl hydrogen sulfate and bis(2-chloroethyl)sulfate, the yield of ethylene dichloride was very high.

There were no by-products detected from the reaction other than ethylene dichloride, except when ethylene was added to the sulfuric acid at a much greater rate than chlorine. In this latter case, diethyl sulfate was detected as a product.

Addition of ethylene and chlorine at equal rates, but at a rate faster than they could react with the sulfuric acid, resulted in the formation of ethylene dichloride.

Conversion of 50.5% of the sulfuric acid under appropriate conditions resulted in the formation of 2-chloroethyl hydrogen sulfate (43.4% yield), bis-(2-chloroethyl)sulfate (39.2% yield), and ethylene dichloride (8.2% yield). Bis(2-chloroethyl)sulfate may be extracted from the sulfuric acid reaction mixture with benzene, more sulfuric acid added to the reaction mixture, and this treated again with ethylene and chlorine. In this manner the 2-chloroethyl hydrogen sulfate formed may be ultimately converted to bis(2-chloroethyl)sulfate without major losses of ethylene and chlorine due to ethylene dichloride formation.

EXPERIMENTAL

Effect of sulfuric acid conversion on formation of bis(chloroethyl)sulfate and ethylene dichloride. Sulfuric acid (140 ml., 98%) was placed in a cylindrical glass tube fitted near the bottom with fritted glass disks. The exit tube from this reactor was passed through two Dry Ice traps to collect chlorine, ethylene dichloride, and other condensable gases and then through two traps containing 20% sodium hydroxide solution to collect hydrogen chloride. Chlorine and ethylene were passed into the acid at approximately the same rate and at a constant rate. Every hour the ethylene and chlorine flow were interrupted and nitrogen passed through the mixture to displace hydrogen chloride. The total volume of the reaction mixture was measured, and 20 ml. was removed and analyzed for bis(2-chloroethyl)sulfate and ethylene dichloride. The flow of ethylene and chlorine was then continued and the above procedure repeated. After 11 hr., the concentration of water soluble materials in the reaction mixture was 8% by volume. The change in composition of the reaction mixture with time is shown in Figure 1.

The samples from the above experiment were analyzed by dissolving the sulfuric acid sample in ice water, extracting the aqueous solution immediately with carbon tetrachloride, drying the organic layer over anhydrous magnesium sulfate, and determining the bis(2-chloroethyl)sulfate and ethylene dichloride present from an infrared spectrum taken on the carbon tetrachloride solution. From standard solutions, it was found these components could be determined with a reproducibility of ± 5% of the amount present.

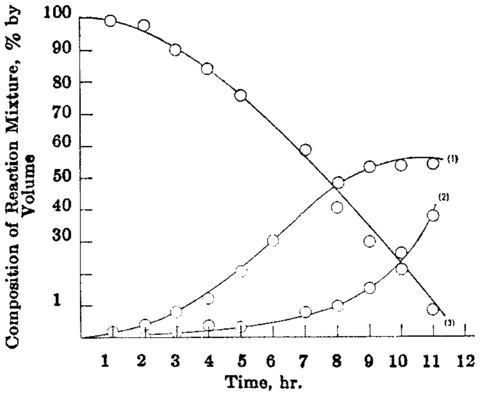

Fig. 1. Effect of sulfuric acid conversion on rate of formation of ethylene dichloride. (1) Bis(2-chloroethyl) sulfate. (2) Ethylene Dichloride. (3) Water-soluble material, 2-chloroethyl hydrogen sulfate and sulfuric acid

Effect of flow rate of ethylene and chlorine on formation of ethylene dichloride. Qualitative experiments indicated that at past flow rates of ethylene and chlorine through the sulfuric acid, the decrease in yield of chloroethylated product due to ethylene dichloride formation would be great.

In the same apparatus as described above was placed 145 ml. of 98% sulfuric acid. Ethylene and chlorine were admitted simultaneously at a rate of 0.98 mole per hour for 1 hr. From the cold trap there was obtained 54.6 g. of ethylene dichloride. A separate liquid layer of 3.8 g. of ethylene dichloride remained in the reaction tube. A total of 58.4 g. (0.592 mole) of ethylene dichloride was obtained which represents a yield of 60.5% based on the ethylene and chlorine consumed.

In a similar experiment in which ethylene and chlorine were admitted at a rate of 0.5 mole per hour for 1 hr., the yield of ethylene dichloride was 8.8%.

Preparation of bis(2-chloroethyl)sulfate. In the apparatus previously described was placed 166.8 g. of 98% sulfuric acid. Chlorine was passed into the acid at a rate of 19.2 g. per hour and ethylene simultaneously at a rate of 8.02 g. per hour. After 4 hr. chlorine and ethylene were discontinued and nitrogen was passed through the mixture for 30 min. Chlorine (7.0 g.) and ethylene dichloride (8.0 g.) were collected in the Dry Ice trap. There was obtained 0.822 mole of hydrochloric acid in the traps containing sodium hydroxide solution.

The reaction mixture (211.8 g.) was diluted with ice and water. The bis(2-chloroethyl)sulfate which separated was taken up in benzene (50 ml.) and the aqueous portion extracted with three 50-ml. portions of benzene. The combined benzene fractions were washed with 50 ml. of water and the water washing added to the original aqueous portion. The benzene layer was dried over anhydrous magnesium sulfate, the benzene removed under vacuum and the bis(2-chloroethyl)sulfate isolated by distillation under vacuum. There was obtained 43.2 g. (0.193 mole, 39.2% yield) of bis(2-chloroethyl)sulfate.

A 10.0-ml. aliquot of the aqueous portion (450 ml.) obtained from the above procedure was analyzed for chloride ion by the Volhard method. The original solution was found to contain less than 0.001 mole of chloride ion.

A 10.0-ml. aliquot of the aqueous portion above was added to 20 ml. of 20% sodium hydroxide solution and heated at reflux temperature for 20 min. From Volhard analysis of this sample, it was found that the original solution contained 0.442 mole of chloride ion which would result on hydrolysis with base.

A portion of this solution (385 ml.) was refluxed for 24 hr. and then distilled on an efficient column. There was obtained 83.9 g. of a water solution which was 35.0% ethylene chlorohydrin. It was assumed that ethylene chlorohydrin was obtained by hydrolysis of 2-chloroethyl hydrogen sulfate.

Thus the original solution was found to contain 0.427 mole of 2-chloroethyl hydrogen sulfate. This corresponds to a 43.4% yield of 2-chloroethyl hydrogen sulfate.

The above yields of bis(2-chloroethyl)sulfate and 2-chloroethyl hydrogen sulfate are calculated on the basis of consumed chlorine.

Preparation of bis(2-chloroethyl)sulfate. In the apparatus previously described was placed 170.2 g. of 98% sulfuric acid. Chlorine was passed into the acid at a rate of 19.2 g. per hour and ethylene simultaneously at a rate of 8.02 g. per hour. After 4 hr. chlorine and ethylene were discontinued and nitrogen passed through the mixture for 30 min. Chlorine (2.7 g.) and ethylene dichloride (5.5 g.) were collected in the cold trap.

The reaction mixture (245.4 g.) was extracted once with 108 ml. of benzene. The benzene layer was washed with distilled water to remove 2-chloroethyl hydrogen sulfate, dried over anhydrous magnesium sulfate, the benzene removed under vacuum and the bis(2-chloroethyl)sulfate isolated by distillation under vacuum. In this manner 25.6 g. (0.115 mole, 22.0% yield) of bis(2-chloroethyl)sulfate was obtained.

The sulfuric acid layer from the above extraction was found to contain 13.3 g. (0.0595 mole, 11.4% yield) of bis-(2-chloroethyl)sulfate and 51.8 g. (0.354 mole, 33.9% yield) of 2-chloroethyl hydrogen sulfate.

The above yields of bis(2-chloroethyl)sulfate and 2-chloroethyl hydrogen sulfate are calculated on the basis of consumed chlorine.

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The Camphenilanic and Camphenanic Acids

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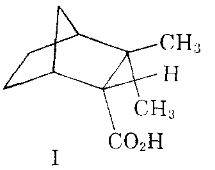
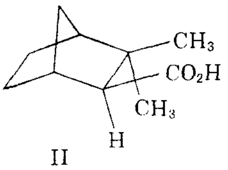
The relationship of camphenilanic acid, m.p. 65°, isocamphenilanic acid, m.p. 118°, camphenanic acid, m.p. 95°, and isocamphenanic acid, m.p. 74°, has remained obscure for many years.[1] Alder,[2] however, has recently demonstrated that pure camphenilanic acid (I) melts at 92°[3] and has suggested that the camphenilanic acid, m.p. 65°, obtained by earlier investigators was a mixture of I and isocamphenilanic acid (II).[4] An obvious corollary to these observations, which we have now verified, is that camphenanic acid is pure I while isocamphenanic acid is a mixture of I and II.



I



II

The oxidation of camphene with potassium permanganate in glacial acetic acid[5] afforded, in 9–15% yield, a mixture of camphenanic acids which on fractional recrystallization gave a camphenanic acid, m.p. 91–92°, whose properties correspond exactly with those cited for pure I.[2] The homogeneity of this acid was confirmed by elution chromatography and by its smooth conversion with lithium aluminum hydride to *endo*-isocamphanol, m.p. 83–84°.[2,6]

Chromatography of the solid found in the mother liquors after removal of camphenanic acid demonstrated it was a mixture of I and II.

The neutral fraction from the permanganate oxidation of camphene was composed of camphenilone, isolated in 20–35% yield, and small amounts of higher boiling unidentified carbonyl compounds. It should be noted that the R-homocamphenilones[7] were not detected among these products.

EXPERIMENTAL

The potassium permanganate oxidation of Camphene. A mixture of 100 g. (0.74 mole) of camphene, 145 g. (0.92 mole) of potassium permanganate, and 350 ml. of acetic acid was stirred at 0° for 4 hr., kept at room temperature overnight and then heated on a steam bath for 4 hr. The mixture was steam distilled and the distillate was extracted with ether. The ether solution was extracted with aqueous sodium carbonate, dried, and distilled affording *ca.* 40 g. of camphenilone, contaminated by appreciable amounts of camphene and tricyclene, b.p. 72–90°/*ca.* 15 mm., m.p. 39.5–41°[8]; and *ca.* 1.0 g. of a liquid b.p. 95–102°/15 mm. Chromatography of the 2,4-dinitrophenylhydrazone derivatives derived from the higher boiling fraction demonstrated the presence of camphenilone and at least three other unidentified carbonyl compounds.

The sodium carbonate extract mentioned above was acidified affording 15 g. of a crystalline mixture of the camphenanic acids. A portion of this mixture was recrystallized five times from petroleum ether affording *camphenanic acid,* m.p. 87–89° (reported,[5] m.p. 87–91°). The melting point of this acid was raised to 91–92.5° by chromatography on silica gel and recrystallization from methanol. Further chromatography or recrystallization from methanol, petroleum ether, or water failed to alter this melting point.

Lithium aluminum hydride reduction of camphenanic acid afforded a solid which on sublimation *in vacuo* afforded *endo*-isocamphanol, m.p. 83–84° (reported,[6] m.p. 83°).

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(1) For a historical review of these $C_{10}H_{16}O_2$ acids derived from camphene see J. L. Simonsen, *The Terpenes,* University Press, Cambridge, 1949, p. 294.

(2) K. Alder and W. Roth, *Ber.,* **90,** 1830 (1957).

(3) W. Hückel and H. Rohrer, *Ber.,* **91,** 198 (1958), claimed to have isolated pure I, m.p. 55–56°, for the first time. The homogeneity of this acid was not rigorously established, nor was a satisfactory explanation offered for the acid melting *ca.* 40° lower than that described by Alder.[2] Hückel's acid was probably a mixture of I and II.

(4) Henderson [*J. Chem. Soc.,* **99,** 1887 (1911)] found that recrystallization of camphenilanic acid, m.p. 65°, from petroleum-ether afforded a solid, m.p. 86°, and therefore postulated that I had rearranged to II. It seems more reasonable to conclude that Henderson had isolated relatively pure I; I certainly does not isomerize to II on recrystallization from petroleum-ether.

(5) O. Aschan, *Chem. Abstr.,* **6,** 3414 (1912).

(6) W. Huckel and H. Schultz, *Ann.,* **575,** 32 (1952).

(7) J. Wolinsky, *J. Org. Chem.,* **26,** 704 (1961).

(8) Camphene apparently does not depress the melting point of camphenilone.