out success. A reaction did occur when the solvent was ethylene glycol. The product, however, was β-hydroxyethyl 4-trifluoromethylsalicylate, formed possibly by a transesterification mechanism as indicated later.

Experimental

Silver 4-Trifluoromethylsalicylate.—4-Trifluoromethylsalicylic acid[1] was neutralized with aqueous ammonia, and allowed to react with silver nitrate solution to give a quantitative yield of silver 4-trifluoromethylsalicylate.

Anal. Calcd. for $C_8H_4O_3F_3Ag$: Ag, 34.47. Found: Ag, 34.27.

4-Trifluoromethylsalicylamide.—Ten grams of methyl 4-trifluoromethylsalicylate,[1] b.p. 97° (10 mm.), was introduced slowly into a three-necked flask containing 100 g. of concentrated ammonia and 0.4 g. of powdered aluminum[6] and heated with stirring at 70° for 2.5 hours. Upon neutralization with a slight excess of concentrated hydrochloric acid, 9 g. (97%) of crude 4-trifluoromethylsalicylamide (m.p. 140–144°) was isolated. The solid was washed with dilute sodium bicarbonate to remove possible traces of organic acid. The precipitate was then redissolved in dilute sodium hydroxide and reprecipitated upon acidification. Upon decolorization with charcoal and repeated crystallization from aqueous alcohol, slightly pink needles of m.p. 149–151° were obtained.

Anal.[7] Calcd. for $C_8H_6O_2NF_3$: C, 46.84; H, 2.95; N, 6.83. Found: C, 47.04; H, 2.93; N, 6.58.

4-Trifluoromethylsalicylanilide.—A mixture of 10.3 g. of I, 5.12 g. of aniline and 15 cc. of dimethylaniline was heated at 100° until the acid dissolved, and 5 cc. of phosphorus trichloride was added dropwise with stirring during ten minutes. The mixture was heated at 100–105° for an additional half-hour and then poured (while hot) into a warm solution of 50 ml. of concentrated hydrochloric acid and 200 ml. of water with vigorous stirring. The crude solid (10 g., 71%) was washed with bicarbonate, dissolved in alkali and reprecipitated with acid. After several recrystallizations from 50% aqueous alcohol (and decolorization with charcoal) pure 4-trifluoromethylsalicylanilide, m.p. 189–190° (white powder), was obtained.

Anal. Calcd. for $C_{14}H_{10}O_2NF_3$: C, 59.79; H, 3.58; N, 4.98. Found: C, 59.69; H, 3.72; N, 4.94.

4-Trifluoromethylsalicylic Acid Hydrazide.—Eleven grams of methyl 4-trifluoromethylsalicylate was added dropwise to a refluxing solution of 3 ml. of 85% hydrazine hydrate and 10 ml. of absolute ethanol. After the addition of water, there was found 10.5 g. of crude material consisting of the desired hydrazide and a product melting at *ca.* 325° which is believed to be di-(4-trifluoromethylsalicylic acid) hydrazide. After several recrystallizations from ethanol, there was isolated 3.5 g. of white, crystalline, 4-trifluoromethylsalicylic acid hydrazide, m.p. 170.5–171.5°.

Anal. Calcd. for $C_8H_7O_2N_2F_3$: C, 43.64; H, 3.21; N, 12.73. Found: C, 43.93; H, 3.36; N, 12.74.

The pure hydrazide which melted to a clear colorless liquid at 171°, upon continued heating formed a new solid at 180–181° with liberation of a gas, which finally melted, with some decomposition, at 319–321°. This is thought to be due to diacyl hydrazide formation.

4-Trifluoromethylsalicylhydroxamic Acid.—Ten grams of methyl 4-trifluoromethylsalicylate was added with stirring to a mixture of 6.95 g. of hydroxylamine hydrochloride, 11.8 g. of potassium hydroxide, 160 ml. of water and 100 ml. of ethanol. The reaction mixture was allowed to stand at room temperature for one day. After addition of hydrochloric acid and recrystallization from ethanol, 8.5 g. of pale pink, almost white, 4-trifluoromethylsalicylhydroxamic acid, m.p. 185.5–186.0°, was obtained.

Anal. Calcd. for $C_8H_6O_3NF_3$: C, 43.45; H, 2.74; N, 6.34. Found: C, 43.74; H, 2.70; N, 6.45.

4-Trifluoromethyl-2-hydroxybenzyl Alcohol.—4-Trifluoromethylsalicylic acid (41.2 g.), dissolved in 150 ml. of ethyl ether was added drop by drop to 7.6 g. of lithium aluminum hydride in 200 ml. of anhydrous ethyl ether over a period of 4 hours.[8] The reaction mixture was worked up in the usual manner. 4-Trifluoromethyl-2-hydroxybenzyl alcohol (36 g., 94%) was isolated. After recrystallization from benzene the white solid, which gave a wine-red ferric chloride reaction, melted at 66–66.5°.

Anal. Calcd. for $C_8H_7O_2F_3$: C, 50.01; H, 3.67. Found: C, 49.92; H, 3.73.

4-Trifluoromethyl-2-hydroxybenzyl alcohol (1.92 g.), *n*-perfluorobutyric acid (2.35 g.) and benzene (20 ml.) were refluxed together for 6 hours. Upon washing the reaction mixture with sodium bicarbonate solution, essentially all of the perfluorobutyric acid was recovered as the sodium salt. After all of the benzene was distilled out of the previously dried organic layer, the product was heated *in vacuo* to 250°. The residue consisted of *ca.* 1 g. of a fluorine-containing resin, m.p. *ca.* 85°, probably resulting from the self-condensation of the 4-trifluoromethyl "saliginen."[9]

Attempted Reaction of I with 1,1-Di-H-perfluoroethanol.—1,1-Di-H-perfluoroethanol (4.05 g.), I (8.7 g.) and 2 ml. of fuming sulfuric acid were refluxed in benzene for 8 hours. Upon washing the mixture with dilute sodium bicarbonate, almost all of I was recovered as the sodium salt, indicating that no reaction occurred.

The Reaction of I with 1,1-Di-H-perfluoroethyl *p*-Toluenesulfonate.—A mixture of 10.3 g. of I, 4.3 g. of sodium bicarbonate in 43 ml. of water and 12.45 g. of 1,1-di-H-perfluoroethyl *p*-toluenesulfonate was refluxed for 8 hours with vigorous stirring. No reaction occurred.

The following modification was then tried. Sodium 4-trifluoromethylsalicylate was prepared by dissolving I in 10% sodium carbonate solution, cooling in ice, and collecting the salt formed. To 7.5 g. of this salt, 8.12 g. of the tosyl ester and 34 ml. of ethylene glycol were added. The mixture was refluxed for six hours. The bottom layer solidified on cooling and the crude product weighed 7.6 g. Upon recrystallization from heptane, a white solid melting at 55.5–57° was obtained. This ester is hydrolyzed easily in cold 10% sodium hydroxide solution to give sodium 4-trifluoromethylsalicylate. Elemental analysis indicated that the ester was not the expected 1,1-di-H-perfluoroethyl 4-trifluoromethylsalicylate, but was rather β-hydroxyethyl 4-trifluoromethylsalicylate.

Anal. Calcd. for $C_{10}H_9O_4F_3$: C, 48.01; H, 3.63. Found: C, 48.35, 48.40; H, 3.66, 3.96.

Since essentially none of the original tosyl ester was recovered, it is possible that the trifluoroethyl ester was indeed first formed but that at the temperature of boiling glycol transesterification occurred. A large excess of glycol and the low boiling point of trifluoroethanol (74°) would displace the equilibrium to the right.

Several other attempts to prepare 1,1-di-H-perfluoroethyl 4-trifluoromethylsalicylate utilizing as solvents Diethyl Carbitol, Dibutoxy Tetraglycol and N-dimethylformamide, failed.

Acknowledgment.—The financial support of the Research Corporation is gratefully acknowledged.

(6) M. Maeda, *et al.*, Japan Patent 5365 (Dec. 17, 1952).

(7) Microanalyses by Clark Microanalytical Laboratory.

(8) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 2548 (1947), prepared *o*-hydroxybenzyl alcohol, similarly, in 99% yield.

(9) For a discussion of the condensation polymerization of *o*-hydroxybenzyl alcohol, see M. M. Sprung and M. T. Gladstone, THIS JOURNAL, **71**, 2907 (1949).

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Direction of Addition of the Nitrate Ion to an Unsymmetrical Oxide[1]

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In a previous publication[3] the nitrate ion was

(1) This paper presents the results of one phase of research carried out at the Jet Propulsion Laboratory, California Institute of Technology, under Contract No. DA-04-495-Ord 18, sponsored by the Department of the Army, Ordnance Corps.

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(3) P. L. Nichols, Jr., A. B. Magnusson and J. D. Ingham, THIS JOURNAL, **75**, 4255 (1953).

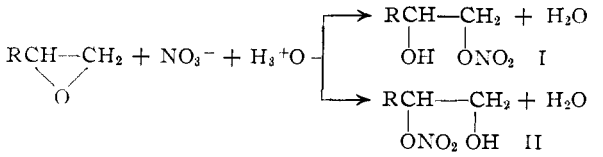
TABLE I

DIRECTION OF OPENING OF GLYCIDOL

Components of reaction mixt. (wt. %)[a]	Nitrogen or chlorine, % Calcd.	Found	Refractive index $n^{20}D$ Lit.	Found	Yield, %	Primary ether or ester in prod., %
HNO_3 (13.2), dioxane (51.1)	10.21	10.19	1.4698	1.4684	51[b]	95
HNO_3 (11.9), 2,2,4-trimethylpentane (72.6)	10.21	9.92	1.4698	1.4631	53[b]	81
HNO_3 (5.2), water (30.3),[c] NH_4NO_3 (60.5)	10.21	10.25	1.4698	1.4694	68	67
HNO_3 (25.4), water (13.7),[c] NH_4NO_3 (40.5)	10.21	10.15	1.4698	1.4667	77	60
HCl (6.6), water (58.5),[d] NaCl (27.0)	32.50	31.56	1.4811[e]	1.4800	66	88
H_2SO_4 (1.1), ethanol (84.0)	...	...	1.441	1.4413	66	78
Ethanol (86.3)	...	...	1.441	1.4410	73	100

[a] The glycidol used brings the total to 100% in each instance. [b] An appreciable quantity of viscous polymer remained after distillation of the ester. [c] The acid and sufficient ammonium nitrate to saturate the solution were dissolved in water; glycidol was then added, maintaining the temperature at 35–40°. [d] This run was carried out as in ref. *c*. [e] At 25°.

added under acidic conditions to several unsymmetrical oxides as shown in the equation



A preliminary determination of the relative amounts of primary nitric ester I and of secondary nitric ester II was made using the benzoylation rate technique.[4] The results indicated that reaction of the nitrate ion in both acidic aqueous solutions of high salt concentrations and chloroform solutions of nitric acid produced predominantly I with epichlorohydrin, allyl glycidyl ether, methoxy glycidyl ether and methoxyethoxy glycidyl ether. Results with propylene oxide in the chloroform solution of nitric acid indicated that a mixture of the two isomeric products was obtained.

Since the benzoylation method gave only a rough indication of the relative amounts of the two isomers, a more thorough investigation seemed desirable. Glycidol was chosen for study since the relative amounts of isomers could be determined by vicinal hydroxyl determination.[5] The reaction was conducted in several acidic media. Basic media were not included in the investigation because it was likely that the primary ester I would be obtained under such conditions.[6] The results are shown in Table I. Data on chloride ion and methoxide ion additions were obtained for comparison, and the results obtained conformed with those in the literature about the addition of methoxide and chloride ions to epoxides.[7] The results agree qualitatively with those obtained by the benzoylation rate method on products derived under similar conditions. The most significant observation arising from this study is the difference in relative amounts of primary nitric ester produced in water and dioxane solutions. Dioxane solutions yield relatively pure primary nitric ester, whereas a water solution allows the formation of appreciable quantities of secondary ester. The reason for this difference is probably partly the fact that reaction in the solvent of high dielectric constant (water) favors appreciable contribution of the carbonium ion mechanism.[8] When the reaction was conducted in 2,2,4-trimethylpentane the 90% nitric acid employed was not completely miscible and accordingly a considerable portion of the reaction occurred in the acid phase. It is not surprising therefore that the specificity in formation of primary nitric ester was not as complete in this case as in dioxane.

Experimental

Materials.—Glycidol was prepared by the treatment of 3-chloro-1,2-propanediol with alcoholic potassium hydroxide solution.[8] The yields were 50 to 60%, and the distilled product generally analyzed 95 to 98% of the calculated epoxide value.

1,2-Epoxy-3-nitratopropane was obtained from the reaction of silver nitrate and epiiodohydrin or epibromohydrin in acetonitrile.[9] The yield was 70 to 72%, and $n^{20}D$ was 1.4360 (lit. 1.4366). Practically pure 3-nitrato-1,2-propanediol was prepared in 51% yield by hydration of glycidyl nitrate[10]; $n^{20}D$ was 1.4682; nitrogen analysis was 10.12% (10.21%, calcd.); and vicinal hydroxyl analysis was 7.40 meq./g. (7.29 meq./g., calcd.).

Reaction of Nitric Acid with Glycidol in the Presence of an Organic Solvent.—The procedure was essentially the same as the non-aqueous solution procedure reported previously[3] except that dioxane or 2,2,4-trimethylpentane was substituted for chloroform. Relative yields of primary and secondary nitrate were estimated from elemental analyses and vicinal hydroxyl determinations.

Reaction of Nitric Acid or Hydrochloric Acid with Glycidol in Aqueous Solution.—The previously reported procedure[3] was employed with appropriate changes in composition of the reaction medium, as shown in Table I. Yields of primary nitrate or chloride were determined from elemental analyses and vicinal hydroxyl determinations and were corrected for theoretical glycerol formation.

Reaction of Ethanol with Glycidol.—A run was carried out in neutral solution under mild conditions by heating glycidol with a nine-molar excess of "super-dry" ethanol under reflux for 14 days. For reaction under acidic conditions[7] the procedure of Chitwood and Freure was employed. The yields of 3-methoxy-1,2-propanediol and 2-methoxy-1,3-propanediol were estimated from careful fractionation of the crude reaction mixtures and vicinal hydroxyl determinations.

Analytical Procedures.—Vicinal hydroxyl was determined by the sodium periodate oxidation method of Dal Nogare and Oemler[11] or by gravimetric determination of the formaldehyde derivative of 5,5-dimethyl-1,3-cyclohexanedione after removal of the periodate ion.[12] In some instances results were duplicated by both procedures; however, the

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(7) H. C. Chitwood and B. T. Freure, THIS JOURNAL, **68**, 680 (1946).

(8) T. H. Rider and A. J. Hill, *ibid.*, **52**, 1521 (1930).

(9) A. F. Ferris, K. W. McLean, I. G. Marks and W. D. Emmons, *ibid.*, **75**, 4078 (1953).

(10) H. Hepworth, *J. Chem. Soc.*, **115**, 842 (1919).

(11) S. Dal Nogare and A. N. Oemler, *Anal. Chem.*, **24**, 902 (1952).

(12) G. Frederick Smith, "Analytical Applications of Periodic Acid and Iodic Acid," G. Frederick Smith Chemical Co., Columbus, Ohio, 1950.

dimedon procedure was applicable only to 1,2-dihydroxy-3-nitratopropane since the α-nitratoacetaldehyde presumbly formed did not yield a derivative with 5,5-dimethyl-1,3-cyclohexanedione as determined by a mixed melting point determination on the formaldehyde derivative. In the oxidation of 3-chloro-1,2-propanediol, the chloroacetaldehyde derivative is not found in quantitative yield under the conditions of test.

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Selective Mercaptole Formation of Steroid Ketones

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The ease of formation and chemical stability of mercaptoles makes these compounds attractive intermediates in multi-stage syntheses. The studies of Hauptmann,[1] of Ruff and Reichstein[2] and of Fieser[3] on the reaction of steroid ketones with ethanedithiol have demonstrated that this dimercaptan will condense with carbonyl functions at the 3-, 6-, 7-, 12-, 17- and 20-positions: the hindered 11-position is the only site of unreactivity. This situation has been used to advantage in selective formation of 7-mercaptoles from 7,11-diones[4] and 12-mercaptoles from 11,12-diones.[5] A higher order of selectivity is required when the competitive reaction is between the 3- and 6-, the 3- and 17-, or the 3- and 20-positions. There has been a recent description of selective reaction at the 3-position in 3,6-diones.[3] A solution to the 3- and 17-positions case is disclosed in the patent literature[6] where the reaction of 4-androstene-3,17-dione with ethanedithiol in the presence of dry hydrogen chloride is said to yield 4-androstene-3,17-dione 3-ethylene mercaptole. No experimental details or physical constants appear in the patent.

We have previously observed[7] that steroid ketones condense with ethanedithiol under very mild conditions, *i.e.*, acetic acid as a solvent and *p*-toluenesulfonic acid as a catalyst. When these conditions were used with di- and tri-ketones, it was found that reaction took place primarily at the 3-position.

Experimental

4-Androstene-3,17-dione 3-Ethylene Mercaptole.—A solution of 1.42 g. (5 mmoles) of 4-androstene-3,17-dione in 20 ml. of acetic acid was treated with 0.471 g. (5 mmoles) of ethanedithiol and a solution of 0.450 g. of *p*-toluenesulfonic acid monohydrate in 5 ml. of acetic acid. After one hour at room temperature, the pale yellow colored solution was poured into water. The resulting suspension was extracted with chloroform. The chloroform solution was washed with water, 5% sodium hydroxide solution and water. After drying over anhydrous sodium sulfate and evaporation of the solvent, there remained 1.93 g. of pale yellow oil. The oil was chromatographed on silica gel. Elution with 1:2 petroleum ether:benzene gave 0.160 g. of solid melting at 173–175°. Crystallization from acetone afforded 0.139 g. of solid, m.p. 174–176°. This compound gave negative color tests for 17-ketone (Zimmermann) and 4-en-3-one (two-stage Rosenheim) and was 4-androstene-3,17-dione 3,17-bis-(ethylene mercaptole).

Anal. Calcd. for $C_{23}H_{34}S_4$ (438.74): C, 62.96; H, 7.81. Found: C, 63.13; H, 7.66.

Elution with 19:1 benzene:ethyl acetate gave 1.38 g. of solid melting at 173–177°. Crystallization from ethyl acetate gave the analytical sample melting at 173–174.5°. The compound gave a positive Zimmermann reaction and showed no 4-en-3-one absorption in the ultraviolet.

Anal. Calcd. for $C_{21}H_{30}OS_2$ (362.57): C, 69.57; H, 8.34; S, 17.68. Found: C, 69.59; H, 8.32; S, 17.83.

Elution with 4:1 benzene:ethyl acetate gave 0.210 g. of starting material which was identified by melting point and mixed melting point.

4-Androstene-3,11,17-trione 3-Ethylene Mercaptole.—A suspension of 0.60 g. (2 mmoles) of 4-androstene-3,11,17-trione in 8 ml. of acetic acid was treated with 0.185 ml. (2.2 mmoles) of ethanedithiol and a solution of 0.180 g. of *p*-toluenesulfonic acid monohydrate in 2 ml. of acetic acid. When the solution was poured into water (after one hour at room temperature), a solid (0.85 g., m.p. 85–158°) separated. Crystallization from methanol–water afforded 0.40 g. of solid melting at 158–167°. Crystallization from ethyl acetate:petroleum ether to constant m.p. gave 0.232 g. melting at 164–165°.

Anal. Calcd. for $C_{21}H_{28}O_2S_2$ (376.55): C, 66.98; H, 7.49. Found: C, 66.80; H, 7.82; $[\alpha]_D$ +205° (1% in acetone); λKBr, 5.75, 5.88, 9.50 μ.

11β-Hydroxy-4-androstene-3,17-dione 3-Ethylene Mercaptole.—The reaction of 3.02 g. (10 mmoles) of 11β-hydroxy-4-androstene-3,17-dione with ethanedithiol (11 mmoles) was conducted as described in the previous preparations. Crystallization of the chloroform soluble products from ethyl acetate gave 1.43 g. of the desired compound melting at 247–249°.

Anal. Calcd. for $C_{21}H_{30}O_2S_2$ (378.57): C, 66.62; H, 7.99; S, 16.94. Found: C, 66.69; H, 7.90; S, 16.60; λ $CHCl_3$, 2.75, 5.78 μ.

Chromatography of the mother liquor material from the above crystallization gave an additional 1.29 g. of the desired product, 0.251 g. of starting material, and 0.127 g. of the **bis-(ethylene mercaptole)** melting at 215–218°.

Anal. Calcd. for $C_{25}H_{34}OS_4$ (454.71): C, 60.75; H, 7.54; S, 28.20. Found: C, 61.19; H, 7.73; S, 27.82; λ $CHCl_3$, 2.78 μ.

4-Pregnene-3,20-dione 3-Ethylene Mercaptole.—A mixture of 7.8 g. (25 mmoles) of progesterone, 125 ml. of acetic acid, 2.3 ml. of ethanedithiol and 2.50 g. of *p*-toluenesulfonic acid monohydrate was kept at room temperature for one hour and then poured into water. Isolation of the products by chloroform extraction gave 10.53 g. of solid melting at 142–174°. Crystallization from 2-propanol gave 5.02 g. of solid, m.p. 169–181°. A 2.0-g. portion was chromatographed on silica gel. Elution with 1:2 petroleum ether:benzene gave 0.110 g. of solid melting at 179–181.5°. It was not further investigated. Elution with 19:1 benzene:ethyl acetate gave 1.70 g. of solid, m.p. 183–186°. Crystallization from ethyl acetate afforded 1.16 g., m.p. 184–186°. The compound showed no maximum at 240 mμ.

Anal. Calcd. for $C_{23}H_{34}OS_2$ (390.62): C, 70.72; H, 8.77; S, 16.42. Found: C, 70.81; H, 8.78; S, 16.65; $[\alpha]_D$ +211° (1% in chloroform).

17α-Hydroxy-21-acetoxy-4-pregnene-3,20-dione 3-Ethylene Mercaptole.—A solution of 11.64 g. (30 mmoles) of 17α-hydroxy-21-acetoxy-4-pregnene-3,20-dione in 250 ml. of warm acetic acid was treated with 2.76 ml. (30 mmoles) of ethanedithiol and a solution of 2.7 g. of *p*-toluenesulfonic acid monohydrate in 30 ml. of acetic acid. After 17 hours at room temperature, 7.16 g. of crystalline solid had separated. This material melted at 227–229°. Crystallization from acetone gave an analytical sample of the same m.p.

Anal. Calcd. for $C_{25}H_{36}O_4S_2$ (464.66): C, 64.62; H, 7.81; S, 13.80. Found: C, 64.44; H, 7.69; S, 13.30; $[\alpha]_D$ +154° (1% in chloroform); λKBr, 2.95, 5.80, 7.30, 7.92, 8.08, 9.58 μ.

17α-Hydroxy-21-acetoxy-4-pregnene-3,11,20-trione 3-Ethylene Mercaptole.—Reaction of 12.06 g. (30 mmoles) of cortisone acetate as described in the previous preparation

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