The *isocamphenanic acid*, m.p. 68–74°, recovered from the mother liquors after the separation of camphenanic acid, was placed on silica gel and eluted with chloroform affording the following fractions: (a) camphenilanic acid (I), m.p. 75–80° to 78.5–80°, whose melting point was raised to 90–91° by recrystallization from petroleum ether; (b) mixtures of (I) and (II), m.p. 55–65°, 47–52°, and 71–79°; and (c) isocamphenilanic acid (II), m.p. 87–90° and 96–105°, whose melting point was raised to 118.5–119.5° by recrystallization from methanol.

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A Convenient Laboratory Preparation of *p*-Diacetylbenzene

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A method for preparing 50-g. samples of *p*-diacetylbenzene in yields of 82% has been developed.

The air oxidation of *p*-diethyl- or *p*-diisopropylbenzene to *p*-diacetylbenzene usually results in a mixture of products.[1,2] The presence of oxidation products formed from *o*- and *m*-dialkylbenzenes, usually present in commercial samples of the *p*-dialkylbenzenes, helps to make this mixture complex.

Riemschneider[3] concluded, after reviewing the literature, that all prior syntheses of *m*- and *p*-diacetylbenzenes were long, difficult, and low in yield. He then described a procedure for the buffered permanganate oxidation of *p*-ethylacetophenone on a 0.05*M* scale, using essentially a 1:1 molar ratio of permanganate to *p*-ethylacetophenone. Yields of *p*-diacetylbenzene were 55%.

Sladkov and Vitt[4] prepared *p*-diacetylbenzene in 50% yield by the buffered permanganate oxidation of 0.1 mole of *p*-ethylacetophenone. They used a 2:1 molar ratio of permanganate to monoketone in a slightly acidic medium.

On scaling up the procedure of Sladkov and Vitt to a 0.4*M* scale, the present authors obtained 70–76% yields of *p*-diacetylbenzene. Changing the molar ratio of permanganate to monoketone to 5:2 gave an 82% yield of the diketone with complete conversion of the *p*-ethylacetophenone.

Several attempts to oxidize 1.2-molar batches of *p*-ethylacetophenone resulted in approximately 20% yields of the diketone. However, this scaled-up process was not thoroughly studied.

(1) R. Mittag, Ger. Patent **767,389** (July 31, 1952).
(2) A. J. Harding and A. W. C. Taylor, Brit. patent **784,681** (October 16, 1957).
(3) R. Riemschneider, *Gazz. chim. ital.*, **77**, 607 (1947); *Chem. Abstr.*, **42**, 5876e (1948).
(4) A. M. Sladkov and S. V. Vitt, *Zhur. Obshchei Khim.*, **26**, 1130 (1956); *Chem. Abstr.*, **50**, 16704c (1956).

EXPERIMENTAL[5]

Magnesium oxide, 40 g. (1.0 mole), 1034 ml. of water, 135 ml. of concd. nitric acid (*d.* 1.4; 2.1 moles), and 158 g. (1.0 mole) of potassium permanganate were charged to a 2-l., three-neck, round-bottom flask fitted with a mechanical stirrer, dropping funnel, and reflux condenser. A thermometer, suspended through the condenser, dipped into the solution.

The oxidizing mixture was stirred rapidly and heated to 60° on a steam bath. *p*-Ethylacetophenone,[6] 59.3 g. (0.40 mole), was added dropwise to the oxidizing mixture during 30 min. while maintaining a reaction temperature of 60 ± 1°. Cooling may be necessary. The mixture was then stirred at 60 ± 2° for an additional 4.5 hr. The mixture of product and manganese dioxide was cooled, filtered by vacuum, and dried. The powdered residue was taken up and stirred vigorously with refluxing benzene to extract the product. This mixture was filtered hot by vacuum using a steam-heated funnel. The residual manganese dioxide was thoroughly washed in a similar manner with more hot benzene. The benzene filtrates were combined and stripped to dryness under reduced pressure, leaving 57.2 g. (88% yield) of residue having no odor of unchanged *p*-ethylacetophenone. This residue was slurried with 250 ml. of cold anhydrous diethyl ether, filtered, and dried to give 53.2 g. (82.1% yield) of white, crystalline product, m.p. 112.4–113.4° (reported,[4] 113–114°).

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(5) All melting points and boiling points are uncorrected.
(6) Prepared according to the procedure of D. T. Mowry, M. Renoll, and W. F. Huber, *J. Am. Chem. Soc.*, **68**, 1107 (1946); b.p. 125.5–126.8°/20 mm., n_D^{25} 1.5277.

Ethyl 2-*S*-Ethyl-1,2-dithio-5-*aldehydo*-α-D-*xylo*(*lyxo*)pentodialdofuranoside

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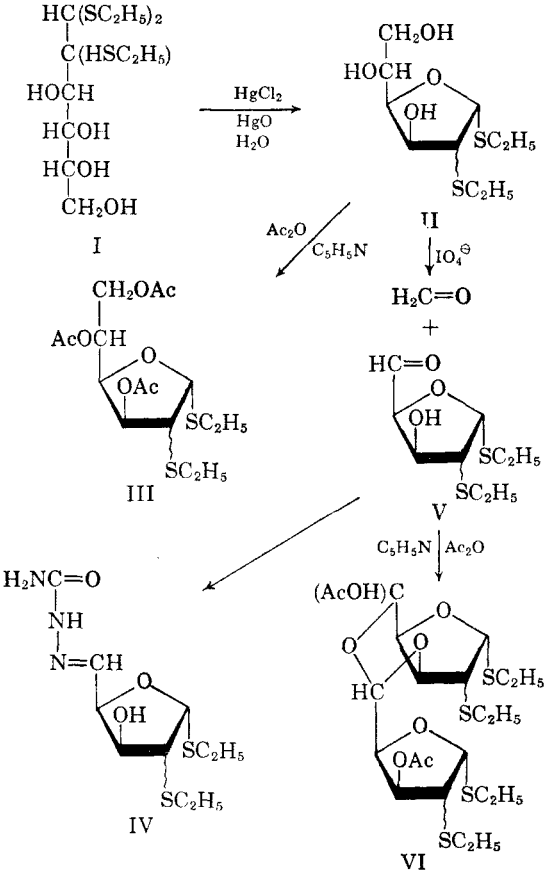
Schneider, Sepp, and Stiehler[2,3] prepared alkyl 1-thio-α-D-glucosides by treating an aqueous solution of dialkyl dithioacetal at room temperature with one mole of mercuric chloride and neutralizing the acid formed with alkali. Green and Pacsu[4] obtained alkyl glucosides when the reaction was effected in alcoholic solution and from the rotation values and ease of hydrolysis of the products, considered that they were furanosides. This ring assignment was

(1) Postdoctoral fellows supported by Grant No. CY-3232(C3) from the Department of Health, Education, and Welfare, U. S. Public Health Service, National Institutes of Health, Bethesda, Md. (O.S.U.R.F. Proj. 759C).
(2) W. Schneider and Johanna Sepp, *Ber.*, **49**, 2054 (1916).
(3) W. Schneider, Johanna Sepp, and Ottilie Stiehler, *Ber.*, **51**, 220 (1918).
(4) J. W. Green and E. Pacsu, *J. Am. Chem. Soc.*, **59**, 1205 (1937).

verified by Wolfrom and co-workers[5] for ethyl 1-thio-α-D-glucofuranoside by periodate oxidation data.

We wish to report herein the preparation of ethyl 2-*S*-ethyl-1,2-dithio-α-D-gluco(manno)furanoside (II) from 2-*S*-ethyl-2-thio-D-glucose(mannose) diethyl dithioacetal (I)[6] essentially by the method of Green and Pacsu.[4] Acetylation of II produced a crystalline triacetate (III). The furanoside structure of II was verified by the production of formaldehyde and (sirupy) ethyl 2-*S*-ethyl-1,2-dithio-5-*adlehydo*-α-D-*xylo*(*lyxo*)-pentodialdofuranoside (V) by periodate oxidation. The latter substance, when freshly prepared, exhibited a strong carbonyl absorption in the infrared which disappeared within twenty-four hours, suggesting that polymerization was occurring. A related substance, 1,2-*O*-isopropylidene-5-*aldehydo*-α-D-*xylo*-pentodialdofuranose, has been shown to form a crystalline dimer.[7] The crystalline semicarbazone (IV) may



be obtained in good yield directly from the freshly prepared reaction mixture but its degree of polymerization is not established. The substance was further characterized by the crystalline acetate of its dimer (VI), the structure of which is drawn only by analogy with that established by Schaffer and Isbell[7] for their dimer.

(5) M. L. Wolfrom, S. W. Waisbrot, D. I. Weisblat, and A. Thompson, *J. Am. Chem. Soc.*, 66, 2063 (1944); M. L. Wolfrom and Z. Yosizawa, *J. Am. Chem. Soc.*, 81, 3474 (1959).

(6) P. Brigl and H. Mühlschlegel, *Ber.*, 64, 2921 (1931).

(7) R. S. Schaffer and H. S. Isbell, *J. Am. Chem. Soc.*, 79, 3864 (1957).

EXPERIMENTAL

Ethyl 2-S-ethyl-1,2-dithio-α-D-gluco(manno)furanoside (II). Following essentially the general method of Green and Pacsu,[4] 2-*S*-ethyl-2-thio-D-glucose(mannose) diethyl dithioacetal[6] (I, 0.6 g.) was stirred, at room temperature, in a suspension of 12 ml. of water containing freshly prepared mercuric oxide (from 1 g. of mercuric chloride, washed free of hydroxyl ion). A solution of 0.26 g. of mercuric chloride (0.5 equiv.) in 30 ml. of water was slowly added. After 20 min. of additional stirring, the mixture was filtered through a bed of Celite[8] and washed with methanol. A drop of pyridine was added to the filtrate and it was evaporated under reduced pressure at 50° to a sirup which crystallized. The crystalline mass was extracted with chloroform, filtered, and the extracted material, after solvent removal, was crystallized twice from benzene–petroleum ether (b.p. 30–60°); yield, 0.3 g. (61%), m.p. 86–88°, after recrystallization from water, m.p. 88–90°, $[\alpha]_D^{24}$ +139° (*c* 2.5, chloroform). The substance upon hydrolysis with acid developed an odor of ethanethiol and reduced Fehling solution.

Anal. Calcd. for $C_{10}H_{20}O_4S_2$: C, 44.75; H, 7.51; S, 23.92. Found: C, 44.57; H, 7.54; S, 23.58.

Ethyl 3,5,6-tri-O-acetyl-2-S-ethyl-1,2-dithio-α-D-gluco(manno)furanoside (III). Ethyl 2-*S*-ethyl-1,2-dithio-α-D-gluco(manno)furanoside (II, 3 g.) was dissolved in 20 ml. of dry pyridine, 5 ml. of acetic anhydride added and the mixture held for 20 hr. at room temperature, after which it was poured into 200 ml. of ice and water. After hydrolysis of the excess acetic anhydride, the aqueous layer was decanted and the sirupy material was triturated with water and dried in a stream of air. The sirup was dissolved in a small amount of methanol and crystallized upon standing overnight at −10°. Recrystallization was effected from ether–petroleum ether; yield 3.1 g. (60%), m.p. 43°, $[\alpha]_D^{24}$ +107.5° (*c* 3.8, chloroform).

Anal. Calcd. for $C_{16}H_{28}O_7S_2$: C, 48.71; H, 6.60; S, 16.25. Found: C, 48.74; H, 6.76; S, 16.16.

Ethyl 2-S-ethyl-1,2-dithio-5-aldehydo-α-D-xylo(lyxo)pentodialdofuranoside (V). Ethyl 2-*S*-ethyl-1,2-dithio-α-D-gluco(manno)furanoside (II, 1 g., 3.7 mmoles) was dissolved in 20 ml. of water and treated with 3.7 mmoles of sodium metaperiodate in 20 ml. of water at 0°, in the dark for 35 min., essentially as described by Wolfrom and Yosizawa.[5] Titration of an aliquot revealed that all of the periodate was consumed. A second aliquot reacted with dimedon (1,1-dimethyl-3,5-cyclohexanedione) solution to form a heavy precipitate, m.p. 185–190°, undepressed upon admixture with the known 1,1-dimethyl-3,5-cyclohexanedione derivative of formaldehyde. Sodium bicarbonate (200 mg.) was added to the remaining solution which was cooled to 10° and extracted with three 100-ml. portions of chloroform. The extracts were dried with anhydrous magnesium sulfate and evaporated under reduced pressure. The remaining sirup solidified to a glass but failed to crystallize. The sirup reduced Benedict solution and developed ethanethiol upon warming with hydrochloric acid. The freshly prepared material exhibited a strong carbonyl adsorption at 5.7 μ which disappeared as the substance aged, suggesting polymerization.

Ethyl 2-S-ethyl-1,2-dithio-5-aldehydo-α-D-xylo(lyxo)pentodialdofuranoside semicarbazone (IV). An amount of 1.0 g. of II was oxidized with sodium metaperiodate as described above. The oxidation mixture was treated with 2 g. of sodium bicarbonate followed by the addition, with stirring, of 3 g. of semicarbazide hydrochloride. Upon standing overnight at 10°, a crystalline product formed; yield 0.4 g. m.p. 183–

(8) A product of the Johns Manville Co., New York, N. Y.

185°. Further purification was effected by two crystallizations from water and one from ethanol–petroleum ether (b.p. 30–60°); m.p. 185–187°, $[\alpha]_D^{28}$ +62° (*c* 1.5, ethanol).

Anal. Calcd. for $C_{10}H_{18}O_3N_2S_2$: C, 40.94; H, 6.52; N, 14.32; S, 21.86. Found: C, 41.35; H, 6.69; N, 14.60; S, 22.16.

Ethyl 3-O-acetyl-2-S-ethyl-1,2-dithio-5-aldehydo-α-D-xylo-(lyxo)-pentodialdofuranoside (dimeric) (VI). The dried sirup (V) resulting from the periodate oxidation of 0.5 g. of ethyl 2-*S*-ethyl-1,2-dithio-α-D-gluco(manno)furanoside, as described above, was aged for 24 hr. and was then acetylated for 8 hr. at room temperature with 10 ml. of pyridine and 2 ml. of acetic anhydride. The solid obtained by decantation after pouring into 200 ml. of ice and water, was crystallized by trituration with methanol. Pure material was obtained by recrystallization from ether–petroleum ether; m.p. 133–134°, $[\alpha]_D^{27}$ +128.5° (*c* 1.2, chloroform).

Anal. Calcd. for $C_{11}H_{18}O_4S_2$: C, 47.43; H, 6.52; S, 23.03; mol. wt. dimer, 556. Found: C, 47.36; H, 6.72; S, 23.07; mol. wt. (Rast), 501.

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The Synthesis of 21-*O*-Alkylhydrocortisone Derivatives and of 11β-Hydroxy-17α,21-methylenedioxy-4-pregnene-3,20-dione[1a]

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The observation[2] that treatment of a polyhydroxylated steroid derivative with potassium *t*-butoxide and methyl iodide results in preferential *O*-methylation of a 21-hydroxy group in the presence of 11β- and 17α-hydroxy groups,[3] prompted us to use this convenient procedure for the preparation of certain 21-*O*-alkyl derivatives of hydrocortisone. We now wish to communicate the results of our investigation.

Several 21-*O*-methyl derivatives have already been reported. Cortisone 21-*O*-methyl ether has been obtained[4] *via* the reaction of 20-cyano-3α,21-dihydroxy-17-pregnene-11-one with methanolic alkali followed by elaboration of the 17α-hydroxy 20-ketone moiety and the ring A Δ⁴-3-one, a relatively complex procedure. More recently, Zorbach and Tamorria described[5] the synthesis of 21-O-methyldeoxycorticosterone by treatment of 21-diazoprogesterone with methanol in the presence of boron trifluoride etherate. Finally, during the course of our study, Neeman and coworkers reported the convenient preparation[6] of 21-O-methyldeoxycorticosterone and 17-*O*-methyltestosterone from the respective free steroids by treatment with diazomethane in the presence of fluoboric acid. No testing results for any of these compounds were reported.

As *t*-butoxide-alkyl halide treatment of a Δ⁴-3-ketone will result in C-4 alkylation,[3,7] and presumably a 17α-hydroxy 20-ketone will undergo D-homoannulation, it was necessary to carry out the *O*-alkylation with a compound having the 3- and 20-carbonyl functions blocked. A suitably blocked starting material for the synthesis of 21-*O*-alkyl derivatives in the glucocorticoid series was therefore, the conveniently available hydrocortisone 3,20-bisethylene ketal (I).[8]

Treatment of bisketal I with potassium *t*-butoxide (3 molar equivalents) and methyl iodide (6 molar equivalents) in hot *t*-butyl alcohol resulted in the anticipated preferential methylation of the 21-hydroxyl group, and afforded the 21-*O*-methyl 3,20-bisketal II. Ketal hydrolysis of II with 1% methanolic sulfuric acid then gave the desired 21-*O*-methylhydrocortisone (IV). By a similar procedure, 21-*O*-hexadecylhydrocortisone (V) was prepared. When bisketal I was treated with potassium *t*-butoxide and 2-bromopyridine, the desired 21-*O*-(2-pyridyl) derivative VI could not be isolated, and instead a low yield of the 17α,21-oxide VII[9] was obtained. Presumably, the initially formed VI underwent internal cyclization to give VII, a reaction facilitated by resonance stabilization of the departing pyridone anion. Preliminary attempts to effect condensation with ethyl bromoacetate and with 2-dimethylaminoethyl chloride were unsuccessful and were not pursued.

In view of the enhanced glucocorticoid activity reported[10] for the *O,O'*-alkylidene derivatives of 16α,17α-diols, it was of interest to prepare a 17,21-*O,O'*-alkylidene derivative[11] of hydrocortisone. Bisketal I was treated with potassium *t*-butoxide and methylene bromide to give the 17α,21-methylenedioxy derivative VIII, treatment of which with refluxing 1% methanolic sulfuric acid for one hour resulted in preferential hydrolysis of the ketal group at C-3 to give IX in 88% crude yield. It may be noted that these hydrolysis conditions

(1) (a) This paper is part of a continuing program of research in the steroid hormone field. For the previous paper in this series see R. E. Schaub and M. J. Weiss, *J. Org. Chem.*, 26, 1223 (1961). (b) To whom inquiries concerning this paper should be addressed.

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(3) N. W. Atwater [*J. Am. Chem. Soc.*, 79, 5315 (1957)] reported no evidence of 17-*O*-alkylation when testosterone was treated with potassium *t*-butoxide and methyl iodide.

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(10) J. Fried, A. Borman, W. B. Kessler, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, 80, 2338 (1958).

(11) 17α,21-Isopropylidenedioxy steroid derivatives have recently been reported [M. Tanabe and B. Bigley, *J. Am. Chem. Soc.*, 83, 756 (1961)].