The 3-buten-1-ol and formate-containing fractions (44.0 g.) were combined, dried over calcium sulfate and distilled in column A. Fraction I, b.p. 76–104.5°, 14.3 g., contained a little water; II, b.p. 105–111°, 17.0 g., $n^{25}\mathrm{D}$ 1.4078, was mostly 3-buten-1-ol formate [literature[10] b.p. 112–113°]; while III, b.p. 111.5–113°, $n^{25}\mathrm{D}$ 1.4160, $n^{20}\mathrm{D}$ 1.4182, 4.5 g. was mostly 3-buten-1-ol [literature[10,11] b.p. 112.5–113.5°, $n^{20}\mathrm{D}$ 1.4200, $n^{25}\mathrm{D}$ 1.4189].

3-Buten-1-ol was obtained essentially free from ester by alkaline saponification of the crude product from another reaction. The compound distilled at 111–113.5°, $n^{25}\mathrm{D}$ 1.4155; its infrared spectrum was identical to 3-buten-1-ol prepared by the reaction of gaseous formaldehyde with allylmagnesium chloride.[12,13]

The yield of the desired compound was not increased in experiments where longer reaction times at lower temperature (20 hours at 200°) or sodium bicarbonate or copper powder as catalyst were tried.

Formaldehyde and Isobutylene.—Reaction of paraformaldehyde and isobutylene in equimolar amounts at 200° for four hours gave in low yield a complex mixture containing only a small amount of I. In separate experiments activated alumina and di-*t*-butyl peroxide were tried as catalysts. Using 99% anhydrous polymeric formaldehyde, the yield of I was not higher than 31%.

A detailed examination of all the distillable products of the reaction was desired. A liquid product of 155 g. obtained from reaction of 3 *M* amounts at 200° for 5.5 hours was fractionated under reduced pressure in column A. The alcohol and formate ester fractions, b.p. 57–70° (52 mm.), 63.5 g., were combined, dried over calcium oxide and refractionated.

A mixture of I and its formate ester distilled at 126.5–130°, $n^{20}\mathrm{D}$ 1.4280 to 1.4323, 25.4 g. Compound I had b.p. 130.5°, $n^{20}\mathrm{D}$ 1.4330, $n^{25}\mathrm{D}$ 1.4312; 26.5 g. (reported[6] b.p. 130°, $n^{20}\mathrm{D}$ 1.4329). Infrared spectra of these fractions indicated a terminal olefinic bond (strong band at 11.25 μ). That of I showed nearly complete absence of the carbonyl band at 5.75 μ.

The material, b.p. above 70° (52 mm.), was separated into several fractions. The major constituent, obtained as fractions, b.p. 124–128° (10.0 mm.), $n^{25}\mathrm{D}$ 1.4713, 10.0 g., and 133–140° (10 mm.), $n^{25}\mathrm{D}$ 1.4742, 9.1 g., was primarily 3-methylene-1,5-pentanediol II (reported[7] b.p. 110–111° (0.5–0.8 mm.), $n^{20}\mathrm{D}$ 1.4785) contaminated with some formate ester (yield 9% as monoformate based on formaldehyde charged). Infrared spectra showed strong hydroxyl group absorption at 3.0 μ, carbonyl absorption at 5.75 μ, and strong double bond ($>C{=}CH_2$) absorption at 6.05 and 11.25 μ.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.05; H, 10.41; hydroxyl no., 968. Found: C, 62.2; H, 9.85; hydroxyl no., 624; ester no., 107.

Formaldehyde exchange of the products boiling above 130° at atm. press. with acid in the presence of methanol to distil out volatile methylal and methyl formate was done with a typical residue, in order to determine the amount of combined formaldehyde and obtain the hydroxy compounds present pure if possible. A mixture of 111 g. of residue ($n^{25}\mathrm{D}$ 1.4600, b.p. above 130°, hydroxyl no. 245, ester no. 33, acid no. 1.9), 100 g. of methanol and 1.0 cc. of concentrated sulfuric acid was heated under an 8-inch packed column with a variable take-off head. Methylal distilled at 40–46° at high reflux (25 cc., 21.8 g., 0.29 mole); then a mixture of methylal and methanol, b.p. 35.5–60° (22 cc.). The residual liquid was neutralized with calcium carbonate and the methanol distilled off.

Fractionation of the remainder (80 g.) gave a number of fractions. Among the compounds identified was II, b.p. 125–132° (10 mm.), $n^{25}\mathrm{D}$ 1.4714, with an infrared spectrum identical to authentic II, prepared by the method of Blomquist and Verdol.[7]

A higher boiling mixture, b.p. 145–154° (2.5 mm.), $n^{25}\mathrm{D}$ 1.4770–1.4800, also was obtained which was converted to acetate esters, but could not be characterized satisfactorily.

Formaldehyde and 1-Octadecene.—Octadecene-1 (252.5 g., 1 mole) and anhydrous polymeric formaldehyde (30.0 g., 1 mole) were heated in a 440-cc. bomb at 226–251° for six hours. Pressure was less than 12 atm. The liquid product, wt. 256 g., was analyzed; found, 0.119% water, hydroxyl no. 28.8, ester no. 49.6, acid no. 2.2. It was distilled through an 8-inch Heli-grid packed column under reduced pressure to give 173 g. (0.70 mole) of recovered octadecene-1, and 49.2 g. of white solid 3-nonadecene-1-ol and formate, b.p. 179–195° (7.0 mm.) and 162–175° (1.0–2.5 mm.) in three fractions.

Anal. Calcd. for $C_{19}H_{38}O$ (alcohol): C, 80.81; H, 13.56; hydroxyl no., 198. Calcd. for $C_{20}H_{38}O_2$ (formate ester): C, 77.5; H, 12.3; ester no., 180. Found, C, 79.3; H, 13.1; hydroxyl no., 85; ester no., 85 (first fraction) and C, 81.0; H, 12.8; hydroxyl no., 106; ester no., 30.0 for last fraction.

The yield of alcohol and ester calculated from the hydroxyl and ester numbers was 0.087 mole carbinol and 0.079 mole ester or 87% on the octadecene-1 used up and 25% on the formaldehyde charged. Infrared analysis showed hydroxyl (band at 3.0 μ) ester group (band at 5.75 μ) and *trans*-RCH=CHR (band at 10.36 μ and *not* at 11.25 μ) groups present.

Formaldehyde and Diisobutylene.—Reaction of 224 g. (2 moles) of diisobutylene (b.p. 102°) and 60 g. (2 moles) of anhydrous polymeric formaldehyde at 200° for six hours gave 266 g. of liquid product.

Distillation gave 32.7 g. of methanol and diisobutylene, b.p. 58–101.5°, $n^{25}\mathrm{D}$ 1.4622; diisobutylene, b.p. 101.5–102°, 132.0 g. (54.2% recovery); and IV, b.p. 71–74° (7.0 mm.), and 78–85° (8.0 mm.), $n^{25}\mathrm{D}$ 1.4455, 58.1 g. (a yield of 66% based on diisobutylene used).

Anal. Calcd. for $C_9H_{18}O$: C, 76.0; H, 12.7; hydroxyl no., 395. Found: C, 75.3; H, 12.3; hydroxyl no., 325; ester no., 25.0. The product contained about 7.6% 3-neopentyl-3-buten-1-ol formate.

Fractionation of the higher boiling liquid gave the diol V, b.p. 135–144° (8.0 mm.), $n^{25}\mathrm{D}$ 1.4620, 12.1 g., together with some formate ester, as indicated by the infrared spectrum and analysis.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.8; H, 11.7. Found: C, 69.4; H, 11.3.

Formaldehyde and Other Olefins.—Cyclohexene, α-methylstyrene, α-pinene, 10-hendecenoic acid and methyl oleate were heated individually in equimolar amount with anhydrous polymeric formaldehyde. In each case, reaction did occur as shown by functional group analysis and distillation of the liquid products. The products isolated by distillation had infrared spectra and analyses which showed that a mixture of olefinic ester and alcohol was obtained in each case.

ORGANIC CHEMICALS DEPARTMENT
E. I. DU PONT DE NEMOURS AND CO., INC.
WILMINGTON 99, DELAWARE

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The Reaction of Cortisol 21-Acetate with Lead Tetraacetate[1]

BY SHLOMO BURSTEIN AND RALPH I. DORFMAN

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In previous publications the occurrence of hydroxylated derivatives of cortisol (hydrocortisone) in guinea pig and in human urine[2–4] has been described. In an attempt to synthesize derivatives of cortisol hydroxylated at C-2 for comparison with unidentified steroids isolated from urine, the reaction of cortisol 21-acetate[5] with lead tetraacetate was studied. Although Rosenkranz, *et al.*,[6] pro-

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tected the 17α-hydroxy groups of the 21-acetates of 11-desoxycortisol and cortisone to prevent attack of the side chain by the reagent, no precautions were taken to protect the 11β- and 17α-hydroxyls in the present study. The reaction was carried out in a similar manner to that described by Sondheimer, *et al.*,[7] for testosterone acetate. A major reaction product (I) (produced in *ca.* 10% yield on the basis of ultraviolet spectrophotometry) was isolated, following paper chromatography, in crystalline form. The compound was more polar than cortisol 21-acetate in the toluene–propylene glycol system, reduced the blue-tetrazolium reagent and had an adsorption maximum at 242 mμ. Infrared analysis[8] showed a doublet in the double bond region which suggested a 1,4-diene-3-one system.[9] The spectrum of I in sulfuric acid had the strongest absorption maxima at 235 and 360 mμ two hours after dissolving the steroid in acid. The corresponding strongest bands for 17β-hydroxy-1,4-androstadiene-3-one have been reported by Bernstein and Lenhard[10] to be located at 232 mμ (inflection) and 327 mμ (maximum).

The isolated reaction product I was identified conclusively with a sample of authentic 21-acetoxy-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione that became available to us through the courtesy of the Schering Corporation. When compound I was tested by the thymolytic test[11] it was found to have *ca.* four times the activity of cortisol 21-acetate. 11β,17α,21-Trihydroxy-1,4-pregnadiene-3,20-dione recently was discovered to have three to four times the activity of cortisol in the eosinopenic response.[12]

When the reaction of cortisol 21-acetate was carried out at 108–110° for 3.5 hours no I was isolated. A complex mixture was produced which upon chromatography on alumina, silica gel and on paper separated into several fractions which resisted crystallization.

Clarke, *et al.*,[13] recently have described the reaction of progesterone, testosterone and desoxycorticosterone acetates with lead tetraacetate in which under mild conditions 21-acetoxy-1,4-pregnadiene-3,20-dione and 17β-acetoxy-1,4-androstadien-3-one were isolated in *ca.* 8% yields.

Experimental

Cortisol 21-acetate (200 mg.) was dissolved by heating in glacial acetic acid (3 cc.) and lead tetraacetate (300 mg.) was added. The mixture was heated in an oil-bath at 100° for 1 hour and then poured on ice, neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with 0.1 *N* NaOH, H_2O, and evaporated under reduced pressure. The residue was chromatographed on 10 paper strips (15 cm. wide) in the toluene–propylene glycol system for 10 hours. The blue-tetrazolium reducing zone, more polar than cortisol 21-acetate, was eluted with methanol, the propylene glycol evaporated *in vacuo* (0.2 mm.) at 35° and the eluate crystallized from ethanol after removal of acetone-insoluble material; prisms, m.p. (uncor.) 230–233°; λ_{max} (methanol) 242 mμ; infrared analysis: 3420 (–OH), 1736 and 1720 (C-21 acetate and C-20 carbonyls showing the C-20 carbonyl and C-21 acetate interaction), 1655 (C-3 conjugated carbonyl), 1615 (inflection) and 1595 (double bond region doublet), and 1229 cm.$^{-1}$ (acetate).

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Synthesis and Reactions of Ethyl 3-Ethoxy-2,4-pentadienoate

BY T. L. CAIRNS, V. A. ENGELHARDT AND W. O. FORSHEY, JR.

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A new polymerizable monomer, ethyl 3-ethoxy-2,4-pentadienoate (I) has been obtained from the reaction of vinylacetylene with ethyl carbonate in the presence of sodium ethoxide.[1]

$$CH_2{=}CHC{\equiv}CH \xrightarrow{(EtO)_2CO} \underset{\text{I}}{CH_2{=}CHC(OEt){=}CHCOOEt} + \underset{\text{II}}{EtOCH_2CH_2C(OEt){=}CHCOOEt}$$

Ethyl 3,5-diethoxy-2-pentenoate (II), the other product of this reaction, apparently results from the 1,6-addition of ethanol to compound I followed by rearrangement of the double bond so that it is conjugated with the ester group. This 1,6-addition is in contrast to the 1,4-addition reported for ethanol and ethyl 3-ethoxy-4-methyl-2,4-pentadienoate to give ethyl 3,3-diethoxy-4-methyl-4-pentenoate.[2]

The structure of ethyl 3-ethoxy-2,4-pentadienoate (I) is based on the following evidence. Carbethoxylation can take place only at the hydrogen-bearing acetylenic carbon atom.[2] A conjugated diene carbonyl system is indicated by the ultraviolet and infrared spectra and by formation of a Diels–Alder adduct with maleic anhydride. The β-position of the ethoxy group is shown by acidic hydrolysis to a β-keto ester which forms a copper chelate.

The designation of compound II as ethyl 3,5-diethoxy-2-pentenoate is based on the following reactions. Elimination of ethanol by action of sodium bisulfate gives compound I. β-Ethoxyethyl methyl ketone is obtained by hydrolysis and decarboxylation. Hydrogenation of compound II followed by saponification yields a diethoxy acid, presumably 3,5-diethoxypentanoic acid, which was shown to have its two ethoxy groups attached to different carbon atoms by its resistance to acidic

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