due was chromatographed on 200 g. of neutral alumina, and the fractions eluted with benzene–hexane (3:1) and with benzene were crystallized from acetone–hexane. The resulting diketone VII weighed 3.3 g. (51%) and showed m.p. 145–148°. The analytical specimen exhibited m.p. 152–154°, $[\alpha]_D$ +146°, λ_{max} 240 mμ, log ε 4.40, ν_{max} 1744 and 1664 cm.$^{-1}$ (Cole and Julian[9] reported m.p. 152°, $[\alpha]_D$ +148°, λ_{max} 241 mμ, log ε 4.40; Allen and Bernstein[10] reported m.p. 153–154°, $[\alpha]_D$ +142°, λ_{max} 238–241 mμ, log ε 4.38).

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.66; H, 8.45.

(b) **By Oppenauer Oxidation of VI.**—A solution of 4 g. of VI in 130 cc. of toluene and 50 cc. of cyclohexanone was distilled until 30 cc. had been removed, 1.5 g. of aluminum isopropoxide in 15 cc. of toluene was added and the mixture was refluxed for 45 minutes. Isolation as above followed by chromatography on neutral alumina and crystallization from acetone–hexane yielded 2.16 g. (54%) of the diketone VII, m.p. 146–149°, ν_{max} 240 mμ, log ε 4.39. Identity with the material obtained by the first route was established through non-depression in m.p. on admixture and by infrared comparison.

Δ^5-Pregnene-3β,21-diol-20-one 3-Formate 21-Acetate (VIIIa).—A solution of 1.5 g. of the diene V in 70 cc. of ethyl acetate was shaken in hydrogen over 200 mg. of a 10% palladium–charcoal catalyst at 22° and 592 mm. After 1 hour *ca.* 1 molar equivalent of hydrogen had been taken up and absorption had almost stopped. The catalyst was removed, the solvent was evaporated and the residue was crystallized from acetone–hexane. The resulting diester VIIIa (1.24 g., 82%) showed m.p. 172–173°, $[\alpha]_D$ +32°, no high-intensity absorption in the ultraviolet, ν_{max} 1740 and 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.66; H, 8.83.

Δ^5-Pregnene-3β,21-diol-20-one 21-Acetate (VIIIb).—The mono-unsaturated diester VIIIa (200 mg.) dissolved in 30 cc. of benzene was passed five times through a column of 10 g. of alkaline alumina. Evaporation of the solvent and crystallization from acetone–hexane furnished 140 mg. (75%) of the diol monoacetate VIIIb, m.p. 183–185°; ν_{max} 1740, 1718 cm.$^{-1}$ and free hydroxyl band (Steiger and Reichstein[11] give m.p. 184–185°). The m.p. was undepressed on admixture with an authentic sample and the infrared spectra were identical.

Δ^5-Pregnen-21-ol-3,20-dione Acetate (Desoxycorticosterone Acetate) (IX).—The Oppenauer oxidation of 800 mg. of the mono-unsaturated diester VIIIa in xylene was carried out exactly as described above for the corresponding diene V. Chromatography on alumina and crystallization from acetone–hexane yielded 380 mg. (51%) of desoxycorticosterone acetate, m.p. 155–157°, λ_{max} 240 mμ, log ε 4.19, ν_{max} 1744, 1718 and 1660 cm.$^{-1}$. The material was identified with an authentic sample (m.p. 156–158°) in the usual way.

MEXICO D.F., MEXICO

[CONTRIBUTION FROM THE NEW YORK STATE AGRICULTURAL EXPERIMENT STATION, CORNELL UNIVERSITY]

The Isolation and Identification of 3-Methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin from Carrots[1]

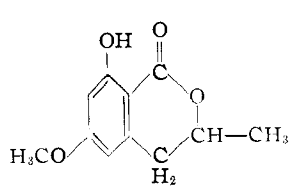
BY ERNEST SONDHEIMER[2]

RECEIVED APRIL 23, 1957

Extraction of bitter carrots with hexane yielded a colorless, optically active, crystalline substance, $C_{11}H_{12}O_4$, (I). The substance is a lactone with one phenolic, one methoxyl and one C-methyl group. Infrared absorption data indicated an 8-hydroxy-3,4-dihydroisocoumarin derivative. The methyl ether of I gives a positive iodoform test and is oxidized by alkaline permanganate to 3,5-dimethoxyphthalic acid. Potassium hydroxide fusion of I yields a phenolic monocarboxylic acid, $C_{11}H_{12}O_4$, which on hydrogenation gives 2-hydroxy-4-methoxy-6-propylbenzoic acid, a previously described compound. From these and other data it is concluded that I is 3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin.

Carrots that have been held in cold storage after harvest frequently acquire a bitter off-flavor.[3] The hydrocarbon extracts from such carrots exhibit ultraviolet absorption characteristics which can be correlated with the flavor score.[4] A crystalline compound with the ultraviolet absorption found in the hydrocarbon extracts has been isolated from bitter carrots and was designated compound A(I).[5] Evidence has been presented that lends support to the belief that the bitter off-flavor of carrots is caused by the presence of several substances and that compound I is one of these.[5a] Data leading to the identification of I as 3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin are reported here.

Except for the lack of reactivity toward diazomethane, I gives the reactions expected of a typical monohydric phenol. The methyl ether of I can be obtained though with dimethyl sulfate in the presence of alkali. Quantitative bromination showed a minimum of two unsubstituted positions on the benzene ring, and coupling of I with diazotized sulfanilic acid indicated a free position *para* to the phenolic hydroxyl.[6] No carboxyl or carbonyl groups were detected, but saponification showed the presence of a lactone. I is optically active and has an absorption band at 6.02 μ. Methylation of I shifts this band to 5.85 μ, a normal value for a con-



I

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(1) Journal Paper No. 1071, New York State Agricultural Experiment Station. Part IV in the series "Bitter Flavor in Carrots." For Part III see ref. 5a.

(2) Department of Chemistry, State University College of Forestry at Syracuse University, Syracuse 10, N. Y.

(3) J. D. Atkin, **Bulletin No. 774,** New York State Agricultural Experiment Station, Geneva, N. Y., March, 1956.

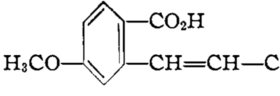
(4) E. Sondheimer, W. P. Phillips and J. D. Atkin, *Food Research*, **20**, 659 (1955).

(5) (a) E. Sondheimer, *Food Research*, **22**, 296 (1957); (b) A. Dodson, H. N. Fukui, C. D. Ball, R. L. Carolus and H. M. Sell, *Science*, **124**, 984 (1956), isolated a compound from bitter carrots, melting 77°, which is probably identical with I.

(6) Chang Wen-Hau, paper partition chromatography of monohydric phenols and its application to the model-lignin degradation reaction, Univ. of Minnesota Master's Thesis, 1951.

jugated 6-membered lactone ring.[7] This shift in the carbonyl absorption is attributed to intramolecular hydrogen bonding with the phenolic hydrogen,[8] since the difference in the carbonyl absorption of I and its methyl ether was unaffected by dilution. The lack of reaction of I with diazomethane and the violet color with ferric chloride are chemical evidence for this assignment.

Oxidation of the methylated ether of I with alkaline permanganate gave 3,5-dimethoxyphthalic acid, which was identified through its dimethyl ester and its anhydride. Assignment of the C-methyl group to C-3 of I was made on the basis of a positive iodoform test with the sodium salt of the methyl ether of I and more conclusively by ozonolysis of the potassium hydroxide fusion product (II). Substance II, an optically inactive, monocarboxylic acid gave acetaldehyde and an aldehydo-carboxylic acid, $C_{10}H_{10}O_5$, on ozonolysis. Permanganate oxidation of II gave 3,5-dimethoxyphthalic acid. II is therefore 2,4-dimethoxy-6-propenylbenzoic acid.



II

Potassium hydroxide fusion of I yields a phenolic, monocarboxylic acid, $C_{11}H_{12}O_4$, which on hydrogenation gives divaricatinic acid,[9] 2-hydroxy-4-methoxy-6-propylbenzoic acid. The degradation of I to this previously described compound is further proof for the structure assignment.

Compound I can be detected in carrots by ultraviolet absorption measurements of hydrocarbon extracts.[4] Although a large number of samples were examined, the substance was not found in freshly harvested carrots. Storage of the carrot roots at 32° for 4 to 8 weeks has most frequently led to the accumulation of detectable amounts.

Compound I is closely related to certain mold and lichen constituents. Thus, mellein, 3-methyl-8-hydroxyl-3,4-dihydroisocoumarin,[10a] has been isolated from *Aspergillus melleus* Yukawa,[10b] divaricatinic acid is found as a depside in *Haermatomma ventosum* (L.) Mass.[11] and 3,5-dihydroxy-2-carboxyphenylacetone[12] is a constituent of *Penicillium brevi-compactum* Dierckx. In contrast to many of the other β-resorcylic acid derivatives, I has no growth inhibiting activity against *Micrococcus pyogenes* var. *aureus*, *Bacillus subtilis* and *Serratia marcescens*. Tests were conducted in liquid media and with pads on agar plates.

Experimental[13]

Isolation of 3-Methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin (I).—A procedure utilizing extraction of canned, bitter carrots with *n*-hexane followed by concentration of the extract was used.[5a] Although this method has repeatedly given satisfactory results, a crystalline preparation was obtained from one batch which did not give pure I after recrystallization from several solvents. However, when this mixture was extracted with 1 *N* sodium hydroxide, the insoluble material removed by filtration, and the filtrate acidified with 6 *N* hydrochloric acid, compound I with the characteristic m.p. of 76° was obtained.

Since we had isolated I previously from canned carrots only, information on the presence of the substance in unheated, bitter carrots was lacking. Double extraction of 1.5 kg. of ground, unheated, bitter carrots with 1.5 l. of hexane and concentration of the extract yielded 122 mg. of product, m.p. 72–75°. Recrystallization from hexane gave 75 mg. of slightly yellow crystals, m.p. 75–76°. The m.p. was not depressed by admixture with I isolated from canned carrots.

I is optically active, $[\alpha]^{24}D$ $-56°$ (c 1 in methanol) and has absorption maxima in 95% ethanol at 302 mμ (ϵ 6000), 267 mμ (ϵ 14800) and 216 mμ (ϵ 22900). The crystalline material, in potassium bromide pellets, has a strong absorption band at 6.02 μ which is shifted to 5.95 μ in 0.02 *M* solution in carbon tetrachloride. The substance has a strong greenish-blue fluorescence in ultraviolet light. I is almost insoluble in water, aqueous hydrochloric acid and sodium bicarbonate but is readily soluble in the common organic solvents and in aqueous sodium hydroxide.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; O, 30.7; mol. wt., 208; OCH_3, 14.9; active H, 0.48; C–CH_3, 7.2 for 1 or 14.4 for 2. Found: C, 63.36; H, 5.78; O, 32.9; mol. wt. (Rast), 183; sapn. equiv., 217; OCH_3, 16.9; active H, 0.48; C–CH_3, 9.3 (Kuhn, Roth).

I gives a violet color with ferric chloride, a positive Millon test, and an orange dye with diazotized sulfanilic acid.[5a] That the position *para* to the phenolic group is unsubstituted may be inferred from the presence of a strong absorption maximum at 395 mμ and a weak band at 305 mμ in the spectrum of the azo dye.[6] Calcium hypochlorite produces no color change. The quantitative bromination procedure for phenols described by Siggia,[14] scaled down to 1/20, was used in the determination of the minimum number of free positions of the aromatic ring. The results obtained with three runs, 1.99 ± 0.04 bromine atoms substituted, were very close to the theoretical value for 2 free positions.

Thirty-six mg. of I was refluxed 3 hr. with 3 ml. of 5 *N* hydrochloric acid. The mixture was cooled, stored overnight at 0°, filtered and the precipitate washed with water and dried, yielding 28 mg. of I, m.p. 75–76°. With the quantitative hydroxylamine procedure of Trozzolo and Lieber,[15] no aldehyde or keto groups could be detected. When compound I was dissolved in 2.8 equivalents of 0.5 *N* sodium hydroxide at room temperature and back-titrated with 0.62 *N* hydrochloric acid, the compound started to crystallize during the titration at *p*H 11.3. No evidence for the presence of an acid with a *pK* below 7 was obtained. However, when the alkaline solution was heated in a boiling water-bath for 30 minutes, cooled and back-titrated, an acid with pK_a 3.1 was detected. On the further addition of hydrochloric acid to the mixture, an oil precipitated which crystallized on overnight storage at 0°. From 64.4 mg. of starting material, 57 mg. (88%) was recovered, m.p. 76°, $[\alpha]^{24}D$ $-54°$ (c 1 methanol).

3-Methyl-6-methoxy-8-acetoxy-3,4-dihydroisocoumarin.—A solution of 59.2 mg. of I in 2 ml. of acetic anhydride and 2 ml. of pyridine was refluxed 1 hour. The cooled solution was concentrated in vacuum, the crystalline residue dissolved in 3 ml. of benzene, and the reaction product was crystallized by the addition of ligroin; yield 55.6 mg., 79%, m.p. 152–154°, $[\alpha]^{24}D$ $-110°$ (c 1 in methanol.)

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.36; H, 5.63. Found: C, 62.75; H, 5.47. The two carbonyl groups at 5.69 and 5.90 μ are assigned to the phenyl acetate and the lactone groups, respectively.

3-Methyl-6,8-dimethoxy-3,4-dihydroisocoumarin.—To 600 mg. of I in 1 ml. of dimethyl sulfate, 15% sodium hydroxide was added dropwise until the mixture remained

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[7] Conjugated 5-membered lactones absorb at lower wave lengths; for example, phthalide and 7-methoxyphthalide have carbonyl absorption bands at 5.72 μ; L. A. Duncanson, J. F. Grove and J. Zealley, *J. Chem. Soc.*, 1331 (1953).

[8] L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 130–134.

[9] A. Sonn, *Ber.*, **64**, 1851 (1931).

[10] (a) J. Blair and G. T. Newbold, *J. Chem. Soc.*, 2871 (1955); (b) E. Nishikawa, *J. Agr. Chem. Soc. Japan*, **9**, 772, 1059 (1934).

[11] C. A. Wachtmeister, *Acta Chem. Scand.*, **6**, 818 (1952).

[12] A. E. Oxford and H. Raistrick, *Biochem. J.*, **27**, 634 (1933).

[13] All melting points were determined on a microscope hot-stage and are corrected. Analysis are by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

[14] S. Siggia, "Quantitative Organic Analysis *via* Functiona Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 111.

[15] A. M. Trozzolo and E. Lieber, *Anal. Chem.*, **22**, 764 (1950).

alkaline. Heating at 80° for 10 minutes caused the disappearance of the residual oil. The solution was cooled, and on acidification with concentrated hydrochloric acid, a colorless oil precipitated which did not crystallize on overnight storage at 0°. The mixture was extracted twice with 15-ml. portions of ethyl acetate, the extracts were dried over sodium sulfate and the solvent evaporated in vacuum. The crystalline residue weighed 590 mg., m.p. 117–125°. Recrystallization from ethyl acetate and ligroin gave 524 mg. (82%) of 3-methyl-6,8-dimethoxy-3,4-dihydroisocoumarin, m.p. 125–128°, $[\alpha]^{24}\text{D}$ −153° (*c* 1 in methanol).

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.43; OCH_3, 27.94; mol. wt., 222. Found: C, 64.95; H, 6.43; OCH_3, 26.8; mol. wt. (Rast), 208.

The crystalline compound in potassium bromide has a carbonyl absorption peak at 5.85 μ. This band is shifted to 5.77 μ in 0.01 *M* solution in carbon tetrachloride.

A small amount of iodoform, m.p. 124°, was obtained on treatment of an alkaline solution of the substance with aqueous iodine.

Methylation of I with diazomethane was unsuccessful. From 50 mg. of I which had been stored at room temperature for 85 hr. with ethereal diazomethane, only starting material was recovered. The excess diazomethane was decomposed with acetic acid, and the recovery of I was 72%.

Oxidation with Alkaline Permanganate.—Four hundred mg. of the methyl ether of I was dissolved in 5 ml. of hot 1 *N* sodium hydroxide. The solution was cooled to room temperature and 5% potassium permanganate solution was added until a violet color was maintained for 2 hr. The excess permanganate was decomposed with methyl alcohol. The mixture was filtered, the filtrate made acid to congo red with concentrated hydrochloric acid, and the solution was concentrated in vacuum to incipient crystallization. After storage at 0° for 4 hr. the mixture was filtered, the precipitate washed with water and air-dried. The product weighed 309 mg., m.p. 140–148°. It was completely soluble in aqueous sodium bicarbonate and was optically inactive. Recrystallizations did not give material with a sharp melting point: from water, m.p. 155–168°; from aqueous methanol, m.p. 149–163°; and from ethyl acetate, m.p. 148–174°. Further concentration of the mother liquors yielded a second crop of 42 mg., m.p. 100–120°. This material was only partially soluble in aqueous sodium bicarbonate and still contained unreacted starting compound. Material with a melting point of 148–174° was analyzed.

Anal. Calcd. for $C_{10}H_{10}O_6 \cdot H_2O$: C, 49.17; H, 4.96; OCH_3, 25.6; wt. loss, 7.45. Found: C, 48.96; H, 4.57; OCH_3, 24.0; wt. loss, 7.6.

The oxidation product was identified as 3,5-dimethoxyphthalic acid by conversion to the anhydride and to the dimethyl ester.

The anhydride was prepared from 70 mg. of oxidation product with m.p. 147–158° by heating with 0.3 ml. of acetic anhydride in a 130°-bath for 75 minutes. The solution was stored at 0° for several hours. The crystalline precipitate was collected by filtration, washed with acetic acid and dried, yielding 16.7 mg. (28%) of needles, m.p. 148–149°; a portion of the material sublimed and melted 152–153°. Synthetic 3,5-dimethoxyphthalic anhydride[16] melts at 152–154°, literature value 149°. A mixture of the synthetic anhydride and the degradation product had a m.p. 152–154°.

Anal. Calcd. for $C_{10}H_8O_5$: C, 57.69; H, 3.88; OCH_3, 29.83. Found: C, 57.45; H, 3.90; OCH_3, 32.5.

The dimethyl ester was prepared by treating 100 mg. of oxidation product, recrystallized from ethyl acetate, with ethereal diazomethane. After 5 hr. the excess diazomethane was decomposed with acetic acid and the solvent evaporated. The residue which was partially crystalline was crystallized from dilute alcohol to yield 52 mg. of needles, m.p. 91–99°. Recrystallization from aqueous ethanol yielded 38 mg. of ester, m.p. 99°, transition 94–96°. Synthetic dimethyl 3,5-dimethoxyphthalate[17] melted 95–97°, literature value[17] 92–94°. A mixture of the synthetic ester and the degradation product melted at 99°, transition 96–97°. The infrared spectra of the two preparations in potassium bromide pellets were superimposable in the entire range of 2–15 μ.

Anal. Calcd. for $C_{12}H_{14}O_6$: C, 56.69; H, 5.50; OCH_3, 48.8. Found: C, 57.01; H, 5.64; OCH_3, 48.0.

Permanganate oxidation does not appear to yield pure 3,5-dimethoxyphthalic acid. Thus, the infrared spectrum of the oxidation product, with a m.p. 149–163°, was very similar to but not identical with the spectrum of synthetic 3,5-dimethoxyphthalic acid,[16] m.p. 157–164°. The value given most frequently in the literature for the m.p. of 3,5-dimethoxyphthalic acid is 158°, although a m.p. of 184° has been reported.[12]

Potassium Hydroxide Fusion.—The methyl ether of I, 380 mg., was ground in a mortar with 800 mg. of powdered potassium hydroxide and heated for 45 minutes at 175–185°. After cooling, the mixture was dissolved in water and acidified with concentrated hydrochloric acid. Two extractions with 10-ml. portions of ethyl acetate, treatment of the extracts with sodium sulfate and evaporation of the solvent yielded 350 mg. of oil which solidified on scratching. Crystallization from benzene and ligroin gave 270 mg., 71%, of II, m.p. 81–88°, raised to 85–87° by a second recrystallization.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 64.85; H, 6.35; neut. equiv., 222. Found: C, 64.45; H, 6.71; neut. equiv., 227.

Oxidation of II with alkaline potassium permanganate yielded 3,5-dimethoxyphthalic acid, identified through its dimethyl ester. From 60 mg. of fusion product 47 mg of acid was obtained, m.p. 148–163° from water. Treatment of 10 mg. of this acid with ethereal diazomethane yielded ester with m.p. 92–95° from aqueous ethanol. The mixed m.p. with synthetic dimethyl 3,5-dimethoxyphthalate was 92–97°.

Ozonolysis yielded acetaldehyde and an aldehydo-carboxylic acid, $C_{10}H_{10}O_5$. A methylene chloride solution of 185 mg. of II was saturated with ozone at −70°. The ozonide was decomposed at room temperature by dropwise addition to a stirred mixture of zinc dust and 95% ethanol. The fraction boiling below 60° was distilled into a solution of 216 mg. of dimedone in 10 ml. of 75% ethanol containing 2 drops of piperidine. After 4-hr. storage at room temperature the methylene chloride was removed by evaporation in vacuum and 3 ml. of water was added to the solution. After overnight storage at 0° the precipitate was collected by filtration, yielding 25 mg. of dimedone derivative, m.p. 141–143°. The dimedone derivative of acetaldehyde had a m.p. 142–145°, and a mixture of the two preparations melted 142–144°.

The other fragment was recovered by filtering the still residue and evaporating the solvent in vacuum. A semicrystalline residue remained which yielded 90 mg. of material, m.p. 187–193° after crystallization from water. Recrystallization from 50% ethanol gave 46 mg., m.p. 190–196°. This material gave a 2,4-dinitrophenylhydrazone, m.p. 237–244°. This degradation product is 2,4-dimethoxy-6-formylbenzoic acid.

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.79; OCH_3, 29.7; neut. equiv., 210. Found: C, 57.27; H, 4.93; OCH_3, 29.2; neut. equiv., 212.

Conversion of I to Divaricatinic Acid. (A) **Potassium Hydroxide Fusion of I.**—A mixture of 200 mg. of I and 500 mg. of potassium hydroxide was heated at 175–180° for 30 minutes, cooled, dissolved in 2 ml. of water and acidified with concentrated hydrochloric acid. After overnight storage at 0° the crystalline precipitate was collected by filtration and dried in a vacuum desiccator over phosphorus pentoxide, yielding 191 mg., 95%, m.p. 153–164. During melting, gas evolution was observed; the melt had a vanilla-like odor. Recrystallization from 4 ml. of 75% methanol gave 135 mg. of product, m.p. 170–178°. Addition of 3 ml. of water to the filtrate gave a second crop weighing 14 mg., m.p. 135–153°. Fractionation of this crop with 4% sodium bicarbonate solution gave 2 mg. of I, m.p. 75–76°, and 9.3 mg. of fusion product, m.p. 152–157°. The fusion product gives a violet color with ferric chloride and forms a soluble cupric salt in the presence of alkali and cupric hydroxide. The latter test was used to distinguish salicylic acid from *meta* and *para* hydroxybenzoic acids.[18] The fusion is 2-hydroxy-4-methoxy-6-propenylbenzoic acid.

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[16] G. D. Graves and R. Adams, THIS JOURNAL, **45**, 2439 (1923).

[17] A. E. Oxford and H. Raistrich, *Biochem. J.*, **26**, 1902 (1932).

[18] Weith, *Ber.*, **9**, 342 (1876).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; OCH_3, 14.9; neut. equiv., 208. Found: C, 63.72; H, 5.70; OCH_3, 14.7; neut. equiv., 214.

B. Catalytic Hydrogenation of the Potassium Hydroxide Fusion Product from I.—A mixture of 57.2 mg. of fusion product in 3 ml. of 95% ethanol and 5.8 mg. of platinum oxide was shaken at room temperature for 10 minutes in the presence of hydrogen at 1 atmosphere pressure. The hydrogen uptake was quantitative for 1 double bond. The mixture was filtered, the catalyst washed with a little ethanol and the combined washings and filtrate concentrated in vacuum to 1–2 ml. The addition of water caused the precipitation of 51.1 mg., crystalline material, 89%, m.p. 158–162°. Divaricatinic acid, obtained through the courtesy of Dr. Wachtmeister, melted 153–164° (literature value[9] m.p. 150–160°). A mixture of these two preparations had a m.p. 152–163°. The infrared absorption spectra in potassium bromide pellets of the hydrogenation product and of divaricatinic acid were identical in the range from 2–15 μ.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71; OCH_3, 14.8. Found: C, 62.73; H, 6.28; OCH_3, 15.3.

Acknowledgments.—The author wishes to thank Dr. Wachtmeister for the divaricatinic acid, Dr. K. H. Steinkraus for conducting the growth-inhibition tests and Dr. G. T. Newbold for helpful discussions.

SYRACUSE, NEW YORK

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, McGILL UNIVERSITY, AND FROM THE WOOD CHEMISTRY DIVISION, PULP AND PAPER RESEARCH INSTITUTE OF CANADA]

3-*O*-Hydroxyethyl-D-glucose and Some of its Derivatives[1]

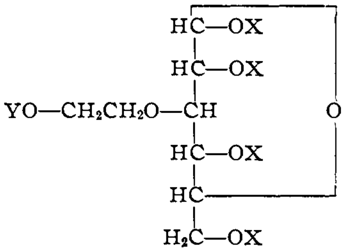
BY G. B. CREAMER, H. H. BROWNELL AND C. B. PURVES

RECEIVED APRIL 4, 1957

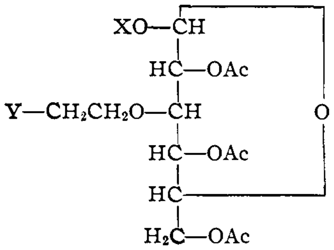
The condensation of ethylene oxide with 1,2;5,6-di-*O*-isopropylidene-β-D-glucofuranose in aqueous alkali was shown to proceed to polyethylene oxide derivatives. Conditions were found for the easy preparation of the monomeric hydroxyethyl derivative, the hydrolysis of which yielded crystalline 3-*O*-hydroxyethyl-α-D-glucose. The sugar was partly decomposed by acetylation with acidic catalysts, and drastic tosylation resulted in partial loss of the hydroxyethyl group. The phenylosazone, β-pentaacetate, acetylated benzyl β-glucoside and a supposed benzyl 3-*O*-iodoethyl-β-glucopyranoside triacetate were obtained in crystalline form. Many other derivatives did not crystallize.

Some years ago,[2b] an attempt was made to determine the mole fraction of primary alcohol units in an *O*-hydroxyethylcellulose by the well known tosylation–iodination method, but some of the hydroxyethyl groups were lost and the results were hard to explain. In order to study the relevant chemistry in a simpler case, a suitable glucose derivative has been hydroxyethylated by the action of ethylene oxide and alkali, and various derivatives of the resulting hydroxyethylglucose have been prepared. The only report of the hydroxyethylation of a sugar found in the literature concerned sucrose; only one of the products was obtained as a pure, crystalline compound, and the structure of this compound was not determined.[3] Crystalline 2-*O*-, 3-*O*- and 6-*O*-hydroxyethyl glucoses have been obtained recently either by the reduction of derivatives of the corresponding carboxymethyl esters ($-CH_2COOCH_3$) with lithium aluminum hydride,[4] or by the column chromatography of a hydrolyzed hydroxyethylcellulose.[5]

Condensation of ethylene oxide with 1,2;5,6-di-*O*-isopropylidene-D-glucofuranose (diacetone glucose, mole ratio 16:1) in aqueous 5% sodium hydroxide solution, followed by extraction with chloroform, yielded a crude product which was fractionally distilled *in vacuo* to separate 26% of the more volatile, unchanged starting material. The next three fractions, which had specific rotations of −37 to −38° in water, consisted of pure or nearly pure 3-*O*-hydroxyethyl-1,2;5,6-di-*O*-isopropylidene glucofuranose, because when hydrolyzed with acid to remove the isopropylidene groups all yielded a solid mass of crystalline 3-*O*-hydroxyethyl glucose (Ia). Neither the diisopropylidene derivative, nor its acetate, benzoate, *p*-toluenesulfonate and iodoethyl analog, could be induced to crystallize and a description of these compounds has been omitted from this article. All were levorotatory compounds and the first three had the expected compositions, the last was not pure.



Ia, X = Y = H
Ib, X = H, Y = $-CH_2CH_2OH$
Ic, X = Y = $-COCH_3$



IIa, X = CH_3; Y = OAc
IIb, X = $C_6H_5CH_2$; Y = OAc
IIc, X = $C_6H_5CH_2$; Y = O − $SO_2C_7H_7$
IId, X = $C_6H_5CH_2$; Y = I

Since the less volatile fractions, with smaller specific rotations of −36 to −32°, failed to give

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[1] Abstracted from Ph.D. Theses submitted to the University by G.B.C. in September, 1950, and by H.H.B. in October, 1953.

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