acidified solution was saturated with sodium chloride and extracted repeatedly with 25-ml. portions of distilled ethylene dichloride until the extracts were colorless. The ethylene dichloride extracts were dried over anhydrous calcium sulfate, filtered, and the volatile materials removed under vacuum at room temperature. A total of 214.2 g. (73.5% yield) of crude I was recovered. This material was distilled at 1–3 μ of mercury and at temperatures of 168–191° using an ASCO molecular still.[4] The distillates of the second and third pass, having indices of refraction of 1.4654 and 1.4653, respectively, were combined. The combined distillates were then percolated through an activated silica gel column, using 5 l. of distilled isopropyl alcohol as eluent. After evaporating the eluent, a total of 158.1 g. of I was recovered.

Anal. Calcd. for $C_{15}H_{23}O_3N_3$:N, 14.2; mol. wt. 293. Found: N(Kjeldahl), 13.8; mol. wt. (ebullioscopic), 292; d^{25}_4 1.0667; $n^{20}D$ 1.4650; η(25°), 24.41 cp.

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(4) ASCO "50" molecular still manufactured by Arthur F. Smith Co., Rochester, N. Y.

Crystalline D-*glycero*-D-*gulo*-Octulose

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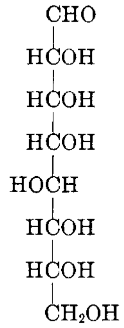
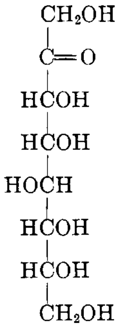
D-*erythro*-L-*talo*-Octose (I) was crystallized first by Merrill, Hann, and Hudson[1] in this laboratory. The sirupy mother liquor from one of their preparations, which had been kept in a Pyrex flask for nearly twenty years, was examined recently by paper chromatography. An ammoniacal silver nitrate spray showed the presence of at least seven components; one of these was suspected of being an octulose because when sprayed with orcinol–hydrochloric acid it gave a color characteristic of this class of compounds. Through cellulose column chromatography we were able to isolate and crystallize this octulose; it melted about 125°, showed $[\alpha]^{20}D$ +34.6° in water (final), and was proved to be D-*glycero*-D-*gulo*-octulose (II)[2a] because it gave a phenylosazone identical with the one derived from D-*erythro*-L-*talo*-octose (I)[1] and D-*erythro*-L-*galacto*-octose (III).[3] We have also prepared the same crystalline octulose deliberately through rearrangement of D-*erythro*-L-*galacto*-octose (III) in boiling pyridine.



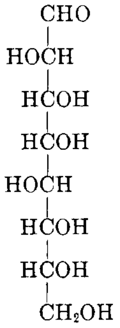
$$\begin{array}{c} CHO \\ | \\ HCOH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ CH_2OH \end{array}$$

I



$$\begin{array}{c} CH_2OH \\ | \\ C{=}O \\ | \\ HCOH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ CH_2OH \end{array}$$

II



$$\begin{array}{c} CHO \\ | \\ HOCH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ HOCH \\ | \\ HCOH \\ | \\ HCOH \\ | \\ CH_2OH \end{array}$$

III

Experimental

D-*glycero*-D-*gulo*-Octulose (II) from D-*erythro*-L-*talo*-octose Mother Liquors.—About 1942, Drs. Raymond M. Hann and Alice T. Merrill, in this laboratory, reduced several batches of D-*erythro*-L-*talo* octonic lactone in the usual manner with sodium amalgam, precipitated most of the sodium salts with methanol, concentrated the filtrate to a sirup, and from that sirup isolated crystalline D-*erythro*-L-*talo*-octose (I)[1] in about a 50% yield. Some of the mother liquors were combined, concentrated, and the sirup kept in a Pyrex distilling flask at room temperature until June, 1961. At that time we dissolved the sirup in water, deionized the solution with Amberlite IR-120 and Duolite A-4 ion-exchange resins, and concentrated to a sirup that weighed 53 g. Paper chromatograms developed in 1-butanol–pyridine–water (6:4:3) and sprayed with ammoniacal silver nitrate showed at least seven spots. Comparison with known substances that might be expected among the reduction products of D-*erythro*-L-*talo*-octonic lactone after nearly 20 years under slightly alkaline conditions (glass or residual sodium salts), indicated that the slowest moving spot was D-*erythro*-L-*galacto*-octose (visualized also with aniline hydrogen phthalate). The second spot had the same mobility as D-*erythro*-L-*talo*-octitol. The third was not identified but the fourth was undoubtedly D-*erythro*-L-*talo*-octose (visualized also with aniline hydrogen phthalate). The fifth and largest spot could be visualized readily with the orcinol-hydrochloric acid spray, with which it gave, when heated at 110°, a crimson color that faded rapidly to gray; this behavior is characteristic of the octuloses.[2c] The resulting spot gave a bluish-white fluorescence under the ultraviolet lamp, as do octuloses and nonuloses but not the lower carbon ketoses. The sixth, and smallest, spot appeared to be a second octulose, and its mobility in three solvent systems was the same as D-*glycero*-D-*ido*-octulose,[4] the epimeric octulose that might be expected from the further action of alkali on D-*glycero*-D-*gulo*-octulose.[5] The seventh and fastest moving spot, as will be mentioned again later, appeared to be an octosaccharinic lactone.

In order to isolate the octulose the 53 g. of sirup was placed on top of a cellulose column 90 cm. long and 4.8 cm. in diameter and the column was eluted with 1-butanol half-saturated with water, 250 ml. of eluate being collected in each fraction. When the fractions were concentrated and dissolved in small amounts of methanol, fraction 32 deposited crystals spontaneously, and fractions 25–37 deposited additional amounts of the same material on seeding. The yield of crystals so far is 4 g. The product was recrystallized from methanol from which it separates as chunky

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(1) A. T. Merrill, R. M. Hann, and C. S. Hudson, *J. Am. Chem. Soc.*, **65**, 994 (1943); R. M. Hann, A. T. Merrill, and C. S. Hudson, *J. Am. Chem. Soc.*, **66**, 1912 (1944).

(2)(a) M. L. Wolfrom and A. Thompson [*J. Am. Chem. Soc.*, **68**, 1453 (1946)] obtained this octulose earlier as a sirup through the diazomethane synthesis starting with D-*glycero*-D-*gulo*-heptonic acid; (b) Similarly, M. L. Wolfrom and P. W. Cooper [*J. Am. Chem. Soc.*, **71**, 2668 (1949)] prepared sirupy D-*glycero*-L-*gluco*-octulose, D-*glycero*-L-*manno*-octulose, and [*J. Am. Chem. Soc.*, **72**, 1345 (1950)] D-*glycero*-D-*galacto*-octulose; (c) A. J. Charlson and N. K. Richtmyer [*J. Am. Chem. Soc.*, **81**, 1512 (1959); **82**, 3428 (1960)] isolated D-*glycero*-D-*manno*-octulose as a sirup from the avocado and from *Sedum* species; (d) J. K. N. Jones and H. H. Sephton [*Can. J. Chem.*, **38**, 753 (1960)] synthesized four sirupy octuloses enzymically, namely, D-*glycero*-D-*altro*-octulose, L-*glycero*-L-*galacto*-octulose, D-*glycero*-L-*gluco*-octulose (see also ref. 2b), and D-*glycero*-L-*galacto*-octulose.

(3) E. Fischer, *Ann.*, **270**, 64 (1892).

(4) H. H. Sephton and N. K. Richtmyer, unpublished results from this laboratory.

(5) *Cf.*, E. M. Montgomery and C. S. Hudson [*J. Am. Chem. Soc.*, **61**, 1654 (1939)] for the alkaline rearrangement of D-*glycero*-D-*galacto*-heptose to both D-*manno*-heptulose and D-*gluco*-heptulose.

prisms melting about 125°, the exact temperature depending on the rate of heating. It showed a small mutarotation with $[\alpha]^{20}\mathrm{D}$ +37.6° (2.5 min.) → +34.6° (19 min., final) in water (*c* 1.4). The specific rotation is thus close to the value of +30.8° reported by Wolfrom and Thompson[2a] for their sirupy D-*glycero*-D-*gulo*-octulose prepared in a different manner. In 1-butanol–pyridine–water and in ethyl acetate–acetic acid–formic acid–water (18:3:1:4) our product migrated at the same rate as a sample of the D-*glycero*-D-*gulo*-octulose kindly supplied by Drs. Wolfrom and Thompson. The D-*glycero*-D-*gulo*-octulose, in butanol–pyridine–water, migrates at about the same rate as D-*manno*-heptulose and slightly faster than sedoheptulosan (2,7-anhydro-β-D-*altro*-heptulopyranose), either of which can serve as a convenient chromatographic standard for the higher carbon ketoses.

Anal. Calcd. for $C_8H_{16}O_8$: C, 40.00; H, 6.71. Found: C, 39.80; H, 6.72.

Our D-*glycero*-D-*gulo*-octulose was converted readily, by heating with phenylhydrazine hydrochloride and sodium acetate in water, to a phenylosazone that decomposed about 220° when heated rapidly. Authentic D-*glycero*-D-*gulo*-octose phenylosazone, prepared similarly from D-*erythro*-L-*galacto*-octose (III), decomposed also about 220°, and a mixture of the two phenylosazones showed the same decomposition point. The infrared spectra of the two phenylosazones were identical.

D-*glycero*-D-*gulo*-Octose Phenylosotriazole.[6]—A suspension of 3.2 g. of finely ground D-*glycero*-D-*gulo*-octose phenylosazone in 300 ml. of water containing 2.1 g. (1.1 mol. equiv.) of copper sulfate pentahydrate was refluxed for 3 hr., filtered, and concentrated *in vacuo* to dryness. The residue was extracted with acetone and the phenylosotriazole obtained readily by concentrating the extract. After two recrystallizations from acetone the compound (needles, 0.35 g., 14%) appeared to sinter about 147° and melt at 155–156° (capillary). Dr. Hann[6] had recrystallized his product from water and recorded m.p. 150–151°, which we have confirmed. Upon recrystallization of his sample from acetone it showed the same melting point behavior as ours. Our product showed $[\alpha]^{20}\mathrm{D}$ +17.3° in pyridine (*c* 0.6); Dr. Hann recorded values of +18.5° in pyridine (*c* 0.8) and +20.9° in water (*c* 0.7).

Anal. Calcd. for $C_{14}H_{19}N_3O_6$: C, 51.69; H, 5.89; N, 12.92. Found (for the two samples): C, 51.70, 51.94; H, 5.88, 5.92; N, 12.92, 12.97.

D-*glycero*-D-*gulo*-Octose Phenylosotriazole Hexabenzoate.[7]—When 5.2 g. (12 mol. equiv.) of benzoyl chloride was added to an ice-cold solution of 1 g. of the phenylosotriazole in 10 ml. of pyridine, and the solution allowed to stand 48 hr. before it was decomposed and extracted with chloroform in the usual manner, the product was 2.3 g. (79%) of the hexabenzoate. The material was recrystallized twice from 50 parts of absolute ethanol from which it separated as elongated prisms with m.p. 139–140° and $[\alpha]^{20}\mathrm{D}$ +34.0° in chloroform (*c* 0.8).

Anal. Calcd. for $C_{56}H_{43}N_3O_{12}$: C, 70.80; H, 4.56; N, 4.42; C_6H_5CO, 66.4. Found: C, 70.66; H, 4.64; N, 4.43; C_6H_5CO, 66.2.

D-*glycero*-D-*gulo*-Octose Phenylosotriazole Pentabenzoate.[7]—When only 6.6 mol. equiv. (2.85 g.) of benzoyl chloride was used for 1 g. of the phenylosotriazole in 10 ml. of pyridine, and the reaction mixture allowed to stand only overnight, 0.5 g. of a different benzoate was obtained. It was recrystallized twice from acetone, yielding small needles with m.p. 211–212° and $[\alpha]^{20}\mathrm{D}$ +7.6° in chloroform (*c* 0.7). Although Dr. Hann did not recognize, from a single carbon and hydrogen determination, that the compound was a pentabenzoate, this fact became evident when we obtained also nitrogen and benzoyl determinations. Furthermore, by subjecting 0.16 g. of the pentabenzoate to a further benzoylation we isolated 0.16 g. of once-crystallized hexabenzoate, m.p. and mixed m.p. 138–139°.

Anal. Calcd. for $C_{49}H_{39}N_3O_{11}$: C, 69.58; H, 4.65; N, 4.97; C_6H_5CO, 62.1. Found: C, 69.81; H, 4.89; N, 5.23; C_6H_5CO, 61.9.

Examination of Other Fractions from the Mother Liquors.—When fractions 12–17 from the cellulose column were concentrated they deposited crystals that corresponded to the fastest moving spot on the original paper chromatogram. The product (*ca.* 0.2 g.), after recrystallization from methanol as rosettes of small, stout prisms, melted at 121° and showed $[\alpha]^{20}\mathrm{D}$ +27 ± 1° in water (*c* 1). It has been identified provisionally as an **octosaccharinic lactone** (the first one known that contains more than six carbon atoms[8]) by its composition, by its typical lactone color reaction with alkaline hydroxylamine followed by ferric chloride spray reagents,[9] and by its great stability in aqueous solution (and hence was not removed by passage through the Duolite A-4 acid-absorbing resin).[10] It could be titrated only very slowly with aqueous alkali.

Anal. Calcd. for $C_8H_{14}O_7$: C, 43.24; H, 6.35; mol. wt., 222.2. Found: C, 43.13, 43.54; H, 6.31, 6.42; mol. wt. (by titration with sodium hydroxide), 221.3.

After practically all the octulose had been removed in the first sixty fractions, the remainder of the material on the cellulose column was recovered by elution with methanol. The solution, upon concentration, deposited about 2 g. of material that was identified, after recrystallization from 50% ethanol as prisms, as D-*erythro*-L-*talo*-octitol by direct comparison with authentic material[1]; m.p. and mixed m.p. 161–162°.

The mother liquor from the octitol, on further standing, deposited about 0.3 g. of fine needles, recognized as D-*erythro*-L-*galacto*-octose dihydrate by melting point, mixed melting point, and paper chromatographic comparison with authentic material.[1]

D-*glycero*-D-*gulo*-Octulose (II) from the Rearrangement of D-*erythro*-L-*galacto*-Octose (III) in Pyridine.—A total of 113 g. of the octose dihydrate (in several portions) was dissolved in enough dry pyridine to make a 10% solution, and the solution refluxed 5 hr. The pyridine was removed by evaporation with water *in vacuo*, and a total of 41 g. of octose dihydrate recovered by crystallization from water by the addition of methanol. The mother liquor was concentrated to remove the methanol and the octose remaining in the aqueous solution was oxidized by stirring with bromine and an excess of calcium carbonate. The mixture was filtered, deionized with Amberlite IR-120 and Duolite A-4 resins, and concentrated to a sirup (26 g.). Paper chromatography showed the sirup to contain at least seven substances, of which the expected D-*glycero*-D-*gulo*-octulose seemed to be in largest amount. This product was isolated by cellulose column chromatography, though so far only in about a 2-g. yield, and identified by melting point, mixed melting point, and infrared spectra with the octulose obtained from the 20-yr.-old sirup as described above. The other substances produced by the pyridine rearrangement, several of which were orcinol-positive and had higher mobilities in 1-butanol–pyridine–water than D-*glycero*-D-*gulo*-octulose, have not been studied further, although one is probably the epimeric D-*glycero*-D-*ido*-octulose.

In an attempted rearrangement of 10 g. of D-*erythro*-L-*galacto*-octose (III) with saturated aqueous calcium hydroxide solution for 2 weeks at 35°, followed by deionization and concentration, only 0.5 g. of a sirup was recovered. It seems probable that most of the starting material was converted into acidic substances that were removed later on

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[6] After we had prepared this phenylosotriazole, we discovered in one of the notebooks of Dr. R. M. Hann that he had made the same compound in 1947.

[7] As prepared by Dr. Hann in 1947.

[8] J. C. Sowden, *Advances in Carbohydrate Chem.*, **12**, 35 (1957).

[9] M. Abdel-Akher and F. Smith, *J. Am. Chem. Soc.*, **73**, 5859 (1951).

[10] G. Machell, *J. Chem. Soc.*, 3389 (1957).

the Duolite A-4 column. Paper chromatographic examination of the sirup showed some D-*glycero*-D-*gulo*-octulose but no evidence of any unchanged octose.

Acknowledgment.—The authors wish to thank Dr. Hugo H. Sephton for his help and advice, and Mr. Harold G. McCann and his associates of the Analytical Services Unit of this laboratory for obtaining the infrared spectra and the elemental analyses.

New Syntheses of Comenaldehyde Methyl Ether[1]

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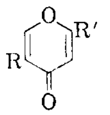
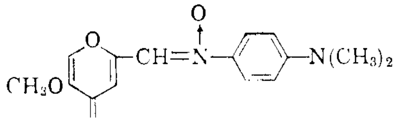
Recent interest has been shown in the synthesis of aldehydes containing the monocyclic γ-pyrone (4*H*-pyran-4-one) nucleus.[2,3] One report involves the preparation of the methyl ether of comenaldehyde (V) by oxidation of the carbinol VII.[3] We report the synthesis of V by two independent routes: from I *via* II, III, and IV in the Kröhnke aldehyde synthesis,[4] and from VII by manganese dioxide oxidation.

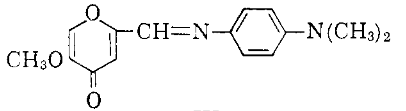
Methylation of chlorokojic acid (I) by the method of Yabuta[5] gave II. Interaction of II with pyridine at room temperature gave the very hygroscopic pyridinium salt III. Reaction of III and *p*-nitroso - *N,N* - dimethylaniline in cold aqueous ethanolic sodium hydroxide led to the orange-yellow nitrone IV. Hydrolysis of IV in cold sulfuric acid gave, in low yield, the colorless comenaldehyde methyl ether (V), m.p. 202–203°, raised after purification by sublimation *in vacuo* to 206–208°. The infrared spectrum of V contained the aldehyde carbonyl stretching band at 1705 (potassium bromide disk) and 1718 cm.$^{-1}$ (chloroform solution). In the potassium bromide disk spectrum, the pyrone carbonyl band was at 1655 cm.$^{-1}$.

Selective methylation of the enolic hydroxyl group of kojic acid (VI) by the method of Campbell[6] yielded the carbinol VII. Oxidation of VII to the aldehyde V was carried out in *t*-butyl alcohol solution by manganese dioxide, prepared from manganous carbonate by the method of Harfenist,[7] at room temperature for eight days. Yield of V, m.p. 205–206°, was 55–60%. This oxidation procedure differs from that of Becker[3] in method for preparation of manganese dioxide, temperature, solvent, and reaction period.





IV



IX

I. R = OH; R′ = CH$_2$Cl
II. R = OCH$_3$; R′ = CH$_2$Cl
III. R = OCH$_3$; R′ = [(CH$_2\overset{+}{\text{N}}$C$_5$H$_5$)Cl$^-$]
V. R = OCH$_3$; R′ = CHO
VI. R = OH; R′ = CH$_2$OH
VII. R = OCH$_3$; R′ = CH$_2$OH
VIII. R = OCH$_3$; R′ = COOH

The aldehyde V was characterized as a thiosemicarbazone, m.p. 244.5–246°, and as the anil IX, m.p. 177–177.5°. Silver oxide oxidation of V by the method of Campaigne and LeSuer[8] gave comenic acid methyl ether (VIII). Comparison of the properties of IV and IX shows that the nitrone, not the anil, is the intermediate in the preparation of V by the Kröhnke reaction.

Experimental

Melting points are uncorrected and were observed by the capillary tube method unless indicated by KHS, in which case Kofler hot stage was used. Analyses are by Micro-Tech Laboratories, Skokie, Ill., and Alfred Bernhardt, Mülheim, Germany.

Chlorokojic Acid Methyl Ether [2-(Chloromethyl)-5-methoxy-4*H*-pyran-4-one] (II).—This substance was prepared by the procedure of Yabuta[5]; m.p. 119–120° (lit.,[5] m.p. 119–121°).

(5-Methoxy-4*H*-pyran-4-on-2-yl)methyl Pyridinium Chloride (III).—A 9-g. quantity of very dry chlorokojic acid methyl ether in 150 ml. of pyridine (previously dried over potassium hydroxide) stood in a tightly stoppered flask for 24 hr. The pyridinium salt formed was collected by filtration, transferred immediately to a vacuum desiccator, and dried over concd. sulfuric acid; yield 12 g. (90%). Recrystallization from absolute ethanol–ether gave the analytically pure pyridinium salt (extremely hygroscopic), m.p. 200.5–201.5°.

Anal. Calcd. for $C_{12}H_{12}ClNO_3$: C, 56.70; H, 4.73; N, 5.51; Cl, 14.15. Found: C, 56.78; H, 4.95; N, 5.52; Cl, 13.79.

(5-Methoxy-4*H*-pyran-4-on-2-yl)-*N*-(*p*-dimethylaminophenyl)-nitrone (IV).—A solution of 6 g. of pyridinium salt III in 30 ml. of water was added to 3.6 g. of *p*-nitroso-*N,N*-dimethylaniline in 45 ml. of ethanol. To this mixture at 5° were added gradually with occasional shaking 25 ml. of 1 *N* sodium hydroxide. Then 200 ml. of ice water mixture were added to complete precipitation of the nitrone. After 1 hr., the crude nitrone was collected, washed with cold water,

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[1] This investigation was supported by a research grant (E-1703) from the National Institute of Allergic and Infectious Diseases, Public Health Service.

[2] L. L. Woods and P. A. Dix, *J. Org. Chem.*, **26**, 1028 (1961).

[3] H.-D. Becker, *Acta Chem. Scand.*, **15**, 683 (1961).

[4] F. Krohnke, *Angew. Chem.*, **65**, 612 (1953).

[5] T. Yabuta, *J. Chem. Soc.*, **125**, 575 (1924).

[6] K. N. Campbell, J. F. Ackerman, and B. K. Campbell, *J. Org. Chem.*, **15**, 221 (1950).

[7] M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

[8] E. Campaigne and W. M. LeSuer, *J. Am. Chem. Soc.*, **70**, 1557 (1948).