[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The 1,5-Anhydride of 2,3,4,6-Tetramethylglucose 1,2-Enediol

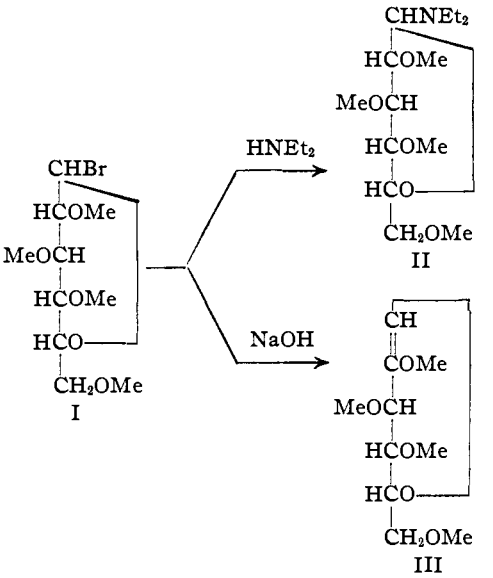
BY M. L. WOLFROM AND DONALD R. HUSTED

In 1927 Maurer and Mahn[1] treated acetobromoglucose with diethylamine and found that the amine removed hydrogen bromide from the acetobromoglucose and the substance known as 1,2-glucoseen tetraacetate or oxyglucal tetraacetate was thus obtained. This very interesting and reactive sugar derivative has been investigated extensively by Maurer and co-workers. Baker[2] later obtained the 1-diethylaminoglucose tetraacetate as its crystalline hydrochloride by a modification of the reaction conditions of Maurer and Mahn.

In the present investigation, we have been concerned with the preparation of the methylated analog of 1,2-glucoseen tetraacetate. When 1-bromo-2,3,4,6-tetramethylglucose (I)[3] was treated with diethylamine under conditions which gave a crystalline reaction product, only the 1-diethylamino-2,3,4,6-tetramethylglucose (II) was obtained. The desired product (III) was formed when 1-bromo-2,3,4,6-tetramethylglucose was treated with sodium hydroxide in anhydrous dioxane–ether solution. These conditions are those which have been reported from this Laboratory[4] for producing the beta to alpha conversion of fully acetylated sugars by alkali.

Products II and III were obtained in crystalline condition by application of the Hickman[5] high vacuum still technique. The 1-diethylaminotetramethylglucose formed crystals melting at 34° while those of the 2,3,4,6-tetramethyl-1,2-glucoseen (III) melted at 12°. The structure of the diethylamino compound was established by the isolation and identification of its hydrolytic products. The substance was very sensitive to hydrolytic agents.

2,3,4,6-Tetramethyl-1,2-glucoseen reduced Fehling's solution only after acid hydrolysis. It absorbed two atoms of iodine when analyzed according to the Wijs procedure and absorbed four atoms of iodine when treated with sodium hypoiodite.



Since 2,3,4,6-tetramethyl-1,2-glucoseen can be considered as the 1,5-anhydride of 2,3,4,6-tetramethylglucose 1,2-enediol, we are at present concerned with its further investigation and in particular with its relation to the possible intermediate in the alkaline conversion of 2,3,4,6-tetramethylglucose into its epimer, 2,3,4,6-tetramethylmannose.[6]

Experimental

Preparation of 1-Bromo-2,3,4,6-tetramethyl-*d*-glucose.—This substance was prepared from tetramethylglucopyranose according to the procedure of Levene and Cortese[3] with some modifications. The acetylation was performed by heating the mixture on the steam-bath for two or three hours, with mechanical stirring, instead of for ten minutes under reflux. For the acetate replacement, 40 g. of 2,3,4,6-tetramethylglucose-1-acetate was dissolved at 0° in 80 cc. of a mixture of equal parts of acetic anhydride and glacial acetic acid containing 60–70 g. of anhydrous hydrogen bromide per 100 cc. of solution. After standing for two hours at 0°, four or five volumes of chloroform, previously cooled to 0° or below, were added and the mixture was washed rapidly with water (twice), aqueous sodium bicarbonate (twice), and again with water (twice). The water and sodium bicarbonate solutions were used at a temperature near 0°. The dried chloroform solution was concentrated under reduced pressure at room temperature (or 35°) and the residual sirupy 1-bromo-2,3,4,6-tetramethylglucose was used immediately.

1-Diethylamino-2,3,4,6-tetramethyl-*d*-glucose.—The 1-bromo-2,3,4,6-tetramethylglucose sirup produced from 52

(1) K. Maurer and H. Mahn, *Ber.*, **60**, 1316 (1927); *cf.* K. Maurer, *ibid.*, **62**, 332 (1929).

(2) J. W. Baker, *J. Chem. Soc.*, 1205 (1929).

(3) P. A. Levene and F. Cortese, *J. Biol. Chem.*, **98**, 17 (1932).

(4) M. L. Wolfrom and D. R. Husted, THIS JOURNAL, **59**, 364 (1937).

(5) K. C. D. Hickman and C. R. Sanford, *J. Phys. Chem.*, **34**, 637 (1930).

(6) M. L. Wolfrom with W. Lee Lewis, THIS JOURNAL, **50**, 837 (1928).

g. of tetramethylglucose-1-acetate was dissolved in 15 cc. of dry benzene and to this was added 35 cc. of diethylamine, previously dried over anhydrous calcium sulfate (Drierite). Crystals of diethylamine hydrobromide soon precipitated. The reaction mixture was allowed to stand for about thirty-four hours at room temperature, whereupon it was diluted with anhydrous ether, filtered, and the residue washed with ether. The ethereal filtrate was concentrated under reduced pressure at 35° and the resultant sirup was dissolved in ethyl acetate, filtered from any diethylamine hydrobromide, treated with decolorizing carbon, and the solvent removed under reduced pressure at 35°. The resultant sirup (48 g.), dark yellow in color, was transferred to a Hickman type[5] high vacuum still and the fraction boiling at 62–65° at 10^{-4} mm., was collected; yield 31.9 g. This fraction crystallized on cooling and was purified by fractional melting. The crystals were warmed to about 25°, filtered with suction, and the crystals well pressed to remove adherent sirup. This process was repeated several times. A water-jacketed funnel was used for the first filtration. The melting point of the purified, colorless material was found to be 34°. The substance was very soluble in all the common organic solvents, including petroleum ether (both high and low boiling). It was only moderately soluble in water at room temperature but dissolved in hot water with hydrolysis (see below).

Anal. Calcd. for $C_{10}H_{17}ON(OCH_3)_4$: N, 4.80; OCH_3, 42.59. Found: N, 4.89; OCH_3, 42.31.

The substance reduced Fehling's solution only very slightly on prolonged boiling, but rapidly after a preliminary treatment with hot dilute hydrochloric acid.

The substance showed no appreciable rotation in chloroform solution, even in the blue portions of the visible spectrum. In methanol solution, the rotation was $[\alpha]^{29}D$ −2.8° (*c*, 2.7; *l*, 2-dm.; no mutarotation). In aqueous solution the substance showed a low initial levorotation, which changed slowly in the dextro direction. This mutarotation probably represents hydrolysis.

In saturated boric acid solution at 25° the compound mutarotated from $[\alpha]D$ −8° (approx.) to $[\alpha]D$ +64.8° (*c*, 3.1; *l*, 2-dm.). If the final rotation value is calculated to the basis of the tetramethylglucose that would be formed on complete hydrolysis, $[\alpha]D$ +79.9° is obtained. The final rotation value of tetramethylglucose in saturated boric acid solution was found to be $[\alpha]D$ +79.2°. The equilibrated boric acid solution rapidly reduced Fehling's solution. The solvent was evaporated and the residue was extracted with chloroform. The crystalline material obtained on chloroform removal was converted to the anilide and identified as 2,3,4,6-tetramethylglucose anilide (m. p. 135°; mixed m. p. unchanged).

A separate portion of the diethylamino compound was boiled with a 50% solution of sodium hydroxide in a flask fitted with a Vigreux column, with the outlet under a saturated solution of oxalic acid in ethanol. A crystalline precipitate formed on the addition of ether and was identified as diethylamine oxalate; m. p. 204–205° (uncorr.; mixed m. p. unchanged).[7]

(7) S. P. Mulliken, "Identification of Pure Organic Compounds," Vol. II, John Wiley and Sons, Inc., New York, 1916, p. 132.

Since Astruc[8] has shown that diethylamine can be determined quantitatively by titration in the same manner as ammonia, a weighed portion of the diethylamino compound was allowed to hydrolyze at 37° for twelve hours with 0.1 *N* hydrochloric acid and the excess acid was titrated with standard alkali; calcd. for $C_{10}H_{19}O_5N(C_2H_5)_2$, N, 4.80; found, N, 4.45.

All the above experiments characterize the crystalline compound of melting point 34° as 1-diethylamino-2,3,4,6-tetramethylglucose.

2,3,4,6-Tetramethyl-1,2-*d*-glucoseen.—The 1-bromo-2,3,4,6-tetramethylglucose sirup produced from 20 g. of tetramethylglucose-1-acetate was dissolved in a mixture of 75 cc. of anhydrous ether and 75 cc. of purified, anhydrous dioxane and transferred to three citrate pressure bottles (50 cc. in each). Drierite was added to each bottle to the extent of about one-fourth of the volume of its liquid contents. Vigorous mechanical shaking was then maintained for approximately thirty minutes, the bottles were removed, 5 to 10 g. of crushed sodium hydroxide was added very rapidly to each bottle and the bottles were returned to the shaker. Vigorous mechanical shaking was maintained until the solution was halogen-free, thirty-six to forty-eight hours being required. The bottles were then removed from the shaker and their contents were filtered rapidly with suction. The combined filtrates were treated with decolorizing charcoal and the solvents were removed under reduced pressure at 40–50°. The resultant sirup (8–12 g.) distilled from a Hickman type[5] high vacuum still at 50–55° at 10^{-3} mm. The compound may be distilled from a Claisen flask with a good oil pump, but better results were obtained when at least a first distillation was performed in the Hickman still under high vacuum.

The water-white distillate (5–6 g.) crystallized on cooling in dry ice (stoppered container) and warming in an ice-bath. The crystals were filtered with suction and pressed. This process of fractional melting was repeated several times. All filtrations were carried out in a cold room at a temperature of 0° or lower and care was taken not to warm the apparatus on handling.

The purified material formed colorless, well-defined crystals; m. p. 12°; b. p. 99.2–99.5° (4 mm.), 55–60° (10^{-3} mm.); $[\alpha]^{30}D$ +15° (H_2O, *c*, 2.0, *l*, 2-dm.), +4° ($CHCl_3$, *c*, 6.4, *l*, 2-dm.). The substance was soluble in water, acetone, ether, dioxane, alcohol and chloroform. The compound was difficult to obtain in a state of analytical purity and a number of preparations gave low carbon and low methoxyl values.

Anal. Calcd. for $C_6H_6O(OCH_3)_4$: C, 55.02; H, 8.31; OCH_3, 56.88. Found: C, 54.57; H, 8.34; OCH_3, 56.3.

The freshly prepared compound reduced Fehling's solution only after hydrolysis with hot, dilute hydrochloric acid. After standing for several weeks, preparations of the compound were found to reduce Fehling's solution slightly on prolonged boiling. In chloroform solution the substance absorbed bromine rapidly. The unsaturation value as determined by the Wijs procedure[9] was 93% of

(8) A. Astruc, *Compt. rend.*, **129**, 1021 (1899).

(9) J. J. A. Wijs, *Ber.*, **31**, 750 (1898); *cf.* A. E. Leach (A. L. Winton), "Food Inspection and Analysis," 4th Edition, John Wiley and Sons, Inc., New York, 1920, p. 509.

the theoretical required for one double bond. Under conditions of alkaline hypoiodite oxidation[10] 200 mg. of the substance consumed 18.4 cc. of 0.1 molar (I_2) iodine solution; calculated for four atoms of iodine per mole of tetramethylglucoseen, 18.3 cc. This iodine consumption is equivalent to an "apparent tetramethylaldohexose value"[6] of 217%.

(10) F. A. Cajori, *J. Biol. Chem.*, **84**, 617 (1922); cf. ref. 6.

Summary

1. 1-Diethylamino-2,3,4,6-tetramethyl-*d*-glucose and 2,3,4,6-tetramethyl-1,2-*d*-glucoseen have been synthesized in crystalline condition. Some of the properties of the latter compound have been noted.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of 3-Substituted Derivatives of Methylcholanthrene

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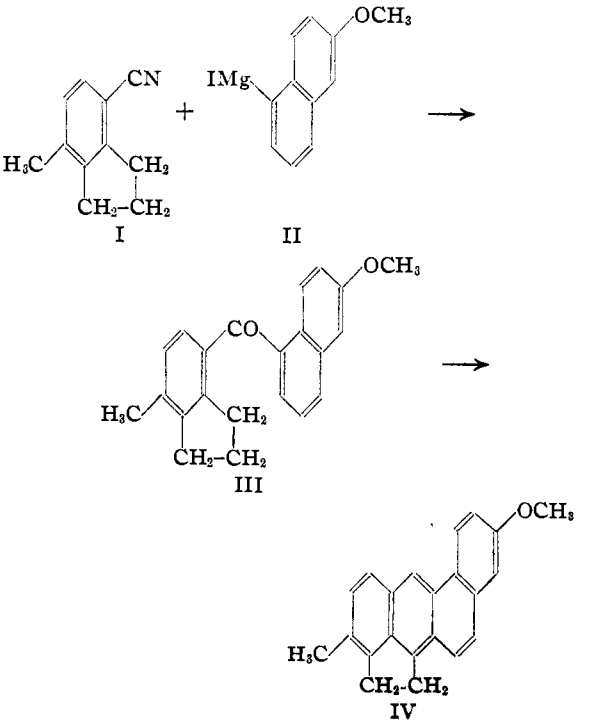
This investigation was undertaken to determine whether the cholanthrene synthesis of Fieser and Seligman[2] can be employed for the preparation of cholanthrene derivatives containing substituents other than alkyl groups, and, in case such compounds should be found to withstand the rather drastic pyrolysis involved in the final step, to synthesize by this method certain 3-substituted methylcholanthrenes (sterol numbering system[2b]). We were particularly interested in the 3-hydroxy compound, since this conceivably may arise in the organism as a product of steroid metabolism, but we temporarily discontinued our work in this direction at an early stage because of the appearance in the autumn of 1936 of a paper containing an announcement of the synthesis of 3-hydroxymethylcholanthrene by Cook and de Worms.[3] No information concerning the method of synthesis or the physical properties of the compound was included either in this announcement or in subsequent discussions of the compound in other publications[4] from the Royal Cancer Hospital and, since our plan of synthesis involved the application of a general method discovered and actively investigated in this Laboratory, we eventually decided to complete our work in order to provide for bioassays a sample of the compound obtained by a synthesis presumably different from that employed by the London group. On communicating our results to Professor Cook in advance of publication, however, we learned that he and de Worms had used the same method, except for a minor variation in an intermediate step. Following Professor Cook's suggestion that the results from the two Laboratories be published simultaneously, we are recording herewith our own observations, but in doing so we cordially acknowledge the priority of the English investigators.

In our synthesis the previously described 4-methyl-7-cyanohydrindene[2d] (I) was first condensed with the Grignard reagent (II) from 6-methoxy-1-iodonaphthalene, prepared from



(1) National Research Fellow in Medicine.

(2) (a) Fieser and Seligman, THIS JOURNAL, **57**, 942 (1935); (b) **57**, 1377 (1935); (c) **57**, 2174 (1935); (d) **58**, 2482 (1936); (e) **59**, 883 (1937); (f) Fieser and Hershberg, *ibid.*, **57**, 1681 (1935); (g) **59**, 394 (1937); (h) Bruce with Fieser, *ibid.*, **59**, 479 (1937).

(3) Cook, Haslewood, Hewett, Hieger, Kennaway and Mayneord, Reports of the II International Congress of Scientific and Social Campaign against Cancer, **1**, 1 (1936).

(4) (a) *Idem*, *Am. J. Cancer*, **29**, 219 (1937); (b) Cook, *Bull. soc. chim.*, [5] **4**, 792 (1937); (c) Bachmann, Cook, Dansi, de Worms, Haslewood, Hewett and Robinson, *Proc. Roy. Soc.* (London), **123B**, 343 (1937),