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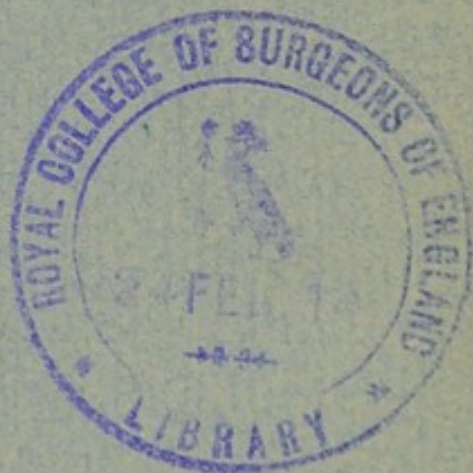
13.

THE SYNTHETICAL PREPARATION
OF THE
d-GLUCOSIDES OF
SITOSTEROL, CHOLESTEROL, AND SOME
FATTY ALCOHOLS

BY

ARTHUR H. SALWAY, PH.D., D.SC.

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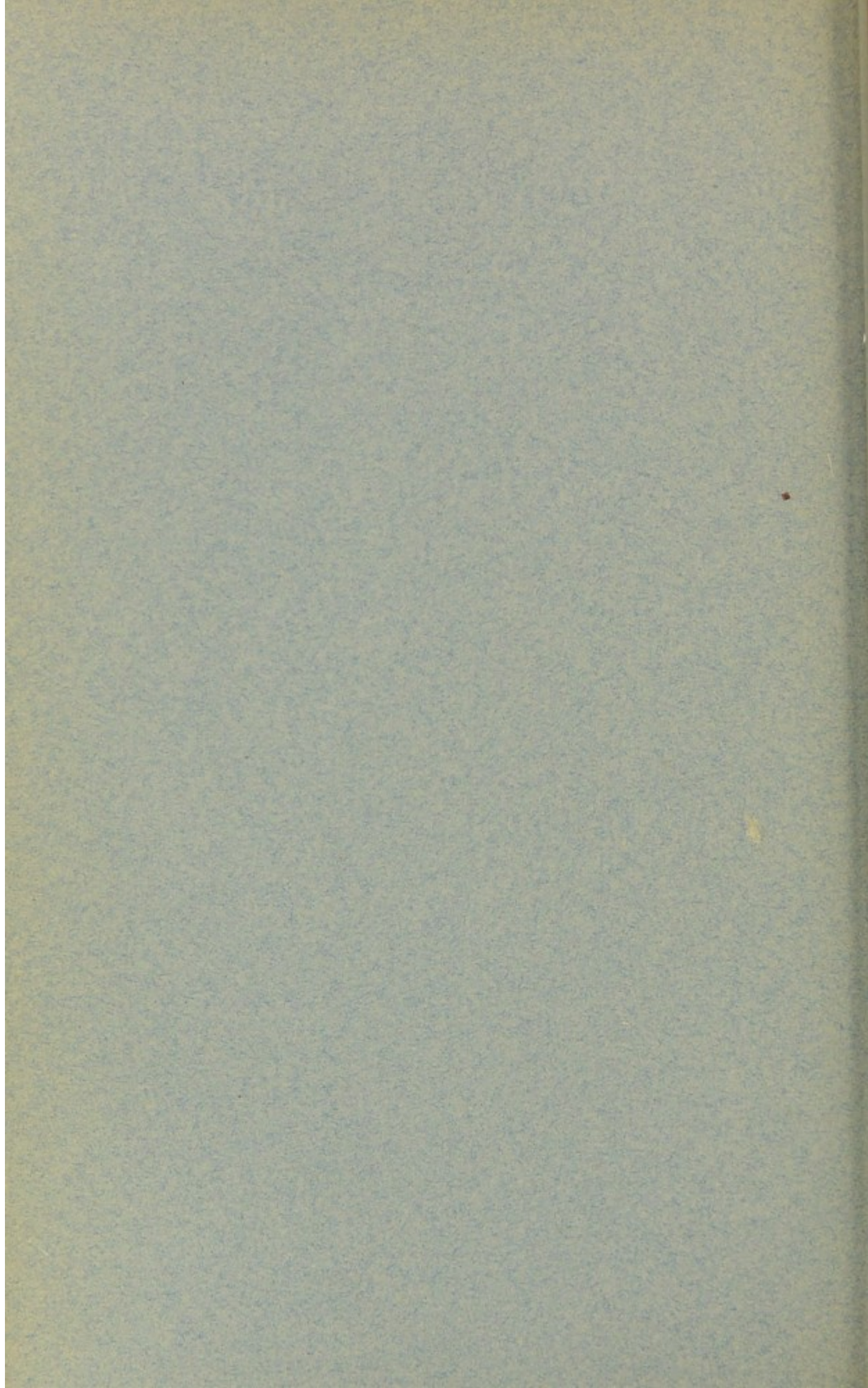


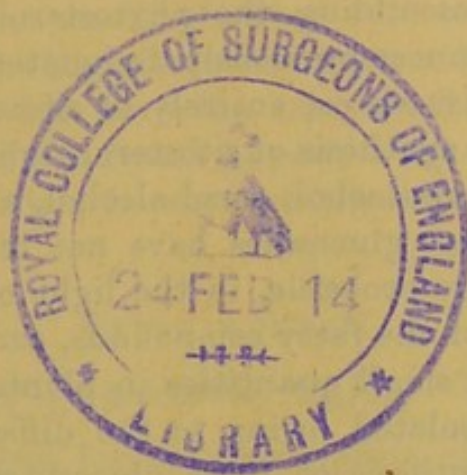
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CVIII.—*The Synthetical Preparation of the d-Glucosides of Sitosterol, Cholesterol, and Some Fatty Alcohols.*

By ARTHUR HENRY SALWAY.

It has recently been shown (T., 1913, 103, 399) that phytosterol glucosides are of frequent occurrence in plants. These substances, which have been designated phytosterolins, vary to some extent in composition and character according to the plant from which they have been isolated. In many cases the phytosterolin appears to consist of sitosterol-*d*-glucoside, $C_{27}H_{45}O \cdot C_6H_{11}O_5$, whilst in other instances it seems to be a mixture of this substance with the glucoside of stigmasterol, $C_{30}H_{49}O \cdot C_6H_{11}O_5$. In order to obtain additional information regarding the character of these natural substances, it was deemed of importance to attempt the synthesis of a phytosterol glucoside, and compare its properties with those of the naturally occurring phytosterolins. The phytosterol

chosen for this purpose was sitosterol, $C_{27}H_{46}O$, since the latter can be prepared in comparatively large quantities from wheat germ, and is uncontaminated with stigmasterol when obtained from this source. It was converted into the glucoside by treatment with bromoacetoglucose in ethereal solution in the presence of dry silver oxide. The sitosterol-*d*-glucoside thus obtained was found to possess properties closely resembling the phytosterolins, and there is no doubt that the substances previously designated ipuranol, cluytanol, and trifolanol consist almost entirely of sitosterol-*d*-glucoside.

In addition to the synthesis of sitosterol-*d*-glucoside, the glucosides of cholesterol, myricyl alcohol, ceryl alcohol, and cetyl alcohol have been prepared. These glucosides have not hitherto been found in nature, but it appears probable, in the light of recent observations, that the glucosides of the fatty compounds, ceryl, cetyl, and myricyl alcohols, do occur in small quantities in plants, and that they have not hitherto been isolated owing to the difficulty attending their separation. The synthesis of these glucosides was of importance, since a knowledge of their properties would greatly facilitate the future examination of plants for the presence of such substances.

It was also intended to prepare the glucoside of the so-called *ischolesterol*, and a commercial specimen of the latter was procured for the purpose. The material was found, however, to be a very impure mixture of substances, since it contained considerable quantities of cholesterol and carnaubyl alcohol, $C_{24}H_{50}O$, and no substance agreeing with the *ischolesterol* of Schulze and his pupils (*J. pr. chem.*, 1873, [ii], **7**, 163; 1874, [ii], **9**, 325; 1882, [ii], **25**, 159), or of Darmstädter and Lifschütz (*Ber.*, 1898, **31**, 97), could be isolated from it. It may furthermore be noted in this connexion that the statements of the above-mentioned authors concerning the properties and composition of *ischolesterol* are so conflicting that further investigation of the subject is desirable.

The question whether the glucosides prepared in this investigation belong to the α - or β -series has been left undecided on account of the fact that the insolubility of these substances in water renders the emulsion test for α - and β -glucosides indecisive. Fischer and Helferich (*Annalen*, 1911, **383**, 68) have shown, however, that in almost all cases the method of preparation of glucosides described by them, and adopted in the present investigation, leads to the formation of β -glucosides, so that the glucosides now obtained probably belong also to this series. In the case of ceryl-*d*-glucoside, however, it is of interest to note that the present author has isolated two distinct modifications, which may possibly represent the α - and β -forms of the glucoside, although no definite evidence to this effect has been obtained.

The formation of two modifications of ceryl-*d*-glucoside, $C_{27}H_{55}O \cdot C_6H_{11}O_5$, is of some interest in connexion with an observation of E. Fischer and Helferich (*loc. cit.*) regarding the properties of cetyl-*d*-glucoside, $C_{16}H_{33}O \cdot C_6H_{11}O_5$. These investigators showed that cetyl-*d*-glucoside melts indefinitely, beginning to change at 78° and finally melting at about 145° ; it now seems probable, in view of the results obtained with ceryl-*d*-glucoside, that this behaviour is due to the presence of two modifications. In order to ascertain whether this were the case, cetyl-*d*-glucoside was prepared, but although it was found to possess the properties described by Fischer and Helferich, it was not possible to separate the two modifications.

EXPERIMENTAL.

I. Sitosterol-*d*-glucoside, $C_{27}H_{45}O \cdot C_6H_{11}O_5$.

The sitosterol required for the preparation of this compound was obtained from wheat-germ (compare Burian, *Monatsh.*, 1897, **18**, 551). The fatty oil from 50.8 kilos. of the latter was hydrolysed with an excess of potassium hydroxide in the presence of alcohol, and the resulting soap solution extracted repeatedly with ether. The ethereal solution was then evaporated, and the residue crystallised from ethyl acetate, when the sitosterol was obtained in colourless needles, melting at 138° . The amount of pure substance isolated from 50.8 kilos. of wheat germ was 130 grams (compare Pickard, *T.*, 1908, **93**, 1928). It possessed the specific rotation $[\alpha]_D -32.2^\circ$ ($c=2.9$ with chloroform), and on analysis gave results agreeing well with the formula $C_{27}H_{46}O$.

In order to ascertain whether the material was quite free from stigmasterol, it was acetylated, and the acetyl derivative treated with bromine according to Windaus and Hauth's method (*Ber.*, 1906, **39**, 4378), but a negative result was obtained, thus showing the absence of stigmasterol.

For the conversion of sitosterol into its glucoside, 15 grams of anhydrous substance and 15 grams of pure bromoacetoglucose were dissolved in dry ether and shaken continuously for eight hours with freshly precipitated, dry silver oxide. The mixture was then filtered, a little dilute nitric acid having been previously added to coagulate the silver oxide and facilitate the filtration, after which the ethereal filtrate was washed, dried, and evaporated. The residue was next crystallised once from alcohol to remove a small amount of soluble by-product formed from the bromoacetoglucose. The substance thus obtained then consisted of a mixture of tetra-acetyl-sitosterol-*d*-glucoside and unchanged sitosterol, and could not be resolved into its components by direct fractional crystallisation. It

was therefore dissolved in hot alcohol, and the solution digested for about a minute with an excess of potassium hydroxide. In this manner the acetyl groups of the glucoside were eliminated without affecting the remaining part of the molecule, and the free glucoside, which is only sparingly soluble in hot alcohol, was deposited. This was collected, washed with hot alcohol, and purified by crystallisation from a mixture of pyridine and alcohol, when it separated in rosettes of small, colourless needles. When heated in a capillary tube, the substance begins to soften at about 270° , and melts and decomposes at $295-300^{\circ}$. The yield of pure substance amounted to 4 grams:

0.1028 gave 0.2721 CO_2 and 0.0960 H_2O . $\text{C}=72.2$; $\text{H}=10.4$.

$\text{C}_{33}\text{H}_{56}\text{O}_6$ requires $\text{C}=72.3$; $\text{H}=10.2$ per cent.

Sitosterol-d-glucoside, $\text{C}_{27}\text{H}_{45}\text{O} \cdot \text{C}_6\text{H}_{11}\text{O}_5$, is insoluble in water and only sparingly soluble in alcohol, ether, chloroform, or benzene. It dissolves readily in pyridine, and can be easily crystallised from this solvent in admixture with alcohol. It yields the characteristic colour reaction of the phytosterols when dissolved in acetic anhydride and chloroform, and a drop of concentrated sulphuric acid then added. When heated with aqueous hydrochloric acid in the presence of amyl alcohol it is readily resolved into its components, sitosterol and dextrose.

Tetra-acetylsitosterol-d-glucoside, $\text{C}_{27}\text{H}_{45}\text{O} \cdot \text{C}_6\text{H}_7\text{O}_5\text{Ac}_4$.—This substance was prepared by heating the glucoside for thirty minutes with an excess of acetic anhydride. The greater part of the latter was then removed by distillation, alcohol added to the residue, and the crystalline solid which separated then recrystallised from alcohol. It was thus obtained in colourless, glistening leaflets, melting at $166-167^{\circ}$:

0.1010 gave 0.2540 CO_2 and 0.0812 H_2O . $\text{C}=68.6$; $\text{H}=8.9$.

$\text{C}_{41}\text{H}_{64}\text{O}_{10}$ requires $\text{C}=68.7$; $\text{H}=8.9$ per cent.

0.5694, made up to 20 c.c. with chloroform, gave $\alpha_D -1^{\circ}18'$ in a 2-dcm. tube, whence $[\alpha]_D -22.9^{\circ}$.

Tetra-acetylsitosterol-d-glucoside is very readily soluble in ether, chloroform, benzene, or hot alcohol, but only sparingly so in cold alcohol. It is immediately hydrolysed in the presence of alkali hydroxides with regeneration of the glucoside.

Tetrabenzoylsitosterol-d-glucoside, $\text{C}_{27}\text{H}_{45}\text{O} \cdot \text{C}_6\text{H}_7\text{O}_5\text{Bz}_4$.—In order to obtain this compound, sitosterol-d-glucoside was dissolved in pyridine, and the solution gently warmed for about a minute with an excess of benzoyl chloride. The mixture was then poured into alcohol, when the benzoyl derivative separated as a flocculent precipitate. This was collected and purified by crystallisation from

chloroform and alcohol, when it was obtained in slender, colourless needles, melting at 198° :

0.1075 gave 0.2988 CO_2 and 0.0721 H_2O . $\text{C}=75.8$; $\text{H}=7.5$.

$\text{C}_{61}\text{H}_{72}\text{O}_{10}$ requires $\text{C}=75.9$; $\text{H}=7.5$ per cent.

0.4733, made up to 20 c.c. with chloroform, gave $\alpha_D + 0^{\circ}52'$ in a 2-dcm. tube, whence $[\alpha]_D + 18.3^{\circ}$.

Tetrabenzoylsitosterol-*d*-glucoside is readily soluble in chloroform, ethyl acetate, or benzene, but sparingly so in alcohol.

The above-described properties of sitosterol-*d*-glucoside closely resemble those of the naturally occurring phytosterolins, and it is evident that the substances previously designated ipuranol, cluytianol, and trifolianol consist almost entirely of sitosterol-*d*-glucoside.

II. Cholesterol-*d*-glucoside, $\text{C}_{27}\text{H}_{45}\text{O} \cdot \text{C}_6\text{H}_{11}\text{O}_5$.

The cholesterol employed in the preparation of the above glucoside melted at 146 — 147° , gave on analysis results agreeing with the formula $\text{C}_{27}\text{H}_{46}\text{O}$, and possessed an optical rotation of $[\alpha]_D - 40.3^{\circ}$ ($c=2.1$ in chloroform).

Five grams of cholesterol and 5 grams of bromoacetoglucose, dissolved in ether, were shaken for eight hours in the presence of dry silver oxide, and the product of the reaction was examined in the manner described in connexion with the preparation of sitosterol-*d*-glucoside. The cholesterol-*d*-glucoside thus obtained was purified by crystallisation from dilute pyridine, when it was deposited in minute, colourless needles, which began to soften about 270° , and completely melted at 285° . The yield of glucoside amounted to 2 grams:

0.0704 gave 0.1864 CO_2 and 0.0651 H_2O . $\text{C}=72.2$; $\text{H}=10.3$.

$\text{C}_{33}\text{H}_{56}\text{O}_6$ requires $\text{C}=72.3$; $\text{H}=10.2$ per cent.

The properties of cholesterol-*d*-glucoside are very similar to those of sitosterol-*d*-glucoside. It is very sparingly soluble in alcohol, chloroform, or ether, but readily so in pyridine or hot amyl alcohol. It yields the characteristic cholesterol colour reactions.

Tetra-acetylcholesterol-d-glucoside, $\text{C}_{27}\text{H}_{45}\text{O} \cdot \text{C}_6\text{H}_7\text{O}_5\text{Ac}_4$.—This substance was obtained by heating the glucoside with acetic anhydride for half an hour. On removing the greater part of the latter and adding alcohol to the residue, a crystalline acetyl derivative was deposited, which was recrystallised from alcohol, and obtained in colourless needles, melting at 159 — 160° :

0.0882 gave 0.2222 CO_2 and 0.0707 H_2O . $\text{C}=68.7$; $\text{H}=8.9$.

$\text{C}_{41}\text{H}_{64}\text{O}_{10}$ requires $\text{C}=68.7$; $\text{H}=8.9$ per cent.

0.1822, made up to 20 c.c. with chloroform, gave $\alpha_D - 0^{\circ}26'$ in a 2-dcm. tube, whence $[\alpha]_D - 23.8^{\circ}$.

III. *Myricyl-d-glucoside*, $C_{30}H_{61}O \cdot C_6H_{11}O_5$.

Five grams of myricyl alcohol were shaken for eight hours with a dry ethereal solution of bromoacetoglucose (5 grams) in the presence of dry silver oxide (5 grams). The mixture was then filtered, the filtrate evaporated, and the solid residue, which contained the desired tetra-acetylmyricyl-*d*-glucoside mixed with unchanged myricyl alcohol, was dissolved in a mixture of equal parts of hot benzene and alcohol. On cooling, the greater part of the myricyl alcohol separated and was collected, whilst the tetra-acetyl derivative of the glucoside remained in the filtrate. The latter was subsequently heated for a very short time (about one minute) with an excess of alcoholic potassium hydroxide, and the glucoside, which separated on cooling, collected and washed with cold alcohol. It was purified by dissolving in hot chloroform and precipitating the glucoside from solution by the addition of ether. This product was then crystallised from hot alcohol, when it separated in small, colourless plates, melting at 99° . The yield of pure glucoside amounted to about 10 per cent. of the myricyl alcohol employed in the reaction:

0.1000 gave 0.2642 CO_2 and 0.1078 H_2O . $C=72.1$; $H=12.0$.

$C_{36}H_{72}O_6$ requires $C=72.0$; $H=12.0$ per cent.

Myricyl-d-glucoside is insoluble in water, sparingly soluble in ether or chloroform, but readily so in pyridine or hot alcohol. It could only be obtained in one modification, thus differing from the glucoside of ceryl alcohol.

Tetra-acetylmyricyl-d-glucoside, $C_{30}H_{61}O \cdot C_6H_7O_5Ac_4$.—This compound was obtained by heating the glucoside with acetic anhydride for some time, then removing the greater portion of the latter by distillation and adding alcohol to the residue. The precipitate of acetyl derivative thus obtained was crystallised from a mixture of ethyl acetate and alcohol, when it separated in small, colourless leaflets, melting at $78-79^\circ$:

0.1010 gave 0.2533 CO_2 and 0.0972 H_2O . $C=68.4$; $H=10.7$.

$C_{44}H_{80}O_{10}$ requires $C=68.6$; $H=10.5$ per cent.

0.1542, made up to 20 c.c. with chloroform, gave $\alpha_D -0^\circ 10'$ in a 2-dcm. tube, whence $[\alpha]_D -10.8^\circ$.

Tetra-acetylmyricyl-*d*-glucoside is readily soluble in ether, chloroform, or benzene, but only sparingly so in cold alcohol.

IV. *Ceryl-d-glucoside*, $C_{27}H_{55}O \cdot C_6H_{11}O_5$.

The preparation and isolation of this compound were effected in a manner precisely similar to that adopted in the preparation of

myricyl-*d*-glucoside. The glucoside was obtained, after being crystallised from methyl alcohol, in small, hexagonal plates, melting at 94° . The yield of pure substance amounted to about 10 per cent. of the ceryl alcohol employed:

0.1460 gave 0.3808 CO_2 and 0.1560 H_2O . $\text{C}=71.1$; $\text{H}=11.9$.

$\text{C}_{33}\text{H}_{66}\text{O}_6$ requires $\text{C}=71.0$; $\text{H}=11.8$ per cent.

Ceryl-d-glucoside was found to exist in two modifications, the one melting at 94° , as described above, whilst the other melts at 135° . The latter was obtained by dissolving the former in hot chloroform, when glistening leaflets of the modification of high melting point immediately separated from the hot solution. If the latter is recrystallised from alcohol, it is more or less transformed into the modification of lower melting point. The glucoside melting at 135° was analysed, with the following result:

0.0871 gave 0.2263 CO_2 and 0.0928 H_2O . $\text{C}=70.9$; $\text{H}=11.8$.

$\text{C}_{33}\text{H}_{66}\text{O}_6$ requires $\text{C}=71.0$; $\text{H}=11.8$ per cent.

Tetra-acetylceryl-d-glucoside, $\text{C}_{27}\text{H}_{55}\text{O}\cdot\text{C}_6\text{H}_7\text{O}_5\text{Ac}_4$.—This compound was prepared in the manner described in connexion with the preparation of tetra-acetylmyricyl-*d*-glucoside. It crystallised from a mixture of alcohol and ethyl acetate in small, colourless leaflets, melting at $85\text{--}87^{\circ}$:

0.0758 gave 0.1883 CO_2 and 0.0696 H_2O . $\text{C}=67.8$; $\text{H}=10.2$.

$\text{C}_{41}\text{H}_{74}\text{O}_{10}$ requires $\text{C}=67.8$; $\text{H}=10.2$ per cent.

0.2010, made up to 20 c.c. with chloroform, gave $\alpha_D -0^{\circ}17'$ in a 2-dcm. tube, whence $[\alpha]_D -14.1^{\circ}$.

V. *Cetyl-d-glucoside*, $\text{C}_{16}\text{H}_{33}\text{O}\cdot\text{C}_6\text{H}_{11}\text{O}_5$.

This glucoside has already been described by Fischer and Helferich (*loc. cit.*). In the present investigation it was prepared by the method of these authors, but a more expeditious way of isolating the product was adopted. Five grams of cetyl alcohol were shaken for eight hours in dry ethereal solution with bromoacetoglucose (5 grams) and dry silver oxide (5 grams). The mixture was then filtered to remove the silver, the ethereal filtrate evaporated, and the residue from the latter hydrolysed in alcoholic solution by heating for about a minute with an excess of potassium hydroxide. Water was then added to the alcoholic liquid, and the precipitated solid extracted with ether. On washing the ethereal solution with water and thus removing the alcohol contained in it, the glucoside separated as a flocculent precipitate, which was collected and crystallised from chloroform. It was thus obtained in small, colourless needles, which began to soften at 78° , and completely melted at about 150° . It yielded an acetyl derivative,

melting at 71—73°, and was thus found to possess the properties previously ascribed to it. The glucoside could not be separated into modifications of definite melting point as in the case of ceryl-*d*-glucoside.

Tetrabenzoylcetyl-d-glucoside, $C_{16}H_{33}O \cdot C_6H_7O_5Bz_4$.—This derivative of cetyl-*d*-glucoside, not hitherto described, was prepared by heating the glucoside with benzoyl chloride for a few minutes in the presence of pyridine. On adding alcohol and keeping the mixture for some time, the benzoyl compound separated in clusters of silky needles, melting at 65°:

0.0969 gave 0.2600 CO_2 and 0.0653 H_2O . $C=73.2$; $H=7.3$.

$C_{50}H_{60}O_{10}$ requires $C=73.2$; $H=7.2$ per cent.

0.2380, made up to 20 c.c. with chloroform, gave $\alpha_D + 0^\circ 22'$ in a 2-dcm. tube, whence $[\alpha]_D + 15.4^\circ$.

Tetrabenzoylcetyl-*d*-glucoside is readily soluble in ether, chloroform, or benzene, but dissolves sparingly in alcohol.

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