A Glycosidic Constituent of Vinca minor *and its Identification as 3-β-D-Glucosyloxy-2-hydroxybenzoic Acid.*

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A new glycoside, hydrolysed to 2 : 3-dihydroxybenzoic acid and D-glucose, has been found in methanolic extracts from the leaves of *Vinca minor*. It has been identified as 3-β-D-glucosyloxy-2-hydroxybenzoic acid by a synthesis of the methyl ester penta-acetate; in addition, the glucosylation of 2 : 4- and of 3 : 4-dihydroxybenzoic acid has been investigated.

Other constituents obtained from the leaves include ursolic acid, independently observed by Le Men and Pourrat (*Ann. pharm. franç.*, 1952, **10**, 349; 1953, **11**, 449), and an alkaloid $C_{21}H_{26}O_3N_2$, which appears to be identical with vincamine described by Schlittler and Furlenmeier (*Helv. Chim. Acta*, 1953, **36**, 2017).

THE genus *Vinca* or periwinkle (fam. Apocynaceae), which is widely distributed in Europe and Western Asia, embraces the evergreen trailing plants *V. minor* and *V. major*, and decoctions of the leaves of these species have long been known to possess astringent and carminative properties. Tannins and a syrupy "glucoside" have been found in the leaves of *V. minor* (Rutishauser, *Bull. Sci. Pharmacol.*, 1932, **39**, 475; *Compt. rend.*, 1932, **195**, 75), and the occurrence of alkaloids in certain *Vinca* species has been reported, *e.g.*, in *V. pubescens*, believed to be identical with *V. major*, from which three crystalline bases of unknown constitution have been obtained (Orekhoff, Gurevich, Norkina, and Prein, *Arch. Pharm.*, 1934, **272**, 70). A further product, present in the flowers of both *V. minor* and *V. major*, is the glycoside robinin, kæmpferol 7-L-rhamnosido-3-robinoside, which has previously been isolated from *Robinia pseudacacia* (Zemplén and Bognár, *Ber.*, 1941, **74**, 1783). This summarises the principal features of the chemistry of the genus prior to a further examination in 1951—53 (J. H. Gilks, Thesis, Nottingham, April, 1954) of the constituents of *V. minor* leaves derived from commercial sources. Other independent contemporary investigations are mentioned in the following account of our work.

The macerated dry leaves and attached stems were extracted with boiling methanol, and after concentration of the resulting solution to small bulk, a dark green solid separated, which was purified by extensive recrystallisation. The eventually colourless product, m. p. 287—290°, gave a positive response to the Liebermann–Burchardt test, and analyses of a rigorously dried specimen indicated a molecular formula of $C_{30}H_{46(48)}O_3$. With aqueous sodium hydroxide a sparingly soluble salt was obtained which reacted with methyl sulphate to give a methyl ester. The compound was thus recognised as a triterpene carboxylic acid and its conversion by acetic anhydride with basic catalysts into a monoacetate established the alcoholic function of the remaining oxygen atom. With perchloric acid as catalyst, however, a crystalline product containing two acetyl residues was obtained which, as it formed with aqueous ethanol a monoacetate, is apparently the monoacetate mixed anhydride. A comparison of the physical constants of the acid and of its derivatives with those of the relevant known triterpenes indicated a possible identity with ursolic acid. This was confirmed by the preparation from authentic ursolic acid of the acetate and acetate-anhydride, of methyl ursolate, and of two new derivatives, *i.e.*, the benzoate and the highly crystalline acetoacetate, the latter from the toluene-*p*-sulphonic acid-catalysed reaction with diketen. Moreover, an account of the distribution of ursolic acid published after the conclusion of these experiments (Le Men and Pourrat, *Ann. pharm. franç.*, 1952, **10**, 349; 1953, **11**, 449) records the isolation of the triterpene from nine *Apocynaceae*, including *V. minor* and *V. major*.

By stirring with dilute hydrochloric acid an evaporated methanol extract prepared from a mixture of the leaves and calcium hydroxide, a solution of the basic constituents

was obtained, from which chloroform removed a crude alkaloid hydrochloride. Treatment of the chloroform solution with alkali yielded a weakly basic product, eventual m. p. 230—231°, of molecular formula $C_{21}H_{26}O_3N_2$, having a picrate, m. p. 228—229°. The base contains one methoxyl group, and the ultraviolet absorption (max. at 228 and 276 mμ) resembles that of alkaloids of the indole group. It clearly corresponds to the alkaloid vincamine, $C_{21}H_{26}O_3N_3$, m. p. 232—233° (picrate, m. p. 220—225°), $\lambda_{max.}$ 230, 278 mμ, shortly afterwards reported by Schlittler and Furlenmeier (*Helv. Chim. Acta*, 1953, **36**, 2017) as a constituent of *V. minor*.

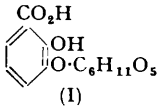
An examination was also undertaken of the methanolic extract of *V. minor* leaves for the so-called glucoside described by Rutishauser (*loc. cit.*). This has been described as a syrupy material precipitated as a lead derivative by basic lead acetate and yielding, when acid-hydrolysed, 2 : 3-dihydroxybenzoic acid and an unspecified ketose also obtained with protocatechuic acid from the amorphous tannin constituents of the extract. A chromatographic analysis of the water-soluble residues after the precipitation of tannins and removal of excess of lead acetate disclosed the presence of fructose and sucrose, and of two phenolic substances, one giving a green ferric colour attributed to residual tannins, and the other an intense violet. The latter compound was precipitated as a heavy yellow complex with basic lead acetate as described by Rutishauer, but when recovered from the lead derivative it was still contaminated with tannins. Accordingly, aqueous solutions of the syrup were chromatographed on columns of powdered cellulose with butanol–ethanol–water as developing solvent, whereupon the glycoside was obtained as a pale brown viscous syrup (0·3% of the dried leaves) which gradually became partly crystalline and slowly liberated carbon dioxide from aqueous sodium hydrogen carbonate. However, the method was tediously slow, and it was found more expedient, although resulting in a slightly impure product, to employ the ion-exchange resin ' Deacidite E ' and to liberate the absorbed glycoside by washing the resin with ammonia, ' Zeo-Karb 215 ' being used to liberate the glycoside from its ammonium salt. From neither process was the compound obtained in a substantially crystalline form although further investigation proved that the material isolated by chromatography on the cellulose was free from observable impurity.

Hydrolysis of the glycoside with boiling dilute sulphuric acid and extraction with ethyl acetate gave 2 : 3-dihydroxybenzoic acid, m. p. 206—207° (decomp.), identical with a specimen synthesised from *o*-vanillin by methylation and oxidation of the product to *o*-veratric acid which was then demethylated with boiling hydrobromic acid. From the carbohydrate remaining in the sulphuric acid solution phenyl-D-glucosazone was obtained and it was shown by paper chromatography that, of the three hexoses from which the osazone could have been derived, only D-glucose was formed during the hydrolysis. The yields of the two hydrolytic products were not inconsistent with the view that the parent substance was a monoglucoside, its intense ferric reaction favouring structure (I) in which the 3-position is the site of the glucosyloxy-group.

Evidence bearing on the supposed orientation of the glucose residue was found in the failure of the phenolic group to react with diazomethane, thereby indicating its chelated condition and hence its proximity to the carboxylic substituent. Methylation with methyl sulphate and aqueous alkali (Haworth, *J.*, 1915, **107**, 8), however, caused hydrolysis of the glucosyloxy-group and the formation of 2 : 3-dimethoxybenzoic acid. This is no doubt due to prior methylation of the 2-position since it has been observed by Fisher, Hawkins, and Hibbert (*J. Amer. Chem. Soc.*, 1941, **63**, 3031) that *o*-methoxyaryl glycosides are unusually sensitive to hydrolytic agents.

The syrupy ester obtained from the glucoside and diazomethane was exhaustively methylated with methyl iodide and silver oxide (Purdie and Irvine, *J.*, 1903, **83**, 1021). The non-crystalline product, which no longer possessed a ferric reaction, was subjected to acid hydrolysis, whence the isolation of the previously unknown 3-hydroxy-2-methoxybenzoic acid (II) left no doubt as to the orientation of the glucose residue. A crystalline derivative, the methyl ester penta-acetate, m. p. 165—166°, was obtained by treating the glucoside with acetic anhydride–sodium acetate followed by diazomethane. Its constitution (III; R = Ac), and hence that of the natural compound, was confirmed by a synthesis from α-tetra-acetobromo-D-glucose and methyl 2 : 3-dihydroxybenzoate; acetylation of

the product yielded a pure methyl ester penta-acetate, m. p. 169°, mixed m. p. 165—168°, which in view of its preparation from the α-acetobromoglucose is presumed to be a β-glucoside. Infrared absorption measurements, for which we thank Mr. M. St. C. Flett, Imperial Chemical Industries Limited, show the very close resemblance of the synthetic and the natural product, slight variations being attributable to impurities in the natural sample. *X*-Ray powder diagrams were prepared by Dr. S. C. Wallwork and they confirm the relationship of the two specimens.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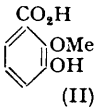
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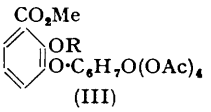
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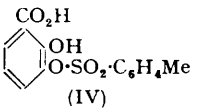
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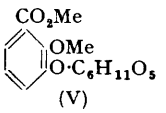
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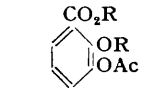
Although the superior reactivity of the 3-hydroxyl group in 2 : 3-dihydroxybenzoic acid leaves little doubt that direct glucosidation will result in a 3-substituted product, some attention was nevertheless given to a possible unambiguous synthesis of the natural glucoside or of a crystalline derivative thereof. A desirable intermediate for this purpose is 2-hydroxy-3-toluene-*p*-sulphonyloxybenzoic acid (IV) since after methylation at the 2-position and hydrolysis of the toluenesulphonyl group it permits of a synthesis of a homogeneous 3-glucoside. The required compound (IV) was readily obtained by the toluenesulphonation of 2 : 3-dihydroxybenzoic acid in aqueous alkali but, under similar conditions, methyl 2 : 3-dihydroxybenzoate gave a mixture of the mono- and di-toluene-*p*-sulphonates, the mono-compound being identical with that prepared from (IV) with methanolic hydrogen chloride. When this ester was methylated with methyl iodide–potassium carbonate, methyl 2-methoxy-3-toluene-*p*-sulphonyloxybenzoate was obtained which was hydrolysed with alkali to 3-hydroxy-2-methoxybenzoic acid (II). The latter had m. p. 151—152° which was depressed by the isomeric 2-hydroxy-3-methoxybenzoic acid, m. p. 152°, and gave no colour with ferric chloride. 2-Ethoxy-3-hydroxybenzoic acid was prepared analogously and also *via* the 3-methanesulphonyl derivative. The methyl ester of 3-hydroxy-2-methoxybenzoic acid was a liquid which reacted with α-tetra-acetylbromoglucose to form the crystalline methyl 3-β-tetra-acetyl-D-glucosyloxy-2-methoxybenzoate (III; R = Me). Deacetylation in methanolic hydrogen chloride yielded methyl 3-β-D-glucosyloxy-2-methoxybenzoate (V), m. p. 187—189°. However, failure to restrict methylation to the 2-position of the natural glucoside prevented its identification by means of this purely synthetic compound.

Other derivatives of 2 : 3-dihydroxybenzoic acid were prepared in order to investigate the glucosidation of this acid at the 2-position. Thus acetylation with acetic anhydride–sodium acetate under conditions used by Lesser and Gad (*Ber.*, 1926, **59**, 233) for the preparation of 4-acetoxy-2-hydroxybenzoic acid, or by Chattaway's process (*J.*, 1931, 2495), gave 3-acetoxy-2-hydroxybenzoic acid (VI; R = H). Methylation of this acid (VI; R = H) gave the 2-methyl ether with, however, some replacement of the acetyl group. Thereafter, hydrolysis to 3-hydroxy-2-methoxybenzoic acid (II) proved that acetylation had occurred in the 3-position. Esterification, therefore, of the acid (VI; R = H) with diazomethane afforded methyl 3-acetoxy-2-hydroxybenzoate which, however, combined with α-tetra-acetylbromo-D-glucose in quinoline with silver oxide to a syrupy product. A non-crystalline substance was formed under similar conditions from methyl 2-hydroxy-3-methoxybenzoate (VII), the latter being prepared either by esterification of the acid with diazomethane or from 2 : 3-dihydroxybenzoic acid with methyl sulphate–potassium carbonate in acetone.

The synthetical experiments were extended to the isomeric 2 : 4- and 3 : 4-dihydroxybenzoic acid. It is known that monoacetylation of the former acid gives 4-acetoxy-2-hydroxybenzoic acid (VIII; R = H) (Lesser and Gad, *loc. cit.*); and a sample of this derivative prepared by Chattaway's method was esterified with diazomethane. The resulting ester (VIII; R = Me) was combined with α-tetra-acetylbromo-D-glucose in the usual way, but the product remained a syrup; analysis indicated its composition to be

substantially that of methyl 4-acetoxy-2-β-tetra-acetyl-D-glucosyloxybenzoate (IX). A comparable synthesis from 2-hydroxy-4-methanesulphonyloxybenzoic acid (X; R = Me) which was esterified and then glucosylated, also gave a syrup after treatment with methanolic sodium methoxide (Zemplén and Pacsu, *Ber.*, 1929, **62**, 1613), possibly owing to incomplete removal of the methanesulphonyl protecting group. The orientation of the latter substituent in (X; R = Me) was established by methylation to the methoxy-ester and hydrolysis, the known 4-hydroxy-2-methoxybenzoic acid (XI) being obtained. Similarly it was proved that the monotoluenesulphonation product of 2 : 4-dihydroxybenzoic acid was the 4-substituted derivative (X; R = C_6H_4Me).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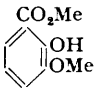
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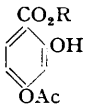
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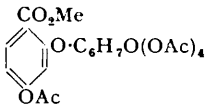
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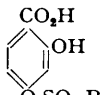
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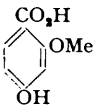
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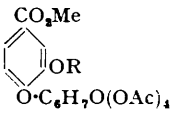
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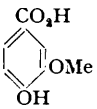
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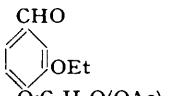
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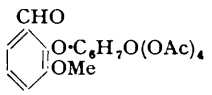
(XV)

Finally, the monoglucoside of methyl 3 : 4-dihydroxybenzoate prepared by Mauthner (*J. prakt. Chem.*, 1915, **91**, 174) and presumed by him to be the 4-glucoside (XII; R = H) has been decisively oriented. Methylation of the methyl tetra-acetylglucosyloxy-hydroxybenzoate to a monomethyl ether (XII; R = Me) obtained by Mauthner (*ibid.*, 1911, **83**, 556) was followed by hydrolysis to 4-hydroxy-3-methoxybenzoic acid (XIII), thus confirming the structure tentatively assigned to the glucoside.

A five-step synthesis of 3-glucosyloxy-4-hydroxybenzaldehyde due to Helferich and Papalambrou (*Annalen*, 1942, **551**, 242) appeared to offer the prospect of a route to the analogous acid glucosides by simple oxidation of the aldehyde group. Trial oxidation experiments were therefore conducted with the more readily available 3-ethoxy-4-tetra-acetylglucosyloxy- and 3-methoxy-2-tetra-acetylglucosyloxy-benzaldehyde (XIV) and (XV), the latter prepared from 2-hydroxy-3-methoxybenzaldehyde. However, these aldehydes failed to undergo oxidation under the necessarily mild conditions employed, or gave non-crystalline neutral products, presumably owing to incipient destruction of the carbohydrate substituent.

Experimental

Extraction of Ursolic Acid from Vinca *Species.*—The finely powdered leaves and stems of *V. minor* (2 kg.) were continuously extracted with boiling aqueous methanol (90%) for 24 hr. The dark green, amorphous solid (25 g.) which separated from the concentrated extract was partly purified by treatment with charcoal in boiling glacial acetic acid and by digestion with acetone, with light petroleum (b. p. 60—80°), and with benzene. By repeated treatment with charcoal in boiling ethanol, this material eventually furnished crude, amorphous ursolic acid, m. p. 268—271°, which on being digested with boiling ethanol was obtained as colourless needles (8 g., 0·4%), m. p. 287—290° (undepressed on admixture with authentic ursolic acid), $[\alpha]_D^{20}$ +67·0° (*c* 0·68 in *iso*propanol), +68·4° (*c* 1·49 in dioxan) (Goodson, *J.*, 1938, 999, records $[\alpha]_D^{21}$ +67·5°) [Found, in material dried at 150°/vac.: C, 78·8; H, 10·9; active H, 0·4%; *M* (Rast), 433. Calc. for $C_{30}H_{48}O_3$: C, 78·9; H, 10·5; 2 active H, 0·4%; *M*, 456]. *V. major* similarly afforded 0·53% of ursolic acid.

The methyl ester had m. p. 167—168°, undepressed on admixture with an authentic specimen (Sell and Kremers, *J. Biol. Chem.*, 1938, **126**, 501).

Acetylursolic Acid.—A solution of the acid (1 g.) in *iso*propenyl acetate (11 ml.) and concentrated sulphuric acid (1 drop) was boiled for 3 hr., concentrated, and diluted with ether. The

crystalline residue from the acid-free ethereal solution gave, on recrystallisation from light petroleum, pure acetylursolic acid (0·3 g.), m. p. 285—288°, undepressed by an authentic specimen (Sando, *J. Biol. Chem.*, 1931, **90**, 477) (Found: C, 77·1; H, 10·0; OAc, 7·8. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·0; OAc, 8·6%).

Acetylursolic Acetic Anhydride.—Ursolic acid (1 g.) dissolved in a mixture of acetic anhydride (10 ml.) and aqueous perchloric acid (60%; 3 drops) on being kept for 2 hr. The brown gum (1·05 g.), precipitated by the addition of water, furnished on crystallisation from light petroleum the mixed anhydride, m. p. 197—198°, with resolidification and melting at 306—308° (decomp.), undepressed by a specimen prepared by the method of Sando (*loc. cit.*) [Found: C, 75·7; H, 9·2; OAc, 13·1%; *M* (*X*-ray), 532. Calc. for $C_{34}H_{52}O_5$: C, 75·6; H, 9·6; 2OAc, 15·4%; *M*, 540]. On being boiled in aqueous ethanol (70%) for 5 hr., this compound afforded acetylursolic acid, m. p. and mixed m. p. 285—287°.

Benzoylursolic acid, obtained by boiling the acid with pyridine and benzoyl chloride for 2½ hr., crystallised from ethanol in needles, m. p. 282—284° (Found: C, 79·2; H, 9·4. $C_{37}H_{52}O_4$ requires C, 79·3; H, 9·3%).

Acetoacetylursolic Acid.—Diketen (4 ml.) was added dropwise to a boiling suspension of ursolic acid (1 g.) in a mixture of ethyl methyl ketone (50 ml.) and toluene-*p*-sulphonic acid (0·5 g.); boiling was continued for 1½ hr. and most of the solvent was evaporated. The gum which was precipitated on the addition of water yielded, on recrystallisation from benzene (charcoal), *acetoacetylursolic acid* as hexagonal-based pyramids, m. p. 221—222° (Found: C, 75·6; H, 9·7. $C_{34}H_{52}O_5$ requires C, 75·6; H, 9·6%).

Extraction of the Alkaloids from V. minor.—A mixture of the powdered plant (2 kg.) and calcium hydroxide (150 g.) was macerated overnight with water (500 ml.) and methanol (6 l.), and refluxed for 6 hr. Extraction with successive quantities of boiling methanol (4·5 l.) was continued until no more methanol-soluble material was extracted. Solvent was removed from these extracts and the residue was boiled for 5 min. with sufficient 2N-hydrochloric acid to render the mixture acid to Congo-red, allowed to cool, and kept at 0° for 24 hr. Alkaloid was removed from the acid-insoluble residue by repeated washing with water. The combined aqueous solutions were concentrated, partially decolorised with kieselguhr, and exhaustively extracted with chloroform. Basic material (4 g.), recovered from the aqueous liquid, failed to yield any pure compound. The chloroform solution on being evaporated afforded a dark brown gum from which crude bases (1·25 g.) were recovered by extraction with hot water and precipitation with sodium hydroxide. The *alkaloid*, m. p. 214—217° (0·15 g., 0·0075%), was eventually obtained as golden needles, m. p. 230—231°, from methanol [Found: C, 70·7; H, 7·5; N, 7·7; OMe, 8·7%; *M* (Rast), 344. $C_{21}H_{26}O_3N_2$ requires C, 71·1; H, 7·4; N, 7·9; OMe, 8·7%; *M*, 354]; light absorption in EtOH: max. at 228 (ε 29,160) and 276 mμ (ε 8213). Its *picrate*, obtained by treatment of a solution of the alkaloid in aqueous lactic acid with sodium picrate, had m. p. 228—229°, after crystallisation from aqueous methanol (Found: C, 55·1; H, 5·4; N, 12·0; OMe, 5·5. $C_{27}H_{29}O_{10}N_5$ requires C, 55·6; H, 5·0; N, 12·0; OMe, 5·3%).

Isolation of the Glucoside from V. minor.—The mother-liquor from the isolation of ursolic acid was concentrated under reduced pressure, kept for 24 hr., filtered, and concentrated to a viscous, red syrup; this was dissolved in methanol and poured into acetone. Tannins were partly removed from an aqueous solution of the precipitate by means of lead acetate. The syrupy product recovered after removal of the excess of lead with hydrogen sulphide was shown by paper chromatography to contain tannins, sucrose, fructose, and the required glucoside.

The paper chromatogram was irrigated during 64 hr. with the upper layer obtained by shaking together butanol, ethanol, and water (4 : 1 : 5). After being dried, the spots were located on separate strips by using aniline phthalate, naphtharesorcinol–trichloroacetic acid, and 2% ferric chloride. All four components responded to the carbohydrate reagents; in addition the tannins afforded a green colour, and the glucoside a violet colour with ferric chloride. The identities of the sucrose and the fructose were established by direct chromatographic comparison with authentic specimens.

The glucoside and tannins were separated from the sugars as their insoluble lead salts, formed on the addition of solution of basic lead acetate, and regenerated by means of hydrogen sulphide in glacial acetic acid; the resulting amorphous solid (13 g.) could not be further purified by means of solvents or by precipitation of the acidic glucoside as a salt.

Accordingly, the mixture was fractionated chromatographically on cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511) with butanol–ethanol–water (4 : 1 : 5) as developing solvent; the course of fractionation was followed by means of ferric chloride reagent. Fractions corresponding to the elution of a pale pink band from the column, on concentration, afforded an

extremely hygroscopic syrup which eventually partly crystallised (yield from 112 g. of plant material, 0·35 g., 0·3%). This material behaved as a homogeneous substance on paper chromatography.

In the ion-exchange method, an aqueous solution of the acetone-precipitated mixture from 2 kg. of plant was passed down a column of basic " Deacidite E " (250 g.). Colouring matter was removed from the column by irrigation with water, and the glucoside was recovered by treatment with dilute solution of ammonia. The effluent was concentrated to a small volume, adjusted to pH 7, filtered, and passed through a column of acid " Zeo-Karb 215 " (250 g.). The syrup (12—15 g.) obtained on concentration of the effluent and drying the ethanol-soluble fraction *in vacuo* over phosphoric oxide consisted of the resinous glucoside (1·2—2·3 g.) slightly contaminated with tannins. By seeding with cystalline glucoside, this material was obtained partly crystalline.

Hydrolysis of the Glucoside.—The syrupy glucoside (0·35 g.) was boiled for 3 hr. with 2·5N-sulphuric acid; the residue obtained on evaporating an ethyl acetate extract of this solution furnished on crystallisation from water 2 : 3-dihydroxybenzoic acid (0·1 g.), m. p. and mixed m. p. 206—207° (Found : C, 54·8; H, 4·0%; equiv., 155. Calc. for $C_7H_6O_4$: C, 54·4; H, 3·9%; equiv., 154). Methyl 2 : 3-dimethoxybenzoate, prepared from this acid by interaction with methyl iodide and potassium carbonate in acetone, had m. p. 47°, undepressed by a sample prepared by methylation of 2 : 3-dimethoxybenzoic acid with diazomethane. On treatment with diazomethane the isolated acid afforded its methyl ester, m. p. 80—81°, undepressed on admixture with methyl 2 : 3-dihydroxybenzoate.

The aqueous liquid remaining from the hydrolysis was neutralised with barium carbonate and examined for the presence of sugars by chromatography; direct comparison with glucose, fructose, and mannose revealed the presence of glucose alone. The osazone (0·07 g.) had the characters of phenyl-D-glucosazone, m. p. 204—205° (decomp.).

2 : 3-*Dihydroxybenzoic Acid.*—*o*-Vanillin (8 g.) was methylated by refluxing (36 hr.) it with methyl iodide (20 ml.) and potassium carbonate (10 g.) in acetone (150 ml.). The resulting 2 : 3-dimethoxybenzaldehyde (7 g., 80%; m. p. 50—52°) was oxidised in 97% yield to the corresponding acid by the procedure of Edwards, Perkin, and Stoyle (*J.*, 1925, **127**, 195). This acid (20 g.) when boiled (3 hr.) with hydrobromic acid (47%, 160 ml.) furnished 2 : 3-dihydroxybenzoic acid (13 g., 77%), m. p. 204—206° (decomp.), raised to 206—207° (decomp.) on recrystallisation from water. Its *p-chlorobenzamidinium salt* separated from aqueous ethanol as rods, m. p. 238—239° (decomp.) (Found : C, 54·6; H, 4·4; N, 8·5. $C_{14}H_{13}O_4N_2Cl$ requires C, 54·4; H, 4·2; N, 9·1%). Its *monobenzoyl ester* crystallised from aqueous acetone as plates, m. p. 212—213° (Found : C, 64·9; H, 4·2%; equiv., 262. $C_{14}H_{10}O_5$ requires C, 65·1; H, 3·9%; equiv., 258); this compound is considered to be 3-benzoyloxy-2-hydroxybenzoic acid, since in ethanol it afforded a violet colour with ferric chloride.

Methylation of the Glucoside.—(i) Methylation by Haworth's method (*loc. cit.*) afforded 2 : 3-dimethoxybenzoic acid, m. p. 122—123°, as the only isolable product (Found : equiv., 187. Calc. for $C_9H_{10}O_4$: equiv., 182).

(ii) On the addition of a large excess of an ethereal solution of diazomethane to a methanolic solution of the glucoside, solid separated immediately; removal of the solvent from the suspension which had been kept at 0° for 24 hr. furnished a syrup. Four such treatments failed to yield material no longer responding to the ferric reaction.

(iii) Dry material (4·7 g.) from the foregoing experiment was refluxed in dry methanol (100 ml.) with methyl iodide (36 g.), dry silver oxide (22 g.) being added gradually during 5 hr.; this methylation was repeated five times. The filtered reaction mixture gave no colour with ferric chloride but resisted all attempts to obtain a crystalline product from it. Accordingly the product (4·1 g.) in methanol (25 ml.) was refluxed for 5 hr. with 5N-sulphuric acid (50 ml.), and freed from tar by filtration. An ethyl acetate extract of the filtrate furnished 3-*hydroxy*-2-*methoxybenzoic acid* (II) (0·15 g.) which crystallised from water as needles, m. p. 151—152°, undepressed on admixture with a specimen prepared as described below (Found : C, 57·0; H, 4·8. $C_8H_8O_4$ requires C, 57·1; H, 4·8%).

Acetylation of the Glucoside.—The mixture obtained by refluxing the glucoside (2 g.) with acetic anhydride (50 ml.) and sodium acetate (5 g.) for 1 hr. afforded a semi-solid precipitate on being poured into water. Since no crystalline product could be recovered from this material, it was treated with diazomethane; the crystals (0·054 g.; m. p. 158—160°) which slowly separated from the concentrated reaction mixture yielded, on recrystallisation from methanol, *methyl* 2-*acetoxy*-3-β-*tetra-acetyl*-D-*glucosyloxybenzoate* (III; R = Ac) (0·03 g.) as colourless prisms, m. p. 165—166°; the mixed m. p. with a synthetic specimen (see below), of m. p. 169°, was

165—168°. The identity of these two specimens was confirmed by infrared absorption measurements and *X*-ray powder diagrams.

Methyl 2 : 3-*Dihydroxybenzoate.*—(i) A solution of 2 : 3-dihydroxybenzoic acid (8 g.) in dry methanol (150 ml.) was saturated with dry hydrogen chloride, boiled for 12 hr., cooled, again saturated with hydrogen chloride, and boiled for 24 hr. The ester (6 g.), isolated by evaporation of most of the solvent, treatment with aqueous sodium hydrogen carbonate and extraction with ether, crystallised from aqueous methanol as needles, m. p. 80—81° (Found : C, 57·1; H, 4·8. Calc. for $C_8H_8O_4$: C, 57·1; H, 4·8%); in D.-R.P. 281,214 the m. p. is reported to be 75—78°.

(ii) A suspension of the sodium salt, made from the acid (15·4 g.) and sodium (2·3 g.) in methanol (30 ml.) and water (15 ml.), when refluxed for 36 hr. with excess of methyl iodide afforded the ester (7 g.), m. p. and mixed m. p. 78—81°.

Methyl 2-*Acetoxy*-3-β-*tetra-acetyl*-D-*glucosyloxybenzoate* (III; R = Ac).—A cold mixture of methyl 2 : 3-dihydroxybenzoate (3 g.), α-acetobromo-D-glucose (8 g.), sodium hydroxide (0·7 g.), acetone (30 ml.), and water (15 ml.) was shaken for 5 hr. The syrup (2·1 g.) remaining after evaporation of the solvent and removal of alkali failed to crystallise. It was boiled with acetic anhydride (100 ml.) and sodium acetate (10 g.) for 1 hr., and poured into water. The semi-solid precipitate was dried by azeotropic distillation with benzene, and covered with dry light petroleum. The crystals which had formed during 5 months were rapidly collected after the addition of a small quantity of ice-cold ethanol, and obtained from ethanol as prisms (0·25 g.), m. p. 169°, $[\alpha]_D^{20}$ −28·3° (*c* 2·02 in acetone) (Found : C, 53·6; H, 5·5; OMe, 6·3; OAc, 39·2. $C_{24}H_{28}O_{14}$ requires C, 53·4; H, 5·2; OMe, 5·7; 5OAc, 39·8%).

2-*Hydroxy*-3-*toluene*-p-*sulphonyloxybenzoic Acid* (IV).—When prepared by warming 2 : 3-dihydroxybenzoic acid (2·9 g.) with toluene-*p*-sulphonyl chloride (3·6 g.) and sodium hydroxide (1·6 g.) in aqueous acetone for 10 min. and acidifying, this *acid* crystallised from aqueous ethanol as plates, m. p. 176—178° (Found : C, 54·6; H, 4·0. $C_{14}H_{12}O_6S$ requires C, 54·4; H, 3·9%). In ethanol solution, it yielded a violet colour with ferric chloride.

The foregoing acid (5·45 g.) was esterified with methanol as described for methyl 2 : 3-dihydroxybenzoate. The *methyl ester* (5 g.) crystallised from methanol as prisms, m. p. 87—88° (Found : C, 55·7; H, 4·5. $C_{15}H_{14}O_6S$ requires C, 55·9; H, 4·3%).

Interaction of Methyl 2 : 3-*Dihydroxybenzoate and Toluene*-p-*sulphonyl Chloride.*—The ester (1·3 g.) was shaken with sodium hydroxide (0·4 g.) and toluene-*p*-sulphonyl chloride (1·4 g.) in aqueous acetone for 10 min. A solution of the solid product in ethanol and dilute hydrochloric acid deposited *methyl* 2 : 3-*di*(*toluene*-p-*sulphonyloxy*)*benzoate*, which after recrystallisation from acetone–propan-2-ol, was obtained as prisms (0·3 g.), m. p. 133—135° (Found : C, 55·3; H, 4·4; S, 13·1. $C_{22}H_{20}O_8S_2$ requires C, 55·6; H, 4·2; S, 13·5%). From the acidified ethanolic mother-liquor, methyl 2-hydroxy-3-toluene-*p*-sulphonyloxybenzoate (0·7 g.), m. p. and mixed m. p. 87—88°, was recovered.

Methyl 2-*Methoxy*-3-*toluene*-p-*sulphonyloxybenzoate.*—This *ester* was produced when 2-hydroxy-3-toluene-*p*-sulphonyloxybenzoic acid (12·3 g.) was boiled with an excess of methyl iodide and anhydrous potassium carbonate (10 g.) in acetone (200 ml.) for 48 hr., and crystallised from methanol as prisms, m. p. 77—78° (12·5 g.) (Found : C, 57·6; H, 5·0; OMe, 18·7. $C_{16}H_{16}O_6S$ requires C, 57·2; H, 4·8; 2OMe, 18·5%).

3-*Hydroxy*-2-*methoxybenzoic Acid* (II).—Methyl 2-methoxy-3-toluene-*p*-sulphonyloxybenzoate (12 g.) was refluxed for 48 hr. with sodium hydroxide (2·9 g.) in aqueous acetone (270 ml.), and part of the solvent was distilled off. The material which separated after acidification furnished 2-*methoxy*-3-*toluene*-p-*sulphonyloxybenzoic acid* (5·4 g.), which crystallised from aqueous methanol as plates, m. p. 132—133° (Found : C, 55·8; H, 4·5; OMe, 9·5. $C_{15}H_{14}O_6S$ requires C, 55·9; H, 4·3; OMe, 9·6%). By extraction of the acid mother-liquor with ethyl acetate there was obtained 3-*hydroxy*-2-*methoxybenzoic acid* (3 g.), which crystallised from water as rods, m. p. 151—152°, depressed to 122—123° on admixture with 2-hydroxy-3-methoxybenzoic acid (Found : C, 57·0; H, 5·0; OMe, 18·3%; equiv., 166. $C_8H_8O_4$ requires C, 57·1; H, 4·8; OMe, 18·5%; equiv., 168). Its *salt* with *p*-chlorobenzamidine had m. p. 243° (decomp.) (Found : C, 56·0; H, 4·3. $C_{15}H_{15}O_4N_2Cl$ requires C, 55·8; H, 4·6%). On methylation with methyl iodide–potassium carbonate, the acid furnished methyl 2 : 3-dimethoxybenzoate, m. p. and mixed m. p. 47°. Demethylation by boiling (½ hr.) hydrobromic acid afforded 2 : 3-dihydroxybenzoic acid, m. p. and mixed m. p. 206—207° (decomp.).

When the hydrolysis was effected with 2N-sodium hydroxide, the reaction was complete in 3½ hr., and the required acid was obtained in 93% yield. 3-Hydroxy-2-methoxybenzoic acid gave no colour with ferric chloride.

Methyl 3-*hydroxy*-2-*methoxybenzoate*, prepared from 3-hydroxy-2-methoxybenzoic acid by the procedure described for methyl 2 : 3-dihydroxybenzoate, had b. p. 146—148°/12—13 mm., n_D^{20} 1·5337 (Found : C, 59·1; H, 5·8; OMe, 34·1. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5; 2OMe, 34·1%).

Methyl 2-*Methoxy*-3-β-*tetra-acetyl*-D-*glucosyloxybenzoate* (III; R = Me).—The foregoing ester (0·85 g.), dry quinoline (10 ml.), α-acetobromo-D-glucose (8 g.), and dry silver oxide (3 g.) were shaken together for 1 hr., kept for 1 hr. and treated with glacial acetic acid (40 ml.). The suspension was filtered and the filtrate poured into ice-cold water (200 ml.). Recrystallisation of the precipitate (2 g.) first from methanol and then from propan-2-ol afforded *methyl* 2-*methoxy*-3-β-*tetra-acetyl*-D-*glucosyloxybenzoate* (1·4 g.) as needles, m. p. 119—120°, $[\alpha]_D^{20}$ −35·0° (*c* 2 in acetone) (Found : C, 53·7; H, 5·8; OMe, 12·4; OAc, 32·2. $C_{23}H_{28}O_{13}$ requires C, 53·9; H, 5·5; 2OMe, 12·1; 4OAc, 33·6%).

Methyl 3-β-D-*glucosyloxy*-2-*methoxybenzoate* (V) was obtained by shaking a suspension of its tetra-acetyl derivative (4 g.) in dry methanolic hydrogen chloride (1%; 50 ml.) for 24 hr.; the resulting homogeneous solution was adjusted to pH 4·5 by the cautious addition of sodium. Most of the solvent was removed and the *methyl* 3-β-D-*glucosyloxy*-2-*methoxybenzoate* (1·5 g.) which crystallised as needles was purified by recrystallisation from methanol; it had m. p. 187—189°, $[\alpha]_D^{20}$ −53·8° (*c* 1·01 in MeOH) (Found : C, 52·3; H, 5·7; OMe, 17·5. $C_{15}H_{20}O_9$ requires C, 52·3; H, 5·8; 2OMe, 18·0%).

Ethyl 2-*Ethoxy*-3-*toluene*-p-*sulphonyloxybenzoate*.—This *ester* was prepared in 73% yield by the method described for the corresponding methyl ester methyl ether and formed prisms, m. p. 64—65°, from methanol (Found : C, 58·9; H, 5·4; OEt, 26·2. $C_{18}H_{20}O_6S$ requires C, 59·2; H, 5·5; 2OEt, 25·3%). When refluxed for 3 hr. with 2N-sodium hydroxide in acetone, it afforded 2-*ethoxy*-3-*hydroxybenzoic acid* which crystallised from water as prisms, m. p. 130—131° (Found : C, 59·5; H, 5·6; OEt, 25·0%; equiv., 179. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5; OEt, 24·8%; equiv., 182); this acid gave no colour with ferric chloride. Its p-*chlorobenzimidinium salt*, m. p. 217° (decomp.), crystallised from water as flat elongated prisms (Found : C, 56·8; H, 4·7; N, 7·9. $C_{16}H_{17}O_4N_2Cl$ requires C, 57·1; H, 5·0; N, 8·3%).

2-*Acetoxy*-3-*toluene*-p-*sulphonyloxybenzoic Acid*.—The phenolic acid (1 g.) and sodium acetate (2·5 g.) in acetic anhydride (25 ml.) when heated on a steam-bath for 1 hr. afforded its *acetyl ester* (0·6 g.), which crystallised from benzene–light petroleum as needles, m. p. 149° (Found : C, 54·8; H, 4·1. $C_{16}H_{14}O_7S$ requires C, 54·8; H, 4·0%).

Methyl 2-*Hydroxy*-3-*methanesulphonyloxybenzoate*.—2-*Hydroxy*-3-*methanesulphonyloxybenzoic acid*, prepared in 73% yield as described for the corresponding toluene-*p*-sulphonyl ester, crystallised from water as elongated flat prisms, m. p. 158—159° (Found : C, 41·4; H, 3·8%; equiv., 232. $C_8H_8O_6S$ requires C, 41·4; H, 3·5%; equiv., 232); this compound gave a violet colour with ferric chloride. On treatment with diazomethane, it afforded its *methyl ester*, elongated prisms, m. p. 110—111° (from aqueous methanol) (Found : C, 44·1; H, 4·3; OMe, 13·4. $C_9H_{10}O_6S$ requires C, 43·9; H, 4·0; OMe, 12·6%). With ferric chloride, an ethanolic solution gave a ruby-red colour.

3-*Methanesulphonyloxy*-2-*methoxybenzoic Acid*.—3-Hydroxy-2-methoxybenzoic acid (1·7 g.) and sodium hydroxide (0·9 g.) in water (25 ml.) and methanesulphonyl chloride (0·9 ml.) were shaken together for 15 min., kept for 30 min., and acidified. The precipitate yielded 3-*methanesulphonyloxy*-2-*methoxybenzoic acid* (2·1 g.) as prisms, m. p. 126—127° when crystallised from water (Found : C, 44·2; H, 3·8. $C_9H_{10}O_6S$ requires C, 43·9; H, 4·1%).

Ethyl 2-*Ethoxy*-3-*methanesulphonyloxybenzoate*.—This *compound* (2·2 g.) was obtained by boiling the phenolic acid (2·25 g.), potassium carbonate (6 g.), and ethyl iodide (4 g.) in acetone (50 ml.) for 24 hr. and occurred as a viscous liquid, b. p. 142°/0·1 mm., $n_D^{20\cdot5}$ 1·5066 (Found : C, 50·4; H, 5·9. $C_{12}H_{16}O_6S$ requires C, 50·0; H, 5·6%). The ester (1·3 g.) in propan-2-ol (15 ml.) was heated on a steam-bath for 1 hr. with sodium hydroxide (0·2 g., 1 mol.) in water (15 ml.). The precipitate obtained on acidification furnished 2-*ethoxy*-3-*methanesulphonyloxybenzoic acid* (0·8 g.) as needles, m. p. 116—117°, when crystallised from water (Found : C, 46·2; H, 4·8. $C_{10}H_{12}O_6S$ requires C, 46·2; H, 4·6%). When the quantity of sodium hydroxide was increased to 3 mols., and the heating prolonged for 2 hr., the product was 2-ethoxy-3-hydroxybenzoic acid.

3-*Acetoxy*-2-*hydroxybenzoic acid* (VI; R = H) was prepared in 55% yield from 2 : 3-dihydroxybenzoic acid by the procedure of Lesser and Gad (*loc. cit.*) and by that of Chattaway (*loc. cit.*) in 82% yield; it crystallised as prisms, m. p. 135—137°, from benzene or hydrated needles, m. p. 85°, from water (Found : C, 55·0; H, 4·2%; equiv., 197. $C_9H_8O_5$ requires C, 55·1; H, 4·0; equiv., 196. Found in hydrated material : loss, 9·1. $C_9H_8O_5,H_2O$ requires

H_2O, 8·4%). On methylation with diazomethane, the acid (4·2 g.) afforded *methyl 3-acetoxy-2-hydroxybenzoate* (3·8 g.), which crystallised from light petroleum (b. p. 60—80°) as prisms, m. p. 70—71°, b. p. 102—104°/0·1 mm., $n_D^{20\cdot5}$ 1·5243 (Found : C, 56·9; H, 4·8; OMe, 14·4. $C_{10}H_{10}O_5$ requires C, 57·2; H, 4·8; OMe, 14·8%). Both these compounds gave a violet ferric reaction. Alkylation by the methyl iodide–potassium carbonate method yielded *methyl 3-acetoxy-2-methoxybenzoate* (VI; R = Me), b. p. 162—164°/13—14 mm. (Found : C, 59·3; H, 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·9%); this on hydrolysis with sodium hydroxide in aqueous acetone gave 3-hydroxy-2-methoxybenzoic acid, m. p. 150—152°.

Attempted Glucosidation of Methyl 3-Acetoxy-2-hydroxybenzoate.—A mixture of the ester (2·1 g.), α-acetobromo-D-glucose (8·5 g.), silver oxide (6 g.), and quinoline (10 ml.) was shaken for 1 hr., and kept overnight. The water-insoluble material obtained after removal of the silver compounds was a syrup which did not crystallise.

Methyl 2-Hydroxy-3-methoxybenzoate (VII).—2-Hydroxy-3-methoxybenzoic acid (Perkin and Stoyle, *J.*, 1923, **123**, 3171) with excess of diazomethane afforded methyl 2-hydroxy-3-methoxybenzoate, m. p. 67—68° (lit., 67—68°), in 74% yield. Treatment of 2 : 3-dihydroxybenzoic acid (1 g.) with methyl sulphate (1·7 g.) in dry acetone (20 ml.) and benzene (80 ml.) in the presence of potassium carbonate (4 g.) gave a 19% yield (Found : C, 59·2; H, 5·7; OMe, 33·7. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5; 2OMe, 34·0%).

Attempted Glucosidation of Methyl 2-Hydroxy-3-methoxybenzoate.—The phenolic ester (0·9 g.), α-acetobromo-D-glucose (8 g.), silver oxide (3 g.), and quinoline (10 ml.) were shaken together for 1 hr., and then kept for 1 hr. The product obtained on working up in the usual way was a syrup.

Methyl 4-acetoxy-2-hydroxybenzoate (VIII; R = Me) was prepared by methylation with diazomethane of 4-acetoxy-2-hydroxybenzoic acid (VIII; R = H) which had been obtained by the method of Lesser and Gad (*loc. cit.*) or in 81% yield by Chattaway's procedure (*loc. cit.*); it crystallised from aqueous methanol as silky needles, m. p. 51—52° (Found : C, 57·0; H, 4·7; OAc, 22·6. $C_{10}H_{10}O_5$ requires C, 57·2; H, 4·8; OAc, 20·5%). On glucosidation by the aceto-bromoglucose–silver oxide–quinoline method, this compound afforded impure methyl 4-acetoxy-2-β-tetra-acetyl-D-glucosyloxybenzoate (IX) as a viscous syrup which failed to crystallise; the syrup was analysed after prolonged drying *in vacuo* over phosphoric oxide (Found : C, 52·8; H, 5·8. Calc. for $C_{24}H_{28}O_{14}$: C, 53·4; H, 5·2%).

2-Hydroxy-4-toluene-p-sulphonyloxybenzoic Acid (X; R = C_6H_4Me).—This *acid* was obtained when 2 : 4-dihydroxybenzoic acid was treated as described for its 2 : 3-isomer; on crystallisation from aqueous methanol, it formed prisms, m. p. 184—185° (Found : C, 54·8; H, 4·0. $C_{14}H_{12}O_6S$ requires C, 54·6; H, 3·9%). Methylation with methyl iodide for 48 hr. gave *methyl 2-methoxy-4-toluene-p-sulphonyloxybenzoate*, prisms, m. p. 56—57° (from aqueous propan-2-ol) (Found : C, 57·4; H, 4·7; OMe, 17·8. $C_{16}H_{16}O_6S$ requires C, 57·2; H, 4·8; 2OMe, 18·5%). Hydrolysis of this compound with an equivalent of sodium hydroxide gave *2-methoxy-4-toluene-p-sulphonyloxybenzoic acid*, plates, m. p. 133—134° (from aqueous methanol) (Found : C, 56·1; H, 4·6; OMe, 9·7. $C_{15}H_{14}O_6S$ requires C, 55·9; H, 4·3; OMe, 9·6%); with 3 equivalents of alkali, the hydrolysis product was 4-hydroxy-2-methoxybenzoic acid, m. p. 188—189° (decomp.) : Bergmann and Dangschat (*Ber.*, 1919, **52**, 383) record m. p. 187—189° (decomp.).

Methyl 2-hydroxy-4-toluene-p-sulphonyloxybenzoate was produced on methylation of the acid (X; R = C_6H_4Me) with diazomethane and crystallised from ethanol–light petroleum as prisms, m. p. 88—89° (Found : C, 56·0; H, 4·0; OMe, 9·2. $C_{15}H_{14}O_6S$ requires C, 55·9; H, 4·3; OMe, 9·6%).

2-Hydroxy-4-methanesulphonyloxybenzoic Acid (X; R = Me).—Prepared in 74% yield from 2 : 4-dihydroxybenzoic acid as described above for the isomeric compound, this *acid* crystallised rom water as elongated, flat prisms, m. p. 175° (Found : C, 41·1; H, 3·6%; equiv., 236. $C_8H_8O_6S$ requires C, 41·4; H, 3·5%; equiv., 232). With diazomethane, it furnished its *methyl ester*, which crystallised from propan-2-ol as elongated prisms, m. p. 96—97° (Found : C, 43·9; H, 4·2; OMe, 12·4. $C_9H_{10}O_6S$ requires C, 43·9; H, 4·0; OMe, 12·6%).

Methyl 4-Methanesulphonyloxy-2-methoxybenzoate.—The foregoing acid, methylated by the methyl iodide–potassium carbonate method (24 hours' heating), furnished *methyl 4-methanesulphonyloxy-2-methoxybenzoate* (77%), b. p. 158°/0·1 mm., n_D^{20} 1·5365 (Found : C, 46·3; H, 4·7; OMe, 24·1. $C_{10}H_{12}O_6S$ requires C, 46·2; H, 4·6; 2OMe, 23·8%). When boiled for 15 min. with an equivalent of sodium hydroxide in aqueous propan-2-ol, this yielded *4-methanesulphonyloxy-2-methoxybenzoic acid*, which separated from water as needles, m. p. 169° (Found : C, 44·0; H, 3·8; OMe, 13·0. $C_9H_{10}O_6S$ requires C, 43·9; H, 4·1; OMe, 12·6%). When hydrolysis was effected with three equivalents of sodium hydroxide, the product was 4-hydroxy-2-methoxybenzoic

acid (XI), m. p. 188—189° (decomp.) (lit., 187—189°) (Found : OMe, 19·0. $C_8H_8O_4$ requires OMe, 18·5%).

Methyl 4-Methanesulphonyloxy-2-β-tetra-acetyl-D-glucosyloxybenzoate.—Dry silver oxide (6 g.) was added to a mixture of methyl 2-hydroxy-4-methanesulphonyloxybenzoate (2·5 g.), α-acetobromo-D-glucose (9 g.) and dry quinoline (10 ml.); the mixture was shaken for 4 hr., diluted with glacial acetic acid, filtered and poured into ice-water. The precipitate furnished the *tetra-acetylglucoside* (3 g.) as needles, m. p. 157°, $[\alpha]_D^{19}$ −31·3° (*c* 2·2 in acetone) on crystallisation from propan-2-ol (Found : C, 48·2; H, 5·3; OMe, 5·3; OAc, 31·2. $C_{23}H_{28}O_{15}S$ requires C, 47·9; H, 4·9; OMe, 5·4; 4OAc, 29·9%). Attempts to hydrolyse this compound (Zemplén and Pacsu, *loc. cit.*) yielded a syrup which failed to crystallise.

Methyl 3-Methoxy-4-β-tetra-acetyl-D-glucosyloxybenzoate (XII ; R = Me).—Methyl 3-hydroxy-4-β-tetra-acetyl-D-glucosyloxybenzoate (Mauthner, *J. prakt. Chem.*, 1915, **91**, 174) (2 g.) and anhydrous potassium carbonate (4 g.) in acetone (50 ml.) were boiled with an excess of methyl iodide for 24 hr. The filtrate from the reaction mixture was concentrated and stirred with water; the insoluble oil when collected in ether, recovered, and crystallised first from aqueous methanol and then from aqueous propan-2-ol gave the 3-methyl ether as needles, m. p. 141—142° (Found : C, 54·1; H, 5·1; OMe, 12·3; OAc, 31·1. Calc. for $C_{23}H_{28}O_{13}$: C, 53·9; H, 5·5; OMe, 12·1; 4OAc, 33·5%); Mauthner (*ibid.*, 1911, **83**, 556) records m. p. 144—145° for this compound. When hydrolysed by boiling for 3 hr. with 2·5N-sulphuric acid it afforded 4-hydroxy-3-methoxybenzoic acid (XIII), m. p. and mixed m. p. 208—209°.

3-Ethoxy-4-β-tetra-acetyl-D-glucosyloxybenzaldehyde (XIV).—3-Hydroxy-4-β-tetra-acetyl-D-glucosyloxybenzaldehyde (Helferich and Papalambrou, *loc. cit.*) (2 g.) was refluxed for 12 hr. with potassium carbonate and an excess of ethyl iodide in acetone (30 ml.); the oil remaining when the filtered reaction mixture was concentrated crystallised when stirred with water and afforded the *3-ethyl ether* as prisms, m. p. 111—113°, $[\alpha]_D^{21}$ −53·2°, on recrystallisation from propan-2-ol (Found : C, 55·5; H, 6·0; OEt, 8·5. $C_{23}H_{28}O_{12}$ requires C, 55·6; H, 5·6; OEt, 9·2%), and gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 202—203° (Found : C, 50·7; H, 4·7; OAc, 29·6. $C_{29}H_{32}O_{15}N_4,C_2H_4O_2$ requires C, 50·7; H, 4·9; OAc, 29·2. Found, in material dried at 120°/vac.: C, 52·1, H, 5·0. $C_{29}H_{32}O_{15}N_4$ requires C, 51·7; H, 4·8%). This aldehyde was recovered unchanged after treatment with hydrogen peroxide in acetic acid. A syrupy product which was without action on sodium hydrogen carbonate was obtained when attempts were made to effect oxidation by potassium permanganate in acetone or by silver oxide (Delépine and Bonnet, *Compt. rend.*, 1909, **149**, 39).

3-Methoxy-2-β-tetra-acetyl-D-glucosyloxybenzaldehyde (XV) was prepared in 31% yield from 2-hydroxy-3-methoxybenzaldehyde by the procedure of Helferich and Papalambrou (*loc. cit.*) and crystallised from propan-2-ol as needles, m. p. 137—138°, $[\alpha]_D^{20}$ −3·5° (*c* 4·5 in acetone) (Found : C, 54·6; H, 5·5; OMe, 6·5. $C_{22}H_{26}O_{12}$ requires C, 54·8; H, 5·4; OMe, 6·4%). By the method of Robertson and Waters (*J.*, 1931, 1881), the yield was 35%. Attempts to oxidise this compound with potassium permanganate in acetone or with silver oxide afforded neutral syrups.

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