439. *Syntheses of Glycosides. Part XIV. The Synthesis of Gein and of the Hexa-acetyl β-Vicianoside of (—)-Mandelonitrile believed to be the Hexa-acetate of Vicianin.*

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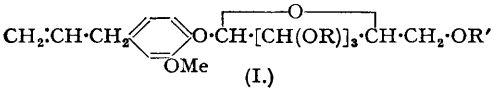
By means of the general method for the synthesis of biosides (Parts VIII and IX) the vicianoside of eugenol has been synthesised and is identical with the natural bioside gein.

The 2 : 3 : 4-triacetyl β-glucoside of (—)-mandelamide was prepared from the β-glucoside of (—)-mandelamide, and on interaction with triacetyl α-(—)-arabinosidyl bromide in the presence of silver oxide gave rise to the hexa-acetyl β-vicianoside of (—)-mandelamide which was dehydrated with phosphoryl chloride to the hexa-acetyl β-vicianoside of (—)-mandelonitrile believed to be the hexa-acetate of vicianin.

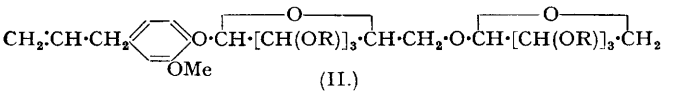
Gein.

From the roots of *Geum urbanum*, Le Bourquelot and Herissey (*Compt. rend.*, 1905, **140**, 870) isolated a glycoside gein which was subsequently shown by Herissey and Cheymol (*ibid.*, 1925, **180**, 384; 1925, **181**, 565; 1926, **183**, 1307) to be a vicianoside (6-L-arabinosido-β-D-glucoside) of eugenol (II; R = H). The structure of this compound has been now confirmed by its synthesis according to the general method (Part VIII, *J.*, 1931, 1881) employed for violutoside (Part IX, *J.*, 1932, 2770), a procedure preferred to the more direct route involving the use of *O*-hexa-acetyl vicianosidyl bromide because of the difficulty in preparing requisite quantities of *O*-hepta-acetyl vicianose (compare McCloskey and Coleman, *J. Amer. Chem. Soc.*, 1943, **65**, 1779) and its bromide.

Attempts to prepare 3-*methoxy*-4-(*tetra-acetyl* β-*glucosidoxy*)-1-*allylbenzene* (I; R and R′ = Ac) from eugenol by the convenient silver oxide–quinoline method (Part VI, *J.*, 1930, 2729) gave only intractable brown products owing, presumably, to the presence of the allyl group. The compound was obtained, however, by means of the classical alkali–aqueous acetone procedure in comparatively good yield, and on deacetylation by the ammonia–methanol method gave rise to 3-*methoxy*-4-β-*glucosidoxy*-1-*allylbenzene* (I; R = R′ = H).



(I.)



(II.)

Prepared in the usual manner the derived solid 6-trityl ether (I; R = H, R′ = CPh_3) was not obtained crystalline but on acetylation gave rise to the well crystallised *triacetate* (I; R = Ac, R′ = CPh_3) of the trityl ether, identical with the product prepared directly without the isolation of the intermediate (I; R = H, R′ = CPh_3). Removal of the trityl residue from (I; R = Ac, R′ = CPh_3) in the usual manner furnished 3-*methoxy*-4-(2′ : 3′ : 4′-*triacetyl* β-*glucosidoxy*)-1-*allylbenzene* (I; R = Ac, R′ = H), and on interaction with *O*-triacetyl α-L-arabinosidyl bromide in chloroform containing silver oxide and "Drierite" this compound gave a satisfactory yield of 3-*methoxy*-4-(*hexa-acetyl* β-*vicianosidoxy*)-1-*allylbenzene* (II; R = Ac). On deacetylation the last acetate furnished the vicianoside (II; R = H) of eugenol, the properties of which are identical with those of gein (*locc. cit.*).

Vicianin.

The bioside vicianin, and analogue of amygdalin, was first isolated from the seeds of *Vicia angustifolia* Roth. by Bertrand (*Compt. rend.*, 1906, **143**, 832) who in collaboration with Weisweiller (*ibid.*, 1908, **147**, 252; 1909, **150**, 180; 1910, **151**, 325, 884) showed that the substance was a β-vicianoside of (−)-mandelonitrile, being hydrolysed by the specific enzyme vicianase to give vicianose. As in the case of gein we preferred to attempt the synthesis of this glycoside by the general stepwise method (Parts VIII and IX, *locc. cit.*) rather than by the direct method involving the use of hexa-acetyl vicianosidyl bromide. For this procedure there are two alternative starting materials, *viz.*, the β-glucoside of (−)-mandelonitrile or the β-glucoside of (−)-mandelamide (III; R = R′ = H). In view of the results of Fischer and Bergmann (*Ber.*, 1917, **50**, 1047) where it is shown that deacetylation of the *O*-tetra-acetyl β-glucoside of (−)-mandelonitrile was accompanied by racemisation of the asymmetric centre in the nitrile residue and that in the separation of the resulting mixture disappointing yields of the pure β-glucoside of (−)-mandelonitrile were obtained, we decided to employ the β-glucoside of (−)-mandelamide as the starting material.

$$NH_2\cdot CO\cdot CHPh\cdot O\cdot \overbrace{CH\cdot[CH(OR)]_3\cdot CH}^{O}\cdot CH_2\cdot OR'$$

(III.)

$$CHPhR\cdot O\cdot \overbrace{CH\cdot[CH(OAc)]_3\cdot CH}^{O}\cdot CH_2\cdot O\cdot \overbrace{CH\cdot[CH(OAc)]_3\cdot CH_2}^{O}$$

(IV.)

Improved yields of the tetra-acetate of ethyl (±)-mandelate β-glucoside facilitated the preparation of the β-glucoside of (±)-mandelamide, from which the requisite β-glucoside of (−)-mandelamide (III; R = R′ = H) was obtained by the Fischer–Bergmann method (*loc. cit.*). Tritylation of the latter glucoside in the usual manner, followed by acetylation of the trityl ether (III; R = H, R′ = CPh_3), which was not isolated, gave the 2 : 3 : 4-*triacetyl* 6-*trityl* β-*glucoside* of (−)-mandelamide, *i.e.*, (III; R = Ac, R′ = CPh_3), which on removal of the trityl group furnished the 2 : 3 : 4-*triacetyl* β-*glucoside* (III; R = Ac, R′ = H) of (−)-mandelamide in comparatively good yield.

Considerable difficulty was encountered in attempting to attach a 2 : 3 : 4-triacetyl arabinosidyl residue at the 6′-position of (III; R = Ac, R′ = H). Under the usual conditions, *e.g.*, those employed in the case of gein, the product was an intractable gum, and similar material resulted from the application of the modified procedure for the synthesis of alcohol glycosides described by Meystre and Miescher (*Helv. Chim. Acta*, 1944, **27**, 231). Finally, it was found that by carrying out the reaction at 40° small yields of the required *hexa-acetate* of the (−)-mandelamide vicianoside (IV; R = CO·NH_2) were obtained and on dehydration with phosphoryl chloride this compound yielded the *hexa-acetyl* β-*vicianoside* (IV; R = CN) of (−)-mandelonitrile. In view of the unsatisfactory yields of (IV; R = CN) which were obtained, the deacetylation of this compound has not been attempted because by analogy with the β-glucoside of (−)-mandelonitrile (Fischer and Bergmann, *loc. cit.*) racemisation of the asymmetric centre of the nitrile residue would be expected to accompany the deacetylation and lead to poor yields of the required isomeride obtained in the separation of the resulting mixture. When a sample of the natural vicianin becomes available, a direct comparison of the foregoing synthetical hexa-acetate will be made with the natural derivative.

Experimental.

3-*Methoxy*-4-β-*glucosidoxy*-1-*allylbenzene* (I; R = R′ = H).—A solution of potassium hydroxide (2·8 g.) in water (50 ml.) was slowly added to eugenol (15 g.) and *O*-tetra-acetyl α-glucosidyl bromide (16 g.) dissolved in acetone (60 ml.), the mixture was kept at room temperature for 16 hours and then extracted

with benzene, and the combined extracts were washed with 2N-aqueous potassium hydroxide (50 ml. × 3 and then with water, dried, and evaporated. Recrystallisation of the residual solid from methanol gave 3-*methoxy*-4-(*tetra-acetyl β-glucosidoxy*)-1-*allylbenzene* (I; R = R′ = Ac) in colourless rectangular prisms (7 g.), m. p. 123°, $[\alpha]_D^{20}$ −26·0° in chloroform (*c*, 1·0) (Found: C, 58·6; H, 6·4. $C_{24}H_{30}O_{11}$ requires C, 58·3; H, 6·1%). This compound is readily soluble in chloroform or ethyl acetate and moderately soluble in alcohol.

Methanol (500 ml.) containing a suspension of this acetate (18 g.) was saturated at 0° with dry ammonia, the resulting solution was kept at 0° for 6 hours, the solvent and ammonia were removed in a vacuum, and the residue was crystallised from water, giving 3-*methoxy*-4-*β-glucosidoxy*-1-*allylbenzene* as a *dihydrate* in slender needles (10 g.), m. p. 130—131°, $[\alpha]_D^{20}$ −44·5° in acetone (*c*, 1·0) (Found, in air-dried specimen: C, 53·3; H, 6·8. $C_{16}H_{22}O_7,2H_2O$ requires C, 53·0; H, 7·0%. Found, in material dried in a high vacuum at 110°: C, 58·8; H, 6·7. $C_{16}H_{22}O_7$ requires C, 58·9; H, 6·7%).

3-*Methoxy*-4-(2′ : 3′ : 4′-*triacetyl β-glucosidoxy*)-1-*allylbenzene* (I; R = Ac, R_1 = H).—A mixture of anhydrous 3-methoxy-4-β-glucosidoxy-1-allylbenzene (10 g.), triphenylmethyl chloride (9 g.), and absolute pyridine (80 ml.) was warmed on the steam-bath for 1 hour, kept for 36 hours, and then mixed with acetic anhydride (100 ml.). 48 Hours later the solution was poured into ice–water (1·5 l.) which was then vigorously stirred for 2 hours. The resulting granular precipitate was crystallised from methanol, giving 3-*methoxy*-4-(2′ : 3′ : 4′-*triacetyl* 6′-*trityl β-glucosidoxy*)-1-*allylbenzene* (I; R = Ac, R′ = CPh_3) in thin glistening plates (15 g.), readily soluble in ethyl acetate, chloroform, benzene, or acetone, and having m. p. 136—137°, $[\alpha]_D^{20}$ +30·0° in chloroform (*c*, 1·0) (Found: C, 71·0; H, 6·2. $C_{41}H_{42}O_{10}$ requires C, 70·9; H, 6·1%).

When a mixture of 3-methoxy-4-β-glucosidoxy-1-allylbenzene (0·8 g.), triphenylmethyl chloride (1 g.), and pyridine (8 ml.) was warmed on the steam-bath for 1 hour and then kept for 3 days, the resulting product obtained by the addition of an excess of ice–water was a gum. Repeated reprecipitation of this material from its methanolic solution by means of ice–water finally gave a flocculent precipitate, but it was not possible to obtain a crystalline product from the latter. On acetylation with acetic anhydride and pyridine the amorphous solid readily gave rise to the well-crystallised 3-methoxy-4-(2′ : 3′ : 4′-triacetyl 6′-trityl β-glucosidoxy)-1-allylbenzene, m. p. 137° (after purification).

A solution of the foregoing trityl ether (15 g.) in acetic acid (40 ml.) at 10° was mixed with a saturated solution of hydrogen bromide in acetic acid (6 ml.) at 0°, and after 1 minute the mixture was rapidly filtered to remove triphenylmethyl bromide, treated with ice–water (300 ml.), and extracted with chloroform. Evaporation of the combined washed and dried extracts left 3-*methoxy*-4-(2′ : 3′ : 4′-*triacetyl β-glucosidoxy*)-1-*allylbenzene* (I; R = Ac, R′ = H). This was dissolved in the minimum amount of warm chloroform and the solution treated with absolute ether until a faint turbidity appeared. On being kept this mixture deposited the triacetate in prismatic needles (4·5 g.), m. p. 124·5—125°, $[\alpha]_D^{20}$ −22·5° in chloroform (*c*, 0·8), which are readily soluble in alcohol (Found: C, 58·4; H, 6·3. $C_{22}H_{28}O_{10}$ requires C, 58·4; H, 6·2%). Acetylation of this compound (0·1 g.) with acetic anhydride (1 ml.) and sodium acetate (0·5 g.) on the steam-bath for 2 hours regenerated 3-methoxy-4-(tetra-acetyl β-glucosidoxy)-1-allylbenzene, m. p. and mixed m. p. 123°.

3-*Methoxy*-4-*β-vicianosidoxy*-1-*allylbenzene* (*Gein*) (II; R = H).—To ensure success in the following preparation it is essential that all the materials are dry. A mixture of 3-methoxy-4-(2′ : 3′ : 4′-triacetyl β-glucosidoxy)-1-allylbenzene (2·26 g.), "active" silver oxide (1·5 g.), "Drierite" (20 g., which had been heated to 240° for 2 hours), and chloroform (20 ml.) was agitated in a closed flask protected from light for 1 hour. A trace of iodine was then introduced, followed by the gradual addition of a solution of triacetyl α-arabinosidyl bromide (Felton and Freudenberg, *J. Amer. Chem. Soc.*, 1935, **57**, 1638) (1·98 g.) in chloroform (20 ml.) during 1 hour, and the mixture was then stirred for 48 hours and filtered. Evaporation of the filtrate in a vacuum left a viscous syrup which was dissolved in warm methanol (15 ml.) and, on cooling, this solution deposited 3-*methoxy*-4-(*hexa-acetyl β-vicianosidoxy*)-1-*allylbenzene* (II; R = Ac) in small needles (1·8 g.) which on recrystallisation had m. p. 157—158°, $[\alpha]_D^{20}$ −27·3° in chloroform (*c*, 1·1) (Found: C, 55·7; H, 5·8. $C_{33}H_{42}O_{17}$ requires C, 55·8; H, 5·9%). Deacetylation of this compound (2·5 g.) in methanol (150 ml.), saturated with ammonia at 0°, for 6 hours, gave rise to gein which separated from 95% methanol as a hydrate in masses of felted needles (1·0 g.), m. p. 146—147°, $[\alpha]_D^{20}$ −55·0° in acetone (*c*, 1·0) (Found, in air-dried specimen: C, 53·1; H, 6·9. Calc. for $C_{21}H_{30}O_{11},H_2O$: C, 52·9; H, 6·7%). The properties of the hydrate are identical with those of the natural compound. On being kept in an desiccator over phosphoric oxide this compound lost water of crystallisation, giving the anhydrous glycoside which had m. p. 183—184° (Found, in specimen dried in a high vacuum at 110°: C, 54·9; H, 6·7. Calc. for $C_{21}H_{30}O_{11}$: C, 55·0; H, 6·6%). Acetylation of the glycoside by the acetic anhydride–sodium acetate method re-formed the hexa-acetate, m. p. and mixed m. p. 157—158°.

2 : 3 : 4-*Triacetyl β-Glucoside of* (−)-*Mandelamide* (III; R = Ac, R′ = H).—The following modification of Fischer and Bergmann's method for the preparation of the tetra-acetyl β-glucoside of ethyl (±)-mandelate (*Ber.*, 1917, **50**, 1047) gave improved yields. A mixture of ethyl (±)-mandelate (15 g.), active silver oxide (12 g.), "Drierite" (40 g., which had been heated to 240° for 2 hours), and chloroform (80 ml.) in a flask protected from light was stirred for 1 hour. Iodine (1 g.) was then added to the mixture, followed by a solution of tetra-acetyl α-glucosidyl bromide (23 g.) in chloroform (100 ml.), added dropwise in the course of 1 hour. After having been stirred for 48 hours the reaction mixture was filtered (the solid being washed with chloroform) and the filtrate and washings were evaporated in a vacuum at 15—25 mm. (water-bath at 35°), leaving a viscous syrup from which unchanged ethyl (±)-mandelate was removed by distillation in a vacuum at 160°/0·1—0·2 mm. The almost colourless, very viscous residue was then dissolved in hot alcohol (50 ml.), and on cooling this solution deposited the tetra-acetate of the glucoside in rosettes of colourless needles (16 g.) which had m. p. 102—109° after sintering at 90°. Fischer and Bergmann (*loc. cit.*) record m. p. 102—109°.

The pyridine complex of the β-glucoside of (−)-mandelamide was prepared from the foregoing tetra-acetate according to the method of Fischer and Bergmann (*loc. cit.*) and dried over sulphuric acid in a desiccator. The resulting amorphous product (12 g.) was gently warmed on the steam-bath with pyridine (30 ml.) and triphenylmethyl chloride (12 g.) until a clear solution was formed and, after having

been kept at room temperature for 24 hours, the reaction mixture was treated with acetic anhydride (30 ml.) and, 36 hours later, was poured into ice–water (500 g.). The mixture was agitated for 3 hours, and the resulting viscous product was purified by being dissolved in the minimum amount of warm methanol and reprecipitated with ice–water (300 g.). When this procedure had been repeated three times the crude 2 : 3 : 4-*triacetyl* 6-*trityl* β-*glucoside* (III; R = Ac, R′ = CPh_3) of (−)-mandelamide was obtained as a white amorphous powder which was dried and dissolved in the minimum amount of warm ethyl acetate. Hot light petroleum (b. p. 60—80°) was then added until the solution became slightly turbid; on cooling, the mixture slowly deposited the triacetate of the trityl ether in prismatic needles (13 g.), m. p. 135—136° with slight sintering at 130°, $[\alpha]_D^{20}$ −35·8° in chloroform (*c*, 1·1) (Found: C, 69·0; H, 5·9; N, 1·7. $C_{39}H_{39}O_{10}N$ requires C, 68·7; H, 5·7; N, 2·1%). This compound is readily soluble in methanol, alcohol, or ethyl acetate.

A saturated solution of hydrogen bromide in acetic acid (30 ml.) at 0° was added with stirring to the foregoing triacetate of the trityl ether of (−)-mandelamide (III; R = Ac, R′ = CPh_3) (13 g.), dissolved in acetic acid (30 ml.) at 8°, and after 1 minute the mixture was filtered to remove triphenylmethyl bromide and poured into ice–water (500 g.). The viscous product was isolated by repeated extraction with chloroform, the extracts were well washed, dried, and evaporated in a vacuum, and the residue was dissolved in the minimum amount of hot ethyl acetate. Warm light petroleum (b. p. 60—80°) was then added to this solution until crystalline material began to separate, and on being kept the cooled mixture deposited the 2 : 3 : 4-*triacetyl* β-*glucoside* (III; R = Ac, R′ = H) of (−)-mandelamide in rosettes of feathery needles (6 g.), m. p. 166—167° with slight sintering at 162° after recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°), $[\alpha]_D^{20}$ −90·0° in chloroform (*c*, 1·0) (Found: C, 54·6; H, 5·8; N, 3·2. $C_{20}H_{25}O_{10}N$ requires C, 54·7; H, 5·7; N, 3·2%). Acetylation of this compound with a warm mixture of acetic anhydride and pyridine gave the tetra-acetyl β-glucoside of (−)-mandelamide, identified by comparison with an authentic specimen (Fischer and Bergmann, *loc. cit.*).

Hexa-acetyl β-*Vicianoside of* (−)-*Mandelamide* (IV; R = $CO{\cdot}NH_2$).—A mixture of the foregoing triacetate (III; R = Ac, R′ = H) (1 g.), "active" silver oxide (3 g.), "Drierite" (20 g.), and chloroform (30 ml.), maintained at 40°, was stirred for 1 hour and then treated with a trace of iodine, followed by a solution of triacetyl α-L-arabinosidyl bromide (1 g.) in chloroform (15 ml.) which was added gradually in the course of 1 hour. The mixture was maintained at 40° for a further 8 hours and then at room temperature for 16 hours with continuous agitation, filtered to remove silver salts (which were washed with chloroform), and evaporated in a vacuum. A solution of the residue in a little methanol was poured into ice–water (200 g.), and the resulting precipitate collected, washed, dried, and crystallised from ethyl acetate–light petroleum (b. p. 60—80°), giving the *hexa-acetyl* β-*vicianoside* of (−)-mandelamide in small colourless needles (0·2 g.), which had m. p. 189—190°, $[\alpha]_D^{20}$ −65·0° in chloroform (*c*, 1·0) after having been twice recrystallised from the mixed solvent (Found: C, 53·6; H, 5·5; N, 2·2. $C_{31}H_{39}O_{17}N$ requires C, 53·4; H, 5·6; N, 2·0%).

Hexa-acetyl β-*Vicianoside of* (−)-*Mandelonitrile* (IV; R = CN).—The foregoing amide (0·15 g.) was treated with phosphoryl chloride (0·7 g.) at 68—70° for 15 minutes, the excess of chloride was removed in a vacuum, and the residue was triturated with ice–water. Crystallisation of the resulting semi-solid product from methanol gave the *hexa-acetyl* β-*vicianoside* of (−)-mandelonitrile in prismatic needles, m. p. 165° (Found: C, 54·6; H, 5·6. $C_{31}H_{37}O_{16}N$ requires C, 54·8; H, 5·5%).

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