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STUDIES ON MONOTERPENE GLUCOSIDES—IX[1, 2]

CHEMICAL CORRELATION BETWEEN ASPERULOSIDE AND LOGANIN

H. INOUYE, T. YOSHIDA, S. TOBITA and M. OKIGAWA
Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto, Japan

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Abstract—The absolute structure of loganin was established by chemical conversion of asperuloside to loganin penta-acetate. The stereochemical relations of a series of the intermediates are also discussed.

LOGANIN*, a bitter glucoside isolated from *Strychnos nux vomica*[3, 4, 5] and other species of *Strychnos*[6, 7], *Menyanthes trifoliata*[8], Lonicera- and Hydrangea-species[9], has recently been the subject of various chemical and biosynthetic investigations. Previously, Merz and Birch[4-7] showed that this glucoside was a β-glucoside with the formula $C_{17}H_{26}O_{10}$, containing a carbomethoxyl group conjugated with an enol ether, one C-methyl group and a secondary hydroxyl group in its aglycone moiety. Birch further suggested a structural similarity between loganin and plumieride.[10] On the other hand, Büchi[11] showed that the acetates **3** and **4** of the two alcoholic C_6-epimers derived from verbenalin (**2**) differed from loganin pentaacetate. Based on these findings, Ramstad *et al.*[12] assigned the structure **1a** to loganin. This assignment, however, lacks chemical and stereochemical support.

Recently, Battersby[13] and Arigoni[14] found that loganin was a key intermediate in the biosynthesis of indole alkaloids. However, no information was available on its structure when we started this work.

This paper reports studies on the structure of loganin (**1a**) including its absolute configuration by chemical transformation of asperuloside (**5**)[15] of known absolute structure to loganin pentaacetate.

On catalytic hydrogenation over Pd-C followed by methylation with diazomethane, asperuloside tetraacetate (**6**) was converted to bisdesoxydeacetylasperulosidic acid methyl ester tetraacetate (**7**)[16] which was oxidized with osmium tetroxide to the diol **8**, $C_{25}H_{34}O_{15}$, m.p. 152–153°. Assuming that the oxidizing reagent approached from the convex side of the aglycone moiety of the compound **7**, the newly formed hydroxyl groups in **8** would be β-oriented. The diol **8**, after conversion to the pentaacetate **9**, $C_{27}H_{36}O_{16}$, m.p. 138–140°, was dehydrated by phosphorous oxychloride and pyridine to a product which gave two spots on a thin layer chromatogram. The nuclear magnetic resonance (NMR) spectrum of this compound shows signals due to vinylic methyl at 8·39 and 8·23τ which indicate that the dehydrated product is a mixture of two substances **10** and **11**. This mixture, without further purification, was subjected to hydrolysis with sodium methoxide followed by acetylation to give ketone **12**, $C_{25}H_{32}O_{14}$, m.p. 108°, as the sole crystalline product, derived from **10**. The NMR spectrum of **12** showed a signal at 8·85τ (doublet, $J = 6$ c/s) due to a secondary methyl group and its

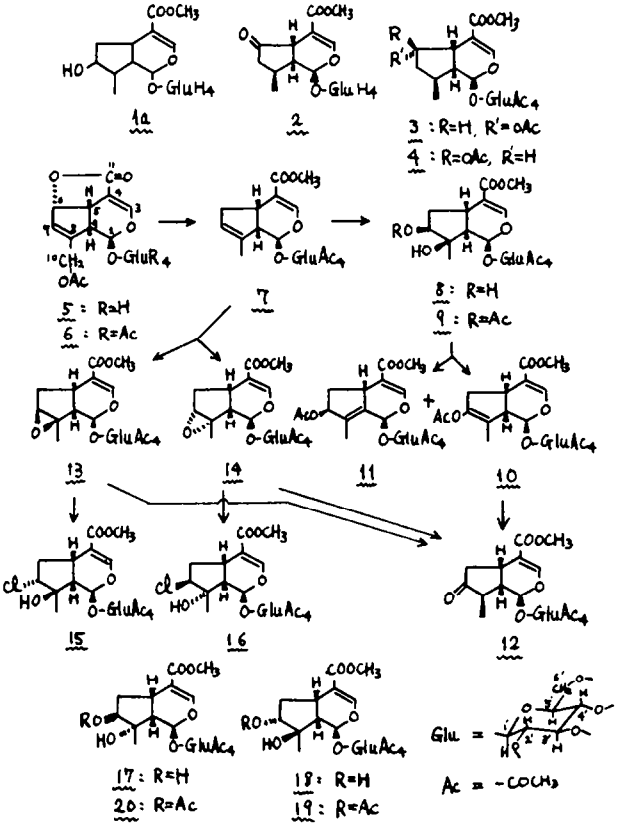
* The corresponding free acid, loganic acid, has been isolated from *Swertia caroliniensis* (C. J. Coscia and R. Guarnaccis, *Chem. Commun.*, 138 (1968)).

ORD curve showed negative cotton effect ($[\phi]_{319}$ −7184°) indicating that the compound **12** was a ketone.

On the other hand, oxidation of **7** with one mole equivalent of *m*-chloroperbenzoic acid gave two isomeric epoxides **13**, $C_{25}H_{32}O_{14}$, m.p. 132–134° and **14**, $C_{25}H_{32}O_{14}$, m.p. 154°. The NMR spectrum of **13** showed a doublet (J= 1 c/s) at 2·62 λ due to a vinyl proton on C_3, a doublet (J= 1 c/s) at 6·72 τ due to an epoxy proton and a singlet at 8·49 τ due to a methyl group on a tertiary carbon. The corresponding signals in the NMR spectrum of **14** appear at 2·75, 6·75 and 8·49 τ. These NMR spectra suggest that only the double bond at C_7–C_8 was oxidized with peracid as is the case with osmium tetroxide, and hence the two oxidation products are stereoisomers differing in the configuration of the epoxide ring at C_7–C_8. Both **13** and **14**, as will be described later, were converted to ketone **12** in fairly good yield.

The configurations of these epoxides were determined by the following reactions.

On treatment with hydrochloric acid in ethylacetate at room temperature, **13** gave chlorohydrin **15**, $C_{25}H_{33}O_{14}Cl$, m.p. 171–173°, in fairly good yield. In the same way, **14** gave the corresponding chlorohydrin **16**, $C_{25}H_{33}O_{14}Cl$, m.p. 166–167°. The newly formed hydroxyl group in **15** or **16** was resistant to acetylation by the usual method indicating that the chlorine atom occupied the C_7 position.



SCHEME 1

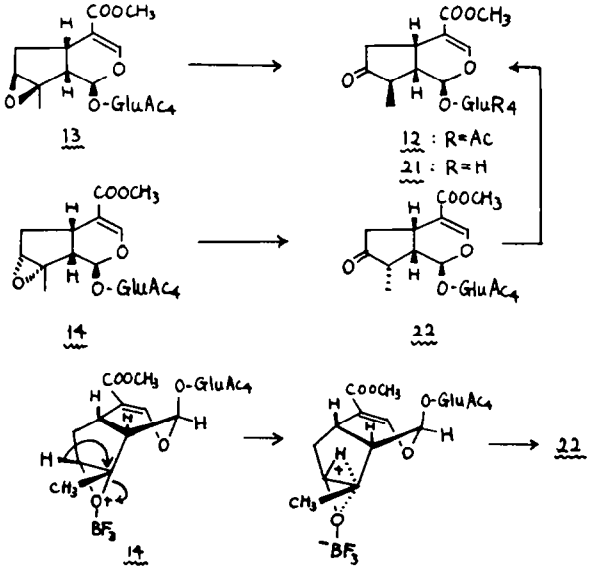
Although nucleophiles are expected to favourably attack the cyclopentane ring from the less hindered β-side, the convex face of the aglyconc moiety, there was practically no difference in the yield of chlorohydrin **15** from **13** and of **16** from **14**.

Epoxide **13** was then treated with perchloric acid in acetone to give two diols, **17**, $C_{25}H_{34}O_{15}$, m.p. 167–170° and **18**, $C_{25}H_{34}O_{15}$, m.p. 91–93° in 14% and 42% yield, respectively. Epoxide **14** was also treated in the same way to afford diols **17** and **18** in yields of 24% and 10%, respectively. On heating with glacial acetic acid, **13** gave pentaacetate **19**, $C_{27}H_{36}O_{16}$, m.p. 190–192° in 52% yield, which was identical with the acetate of diol **18**. In the same way, epoxide **14** gave pentaacetate **20**, $C_{27}H_{36}O_{16}$, m.p. 149–151°, in 27% yield, which was identical with the acetate of diol **17**. These results show that C_7 is more accessible than C_8 to the nucleophile, but these results are not sufficient to determine the configuration of the epoxides conclusively.

On the other hand, **13** was treated with BF_3-etherate to give an isomer, $C_{25}H_{32}O_{14}$, m.p. 109°, in 48% yield, which was identified as the ketone **12** derived from **10** by its mixed melting point, and IR and NMR spectra. Ketone **12** was also obtained by analogous treatment of **14**, in 41% yield. The fact that both **13** and **14** gave the same compound **12** and that on treatment with sodium methoxide, **12** afforded the deacetylated compound **21**, $C_{17}H_{24}O_{10}$, m.p. 193–195°, from which **12** was regenerated by acetylation, indicate that the methyl group at C_8 in **12** has a stable configuration.

Treatment of **14** with BF_3-etherate for a short period, however, afforded a ketone **22**, $C_{25}H_{32}O_{14}$, m.p. 146–148°, which was isomerized to ketone **12** by prolonged treatment with the same reagent. This indicates that the C_8 methyl group of compound **22** has an unstable configuration. Since the C_8 methyl group of **12** has a β-orientation, that of ketone **22** should have an α-configuration.

Assuming that this ketone was formed from the epoxides by a backbone hydride rearrangement,[17] **14** should have an α-oriented epoxide ring (Scheme 2). This conclusion was supported by the following NMR spectral data.



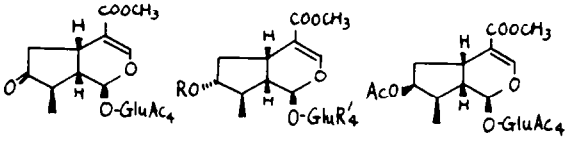
SCHEME 2

Compound **14** showed a doublet at 2·75 τ (J = 1 c/s) corresponding to the enol proton at C_3 and a doublet at 4·40 τ (J = 1 c/s) due to the acetal proton at C_1. The coupling constant of $J_{1,9}$ (1 c/s) is compatible with a conformation in which the C_1 proton is in an equatorial position. In this conformation with an α-oriented epoxide ring, the NMR signal of the C_1 proton, which lies to the side of epoxide ring, is expected to shift to a lower field. On the other hand, the signal of the C_3 proton would shift a little to higher field as this proton is located above the plane of the epoxide ring. On the contrary, neither the C_1 nor C_3 proton of a β-epoxide should be affected by such an anisotropy effect.

In fact, the NMR spectrum of **13**, as previously mentioned, shows a doublet (J = 1 c/s) assignable to the C_3 proton at 2·62 τ and a signal due to the C_1 proton overlapping the methine signals of the glucose moiety at 4·7–5·1 τ. Thus comparisons of the NMR signals of **13** and **14** revealed that the epoxide ring in **14** is α-oriented while that in **13** is β-oriented. Consequently, compounds **15-22** should be represented by the absolute structures shown in schemes 1 and 2.

The ketone **12** was reduced with sodium borohydride to yield the 7-hydroxyl compound **23**, $C_{25}H_{34}O_{14}$, m.p. 150–151°, $[\alpha]_D$ −102·7°, which was converted to the pentaacetate **24**, $C_{27}H_{36}O_{15}$, m.p. 144°, $[\alpha]_D$ −141·8°. However, as compound **24** was entirely different from authentic loganin pentaacetate, Walden inversion of the 7-hydroxyl group of **23** was attempted.

Treatment of **23** with tosyl chloride gave monotosylate **25**, $C_{32}H_{40}O_{16}S$, m.p. 113–115°, which was refluxed with tetraethyl-ammoniun acetate in acetone to yield the epimeric acetate **26**, $C_{27}H_{36}O_{15}$, m.p. 132–133°, $[\alpha]_D$ −80·4°. This compound was identified as loganin pentaacetate by comparisons of the IR and NMR spectra, specific rotations and by the mixed melting point. Thus, the absolute configurations of the asymmetric centres at C_1, C_5 and C_9 of loganin were established as identical with those of asperuloside.



12

23 : R=H, R'=Ac
24 : R=Ac, R'=Ac
25 : R=Ts, R'=Ac
27 : R=Bz, R'=Ac
29 : R=H, R'=H

26

SCHEME 3

The absolute configuration at C_7 of loganin (**1**) was determined in the following two ways. First, the benzoate rule[18] was applied to 7-epibenzoylloganin tetraacetate (**27**) and 7-epiloganin tetraacetate (**23**). **27**, $C_{32}H_{38}O_{15}$, m.p. 109–110°, $[\alpha]_D$ −126·5°, was prepared from **23** by the action of benzoyl chloride in pyridine. The difference in molecular rotation $[M]_{D(27)}-[M]_{D(23)} = -265°$ (in $CHCl_3$), suggests that the hydroxyl group at C_7 in **23** has an α-configuration. The application of the dissymmetry rule[19] also led to the same conclusion. For, when the molecular rotation of bisdesoxydihydrodea-

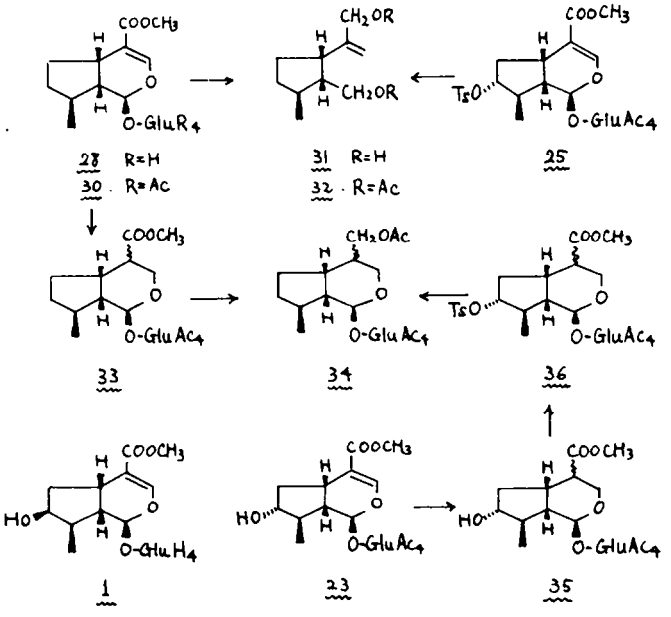
cetylasperulosidic acid methyl ester (**28**)[16, 20] ($[M]_D$ −332°), in which the C_8 methyl group is already known to be β-oriented, is used as a standard, the predicted shift in rotation caused by the introduction of an α-hydroxyl group into the C_7 position of this compound **28** is −50° (predicted $[M]_D$ −382°), while that due to the β-hydroxyl group is 0° (predicted $[M]_D$ −332°). The observed $[M]_D$ for loganin (**1**) and 7-epiloganin (**29**), $C_{17}H_{26}O_{10}$, derived from **23** are −320° and −392° respectively, in good agreement with the predicted values.

The configuration of the C_8 methyl group was determined as follows. Bisdesoxydihydrodeacetylasperulosidic acid methyl ester tetraacetate (**30**) was reduced with LAH to give an oily diol **31**, which was then acetylated to an oily diacetate **32**, $C_{14}H_{22}O_4$. In the NMR spectrum of **32**, the two doublets of the terminal methylene protons appear at 4·85 and 5·02 τ. The signal of the two protons due to allylic methylene bearing an acetoxyl group appear at 5·43 τ and another signal of acetoxymethylene protons at 6·10 τ, two acetoxyl groups at 7·90 and 8·00 τ and the C_8 methyl group at 8·95 τ (doublet, $J=6$ c/s). These NMR data support the conclusion that the diacetate can be represented by **32**.[21]

In the same way, 7-epitosylloganin tetraacetate (**25**) was converted to an oily diol and then to its acetate, also an oil. The diacetates derived from **30** and **25** were found to be identical by comparisons of their IR, NMR and mass spectra. Their ORD curves also gave the same sign.

Although we thus tentatively concluded that the C_8 methyl group of loganin (**1**) is β-oriented, this was still not fully established since identification involved oily substances.

Conclusive proof was obtained as follows.



SCHEME 4

Bisdesoxytetrahydrodeacetylasperulosidic acid methyl ester tetraacetate (**33**), $C_{25}H_{36}O_{13}\cdot\frac{1}{2}H_2O$, m.p. 154–156°, derived from the corresponding bisdesoxydihydro compound **30** by catalytic hydrogenation over prereduced PtO_2, was reduced with LAH and subsequently acetylated to give pentaacetate **34** as colourless plates, $C_{26}H_{38}O_{13}$, m.p. 98–99°, $[\alpha]_D$ −52·9°. The NMR spectrum of **34** shows a signal due to the C_8 methyl group at 9·02 τ (doublet, $J=6$ c/s) and five acetoxyl groups at 7·94–7·99 τ. On the other hand, 7-epiloganin tetraacetate (**23**) was hydrogenated in acetic acid with Adams catalyst at 40° to give the dihydro compound **35**, $C_{25}H_{36}O_{14}$, m.p. 150–151°, the IR spectrum of which shows no enol band. Reduction of the tosylate **36**, $C_{32}H_{42}O_{16}S$, m.p. 145–146°, derived from **35**, with LAH followed by acetylation gave colourless plates, m.p. 97–99°, $[\alpha]_D$ −45·0°. This compound was identified as **34** by the mixed melting point, $[\alpha]_D$ and by IR and NMR spectral comparisons.

Hence, the absolute configuration of loganin was established to be as in **1**.

Recently, Battersby[22] and Arigoni[23] also reached the same conclusion in investigations,[13,14] by differing methods, on the role of loganin (**1**) as an intermediate in indole alkaloid biosynthesis. Battersby also found that loganin (**1**) is a component of *Vinca rosea*.

We recently demonstrated[24] that loganin (**1**) is a precursor of gentiopicroside as well as highly oxygenated iridoid glucosides such as asperuloside.

Addendum—After the preparation of the manuscript of this work we received the report on the structural elucidation of loganin by X-ray analysis of a derivative, which is also in accord with ours (P. J. Lentz, Jun. and M. G. Rossmann, *Chem. Commun.*, 1269 (1969)).

EXPERIMENTAL

M.ps. are uncorrected. NMR spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are given in τ values with TMS as the internal standard and coupling constants (J) in c/s.* Specific rotations were determined with a Rex Photoelectric polarimeter. ORD curves were measured with a Japan Spectroscopic Company ORD/UV-5 spectropolarimeter. Mass spectra were obtained on a Hitachi RMU-6D mass spectrometer equipped with an all glass inlet system and operating with an ionization energy of 80 eV. Silica gel G acc. to Stahl (Merck) was used for thin-layer chromatography. Detection was carried out on exposure to iodine vapour. Silica gel (Mallinckrodt) was used for column chromatography.

Oxidation of Bisdesoxydeacetylasperulosidic acid methyl ester tetraacetate (**7**) *with Osmium tetroxide*

A soln of OsO_4 (0·97 g) in ether (10 ml) was added dropwise under stirring to a soln of **7** (2·2 g) in ether (60 ml) containing pyridine (2 ml). After standing the mixture overnight at room temp, the black ppt was collected, washed well with ether and dissolved in EtOH. Gaseous H_2S was passed into the EtOH soln and the resulting ppt was filtered off and washed with EtOH. The washings were combined with the filtrate and evaporated *in vacuo* to give a brown oily residue, which was recrystallized from EtOH to give 0·8 g of the diol **8**, m.p. 152–153°. $[\alpha]_D^{15}$ −90·9° (c=0·29, $CHCl_3$); IR (Nujol): 3260, 1750, 1640 cm^{-1}; UV (MeOH) λ_{max}: 235 mμ (log ε 3·96); NMR ($CDCl_3$): 8·82 (3H, s, C_8–Me), 6·29 (3H, s, COOMe), 4·55 (1H, d, $J=1·5$ c/s, C_1–H) (Found: C, 51·97; H, 6·16. $C_{25}H_{34}O_{15}$ requires: C, 52·26; H, 5·96%).

Acetylation of cis-Diol **8**

8 (600 mg) was dissolved in 2 ml each of pyridine and Ac_2O. After standing overnight at room temp, the reaction mixture was poured into ice water. The resulting solid was recrystallized from EtOH-n-Hexane to yield 506 mg of acetate **9**, m.p. 138–140°. $[\alpha]_D^{15}$ −121·3° (c=0·559, $CHCl_3$); IR (Nujol): 3450, 1754, 1710, 1640 cm^{-1}; NMR ($CDCl_3$): 8·75 (3H, s, C_8–Me), 6·30 (3H, s, COOMe), 4·54 (1H, d, $J=1$ c/s, C_1–H), 2·72 (1H, diffused s, C_3–H) (Found: C, 52·77; H, 5·86. $C_{27}H_{36}O_{16}$ requires: C, 52·59; H, 5·88%).

* Abbreviations: s = singlet, d = doublet, m = multiplet.

Epoxidation of Bisdesoxydeacetylasperulosidic acid methyl ester tetraacetate (7)

To a soln of 7 (1·2 g) in benzene (8 ml) was added a soln of *m*-chloroperbenzoic acid (0·45 g) in benzene (8 ml) under cooling and the reaction mixture was allowed to stand overnight in a refrigerator. The soln was washed with 2N NaOH and then with water, dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil (1·13 g), which was chromatographed on silica gel (70 g) using ether as eluent, 5 ml fractions of eluate were collected. The crystalline residue from fractions Nos 32–50 was recrystallized from ether to give colourless needles of epoxide **13**, m.p. 132–134° (343 mg). $[\alpha]_D^{15}$ −84·7° (c=0·497, $CHCl_3$); IR (Nujol): 1740, 1700, 1640 cm^{-1}; UV (MeOH) λ_{max}: 236 mμ (log ε 4·02); NMR ($CDCl_3$): 8·49 (3H, s, C_8–Me), 6·72 (1H, d, J=1 c/s, C_7–H), 6·29 (3H, s, COOMe), 2·62 (1H, d, J=1 c/s, C_3–H) (Found: C, 54·00; H, 5·65. $C_{25}H_{32}O_{14}$ requires: C, 53·95; H, 5·80%).

Another epoxide **14** obtained from fractions Nos 61–70, which travelled slower than **13** in TLC (SiO_2–ether), was recrystallized from ether to give colourless needles, m.p. 154° (105 mg). $[\alpha]_D^{20}$ −151·9° (c=0·678, $CHCl_3$); IR (Nujol): 1740, 1706, 1640, 900 cm^{-1}; NMR ($CDCl_3$): 8.49 (3H, s, C_8–Me), 6·75 (1H, diffused s, C_7–H), 6·32 (3H, s, COOMe), 4·40 (1H, d, J=1 c/s, C_1–H), 2·75 (1H, d, J=1 c/s, C_3–H) (Found: C, 53·92; H, 5·98. $C_{25}H_{32}O_{14}$ requires: C, 53·95; H, 5·80%).

7-*Ketologanin tetraacetate* (12)

(a) From pentaacetate **9**: $POCl_3$ (0·6 ml) was added to a soln of **9** (243 mg) in pyridine (2 ml). The reaction mixture was allowed to stand overnight at room temp, and then poured into ice water. The resulting pale brown amorphous substance was dissolved in $CHCl_3$ and passed through a column of alumina (10 g, Woelm, neutral, activity III). The colourless syrup (195 mg, TLC; SiO_2-ether, 2 spots) obtained on evaporation of the eluate was heated under reflux for 10 min with MeOH-NaOMe. The soln was neutralized on an ion exchange resin (Amberlite IR-120) and the soln was evaporated *in vacuo*. Acetylation of the oily residue in the usual manner followed by chromatography on alumina (15 g, activity III) with ether as eluent furnished the ketone **12**, as sole crystalline product, recrystallized from EtOH to give colourless needles, m.p. 108° (65 mg). $[\alpha]_D^{30}$ − 140·7° (c = 1·12, $CHCl_3$); IR (Nujol): 1750, 1740, 1705, 1630 cm^{-1}; NMR ($CDCl_3$): 8·85 (3H, d, J=6 c/s, C_8-Me), 6·30 (3H, s, COOMe), 4·57 (1H, d, J=1 c/s, C_1-H), 2·62 (1H, d, J=1 c/s, C_3-H) (Found: C, 53·83; H, 5·82. $C_{25}H_{32}O_{14}$ requires: C, 53·95; H, 5·80%).

(b) From epoxide **13**: BF_3–etherate (0·2 ml) was added dropwise to a soln of epoxide **13** (200 mg) in benzene (20 ml) at room temp. The pink coloured reaction mixture was allowed to stand at room temp for 2 h and then poured into ice water. The benzene layer was separated and the aqueous layer re-extracted with benzene. The combined benzene soln was washed with water and dried over $MgSo_4$. Removal of the solvent gave a crystalline residue, which was recrystallized from EtOH to give fine colourless needles, m.p. 109° (96 mg). This product was identical with **12** obtained from **9**. The ketone **12** was also obtained from epoxide **14** by the same treatment (Yield: 83 mg from 200 mg of **14**).

Treatment of Epoxide **13** *with conc* HCl

A soln of **13** (50 mg) in AcOEt (5 ml) containing conc HCl (0·05 ml) was stirred for 15 min to give a colourless syrup which was crystallized from CH_2Cl_2—light petroleum. Recrystallization from the same solvent afforded fine colourless needles of chlorohydrin **15**, m.p. 171–173° (11 mg), which gave a positive Beilstein flame test. IR (Nujol): 3300, 1745, 1705, 1640 cm^{-1}; NMR ($CDCl_3$): 8·47 (3H, s, C_8–Me), 6·29 (3H, s, COOMe), 4·62 (1H, d, J=4 c/s, C_1–H), 2·62 (1H, d, J=1·5 c/s, C_3–H) (Found: C, 50·50; H, 5·89. $C_{25}H_{33}O_{14}Cl$ requires: C, 50·64; H, 5·61%).

Treatment of Epoxide **14** *with conc* HCl

To a soln of **14** (50 mg) in AcOEt (5 ml) conc HCl (0·05 ml) was added. After standing for 15 min, the reaction mixture was washed with 10% NaOH and then with water. The AcOEt layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a colourless oil. Ether was added to the oily residue which crystallized immediately. Recrystallization from $CHCl_3$–ether gave colourless prisms of chlorohydrin **16**, m.p. 166–167° (38 mg). IR (Nujol): 3300, 1745, 1705, 1640 cm^{-1}; NMR($CDCl_3$): 8·47 (3H, s, C_8–Me), 6·29 (3H, s, COOMe), 4·62 (1H, d, J=1 c/s, C_1—H), 2·62 (1H, d, J=1·5 c/s, C_3–H) (Found: C, 50·37; H, 5·67. $C_{25}H_{33}O_{14}Cl$ requires: C, 50·64; H, 5·61%).

Diol **17** *and* **18**

(a) From epoxide **13**: To a soln of **13** (1 g) in acetone (160 ml) was added 6% aq $HClO_4$ (10 ml). After standing at 38° for 15 h, the reaction mixture was dried over anhydrous K_2CO_3 and evaporated *in vacuo*.

The resulting brown syrup was chromatographed on silica gel (50 g) using $CHCl_3$–MeOH (99 : 1 v/v) as eluent, and 8 ml fractions of eluate were collected. Fractions Nos 87–120 were evaporated to give a crystalline residue which was recrystallized from ether to give 143 mg of **17** as colourless plates, m.p. 167–170°. $[\alpha]_D^{25} - 12{\cdot}3°$ (c = 0·93, $CHCl_3$); IR (KBr): 3500, 1750, 1696, 1650 cm^{-1}; UV (EtOH) λ_{max}: 237 mμ (log ε 4·02); NMR ($CDCl_3$): 8·59 (3H, s, C_8–Me), 6·29 (3H, s, COOMe), 4·64 (1H, d, J = 4 c/s, C_1–H), 2·65 (1H, d, J = 1 c/s, C_3–H) (Found: C, 50·89; H, 6·20. $C_{25}H_{34}O_{15}.H_2O$ requires: C, 50·68; H, 6·11%).

Analogous treatment of fractions Nos 124–235 gave colourless plates of another diol **18**, m.p. 91–93° (423 mg). $[\alpha]_D^{23} - 51{\cdot}4°$ (c = 0·63, $CHCl_3$); IR (KBr): 3550, 3370, 1760, 1700, 1640 cm^{-1}; NMR ($CDCl_3$): 8·81 (3H, s, C_8–Me), 6·30 (3H, s, COOMe), 4·52 (1H, d, J = 2·5 c/s, C_1–H), 2·70 (1H, diffused s, C_3–H) (Found: C, 49·24; H, 6·20. $C_{25}H_{34}O_{15}.2H_2O$ requires: C, 49·18; H, 6·27%).

(b) From epoxide **14**: **14** (500 mg) was dissolved in acetone (80 ml) and 6% aq $HClO_4$ (5 ml) was added. After standing at 38° for 30 h, the soln was neutralized with anhydrous K_2CO_3 and the solvent was removed *in vacuo*. The resulting syrup was chromatographed on silica gel (50 g) with $CHCl_3$–MeOH (98 : 2) as eluent and 5 ml fractions of eluate were collected. Fractions Nos 65–70 and 72–84 gave 120 mg of diol **17** and 48 mg of diol **18**, respectively.

Pentaacetate **19**

(a) From epoxide **13**: **13** (500 mg) was dissolved in AcOH (60 ml) and heated on a boiling water bath for 8 h. After cooling, the soln was concentrated *in vacuo* to give a yellow syrup, which was chromatographed on silica gel (40 g) with ether as eluent. Fractions of 5 ml of eluate were collected. Fractions Nos 28–50 gave a crystalline residue which was recrystallized from ether to afford 266 mg of **19** as colourless plates, m.p. 190–192°. $[\alpha]_D^{22} - 98{\cdot}7°$ (c = 0·70, $CHCl_3$); IR (KBr): 3550, 1760 (shoulder), 1740, 1710, 1650 cm^{-1}; UV (EtOH) λ_{max}: 235 mμ (log ε 4·08); NMR ($CDCl_3$): 8·80 (3H, s, C_8–Me), 6·29 (3H, s, COOMe), 4·50 (1H, d, J = 2 c/s, C_1–H), 2·69 (overlapped by $CHCl_3$ signal, C_3–H) (Found: C, 52·33; H, 6·01. $C_{27}H_{36}O_{16}$ requires: C, 52·59; H, 5·89%).

(b) From diol **18**: **18** (80 mg) was dissolved in pyridine (0·8 ml) and Ac_2O (0·8 ml) was added. After standing overnight, the reaction mixture was poured into ice water. The resulting ppt was recrystallized from ether to yield 45 mg of colourless plates, m.p. 190–191°, and identified with compound **19** obtained from **13**.

Pentaacetate **20**

(a) From epoxide **14**: **14** (455 mg) in AcOH (60 ml) was worked up in a similar way to **13** to give 124 mg of **20** as fine colourless needles, m.p. 149–151°. $[\alpha]_D^{22} - 16{\cdot}9°$ (c = 0·76, $CHCl_3$); IR (KBr): 3500, 1735, 1710, 1645 cm^{-1}; UV (EtOH) λ_{max}: 235 mμ (log ε 4·07); NMR ($CDCl_3$): 8·69 (3H, s, C_8–Me), 6·29 (3H, s, COOMe), 4·59 (1H, d, J = 3·5 c/s, C_1–H), 2·62 (1H, d, J = 1 c/s, C_3–H) (Found: C, 52·54; H, 5·89. $C_{27}H_{36}O_{16}$ requires: C, 52·59; H, 5·89%).

(b) From diol **17**: **17** (30 mg) was acetylated in a similar manner to **18** to give 21 mg of colourless needles, m.p. 149–151°. This acetate was identified with compound **20** obtained from **14**.

7-*Ketologanin* (**21**)

To a soln of 7-ketologanin tetraacetate (**12**) (300 mg) in hot MeOH (5 ml) was added 0·1N NaOMe soln and the mixture was heated under reflux for 10 min. The soln was cooled and neutralized on an ion exchange resin (Amberlite IR-120), and concentrated *in vacuo* to give a syrupy residue which was crystallized from EtOH-n-Hexane. Recrystallization from the same solvent gave 156 mg of colourless needles, m.p. 193–195°. NMR (CD_3OD): 8·99 (3H, d, J = 6·5 c/s, C_8–Me), 6·30 (3H, s, COOMe), 4·39 (1H, d, J = 2 c/s, C_1–H), 2·54 (1H, d, J = 1·5 c/s, C_3–H) (Found: C, 51·43; H, 6·27. $C_{17}H_{24}O_{10}.\frac{1}{2}H_2O$ requires: C, 51·41; H, 6·34%). **12** was regenerated by acetylation of this compound **21**.

8-*Epi*-7-*ketologanin tetraacetate* (**22**)

A soln of **14** (100 mg) in dry benzene (10 ml) was mixed with BF_3-etherate (0·5 ml), stirred at room temp for 10 min and poured into ice water. The benzene layer was separated and the aqueous layer was re-extracted with benzene. The combined benzene soln was washed with water and dried over $MgSO_4$. Removal of the solvent gave a yellow syrup, which was chromatographed on silica gel (10 g) with CH_2Cl_2 as eluent and 10 ml fractions of eluate were collected. Fractions Nos 22–24 afforded a colourless syrup which was recrystallized from light petroleum–ether to give 42 mg of **22** as colourless needles, m.p. 146–148°. $[\alpha]_D^{30} - 76{\cdot}8°$ (c = 0·61, $CHCl_3$); NMR ($CDCl_3$): 8·84 (3H, d, J = 7 c/s, C_8–Me), 6·27 (3H, s, COOMe), 2·54 (1H, diffused s, C_3–H) (Found: C, 53·76; H, 5·87. $C_{25}H_{32}O_{14}$ requires: C, 53·95; H, 5·80%).

Isomerization of 8-*Epi*-7-*ketologanin tetraacetate* (**22**)

BF_3–etherate (0·5 ml) was added to a soln of **22** (26 mg) in benzene (5 ml). The mixture was stirred for 40 min at room temp and then poured into ice water. The benzene layer was separated and dried over $MgSO_4$. Removal of the solvent afforded a crystalline residue which was recrystallized from ether-light petroleum to give 21 mg of colourless needles, m.p. 109°. This substance was identical with compound **12** in all respects.

7-*Epiloganin tetraacetate* (**23**)

To a soln of **12** (44 mg) in dioxane (5 ml) was added $NaBH_4$ (10 mg) in water (0·5 ml). After standing for 30 min at room temp, AcOH was added, and the mixture was evaporated *in vacuo*. The residue was extracted with $CHCl_3$, washed with water and dried over $MgSO_4$. The soln was concentrated *in vacuo* to give an oily residue, which crystallized on addition of ether. Recrystallization from the same solvent gave **23** as colourless needles, m.p. 150–151° (23 mg). $[\alpha]_D^{25} - 102·7°$ (c = 1·08, $CHCl_3$); IR (Nujol): 3350, 1740, 1690, 1635 cm^{-1}; NMR ($CDCl_3$): 8·87 (3H, d, J = 6 c/s, C_8–Me), 6·29 (3H, s, COOMe), 2·65 (1H, diffused s, C_3–H) (Found: C, 53·68; H, 6·01. $C_{25}H_{34}O_{14}$ requires: C, 53·76; H, 6·13%).

7-*Epiloganin pentaacetate* (**24**)

23 (50 mg) was acetylated with 1 ml each of pyridine and Ac_2O to give 18·2 mg of **24** as colourless needles on crystallization from EtOH, m.p. 144°. $[\alpha]_D^{30} - 141·8°$ (c = 0·71, $CHCl_3$); IR (Nujol): 1753, 1708, 1635 cm^{-1}; NMR ($CDCl_3$): 8·90 (3H, d, J = 6 c/s, C_8–Me), 6·30 (3H, s, COOMe), 2·70 (1H, d, J = 1 c/s, C_3–H) (Found: C, 53·95; H, 5·99. $C_{27}H_{36}O_{15}$ requires: C, 54·00; H, 6·04%).

7-*Epitosylloganin tetraacetate* (**25**)

Tosyl chloride (300 mg) was added to a soln of **23** (100 mg) in pyridine (1·5 ml) and the mixture was allowed to stand at room temp for 12 h. Then it was poured into ice water and the resulting ppt was recrystallized from EtOH to give 84 mg of tosylate **25** as colourless needles, m.p. 113–115°. $[\alpha]_D^{20} - 95·4°$ (c = 0·89, $CHCl_3$); NMR ($CDCl_3$): 9·00 (3H, d, J = 6 c/s, C_8–Me), 7·55 (3H, s, aromatic Me), 6·32 (3H, s, COOMe), 2·65 (3H, diffused d, J = 8 c/s, C_3–H and aromatic H), 2·25 (2H, diffused d, J = 8 c/s, aromatic H) (Found: C, 52·64; H, 5·91. $C_{32}H_{40}O_{16}S.H_2O$ requires: C, 52·60; H, 5·80%).

Epimerization of 7-*Epitosylloganin tetraacetate* (**25**)

A soln of **25** (73 mg) and tetraethylammonium acetate (164 mg) in acetone (3 ml) was heated under reflux for 22 h and then the solvent removed *in vacuo*. The residue was dissolved in $CHCl_3$ and washed with water and sald ag NaCl. The $CHCl_3$ soln was dried over $MgSo_4$ and evaporated to give a brown oily residue which was chromatographed on silica gel (30 g) using $CHCl_3$ as eluent and 2 ml fractions of eluate were collected. Fractions Nos 25–39 were combined and evaporated to give a crystalline residue. Recrystallization from AcOEt–light petroleum afforded 20 mg of colourless needles, m.p. 132–133°. $[\alpha]_D^{25} - 80·4°$ (c = 0·77, $CHCl_3$); IR (Nujol): 1760, 1738, 1710, 1645 cm^{-1}; NMR ($CDCl_3$): 8·99 (3H, d, J = 6 c/s, C_8–Me), 6·32 (3H, s, COOMe), 2·72 (1H, D, J = 1 c/s, C_3–H) (Found: C, 53·93; H, 6·17. $C_{27}H_{36}O_{15}$ requires: C, 54·00; H, 6·04%). This compound was identical with authentic loganin pentaacetate in all respects.

7-*Epibenzoylloganin tetraacetate* (**27**)

A mixture of **23** (54 mg), C_6H_5COCl (40 mg) and pyridine (2 ml) was allowed to stand overnight at room temp, and then poured into ice water. The resulting ppt was recrystallized from ether-light petroleum to give colourless needles, m.p. 109–110° (37 mg). $[\alpha]_D^{25} - 126·5°$ (c = 0·65, $CHCl_3$); IR (Nujol): 1745, 1710, 1625, 1600 cm^{-1}; NMR ($CDCl_3$): 8·79 (3H, d, J = 6 c/s, C_8–Me), 6·32 (3H, s, COOMe), 2·75–1·90 (6H, C_3–H and aromatic H) (Found: C, 57·69; H, 6·00. $C_{32}H_{38}O_{15}$ requires: C, 57·99; H, 5·78%).

7-*Epiloganin* (**29**)

To a soln of **23** (130 mg) in MeOH (3 ml) was added 0·1N NaOMe (0·1 ml) and the mixture was heated under reflux for 15 min. After cooling, the soln was neutralized on an ion exchange resin (Amberlite IR-120). The filtrate was evaporated *in vacuo* to give a pale yellow syrup, which was chromatographed on a Carbon column consisting of 5 g each of carbon and celite using water as eluent. Evaporation of the eluate yielded a colourless syrup. $[\alpha]_D^{30} - 100·5°$ (c = 0·64, EtOH); NMR (D_2O): 8·99 (3H, d, J = 6 c/s, C_8–Me), 6·29 (3H, s, COOMe), 3·75 (1H, d, J = 3·5 c/s, C_1–H), 2·54 (1H, d, J = 1 c/s, C_3–H) (Found: C, 49·44; H, 6·91. $C_{17}H_{26}O_{10}.H_2O$ requires: C, 49·67; H, 6·91%).

Reduction of Bisdesoxydihydrodeacetylasperulosidic acid methyl ester tetraacetate (**30**) *with* LAH

A soln of **30** (2·4 g) in THF (20 ml) was added dropwise to a suspension of LAH (3 g) in ether (80 ml). The reaction mixture was refluxed for 3 h. After decomposition of excess reagent with AcOEt, 2N NaOH soln was added to the mixture to dissolve the inorganic salts. The soln was extracted with ether and dried over $MgSO_4$ and the solvent removed. The resulting colourless syrup (360 mg) was then applied to an alumina column (10 g), eluted first with benzene (50 ml) and then with benzene–ether (6:4 v/v; 100 ml). Fractions with the latter eluent provided 147 mg of a colourless syrup **31**. IR ($CHCl_3$): 3350, 1640, 905 cm^{-1}; NMR ($CDCl_3$): 4·80, 5·07 (2H, C=CH_2), 5·89 (2H, s, allylic CH_2OH), 6·50 (2H, m, CH–CH_2OH). This substance **31** was acetylated in the usual manner to give a colourless syrup which was chromatographed on silica gel (10 g). The column was eluted succesively with benzene (40 ml), benzene-ether (99:1 v/v; 80 ml) and finally benzene-ether (98:2 v/v; 80 ml); 4 ml fractions were collected. Fractions Nos 37–48 (benzene–ether 98:2 v/v) yielded 58 mg of diacetate **32** as a colourless syrup. IR ($CHCl_3$): 1730, 1650, 900 cm^{-1}; NMR ($CDCl_3$): 4·85, 5·02 (2H, C=CH_2), 5·43 (2H, s, allylic CH_2OAc), 6·10 (2H, m, CH—CH_2OAC), 7·90, 8·00 (2×OAc), 8·95 (3H, d, J=6 c/s, CH—CH_3) (Found: C, 66·19; H, 8·89. $C_{14}H_{22}O_4$ requires: C, 66·13; H, 8·72%).

Reduction of 7-Epitosylloganin tetraacetate (**25**) *with* LAH

A soln of **25** (1·12 g) in THF (20 ml) was added dropwise to a suspension of LAH (2 g) in ether (60 ml). The reaction mixture was worked up in an analogous way to **30** to give a yellow syrup (140 mg), which was chromatographed on alumina (8 g) with benzene and then benzene–ether (1:1 v/v) as eluents. The eluate with benzene–ether (1:1 v/v) afforded a syrup of the diol **31** (21 mg). This substance was acetylated in the usual manner and chromatographed on alumina (5 g) using ether as eluent to furnish a colourless syrup of the diacetate **32** (9 mg). This was identified with the acetate **32** obtained from **30** by comparisons of the IR, NMR and mass spectra.

Bisdesoxytetrahydrodeacetylasperulosidic acid methyl ester tetraacetate (**33**)

30 (320 mg) was hydrogenated in AcOH (30 ml) with prereduced PtO_2 (200 mg) at atmospheric pressure for 3 h. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to give a crystalline residue. Recrystallization from EtOH afforded a colourless prisms of the tetrahydro compound **33**, m.p. 154–156° (106 mg). $[\alpha]_D^{25}$ −61·0° (c=0·42, $CHCl_3$); IR (Nujol): 1760 cm^{-1}; NMR ($CDCl_3$): 8·97 (3H, d, J=5 c/s, C_8–Me), 6·35 (3H, s, COOMe) (Found: C, 54·24; H, 6·73. $C_{25}H_{36}O_{13}\cdot\frac{1}{2}H_2O$ requires: C, 54·18; H, 6·81%).

Reduction of Bisdesoxytetrahydrodeacetylasperulosidic acid methyl ester tetraacetate (**33**) *with* LAH

A soln of **33** (259 mg) in THF (20 ml) was added to a suspension of LAH (280 mg) in ether (20 ml) with stirring and the mixture was refluxed for 4 h. After decomposition of the excess reagent with AcOEt, satd aq Na_2SO_4 was added to the reaction mixture and a white ppt formed. The soln was decanted off and the ppt was triturated with EtOH. The ethanolic soln was neutralized on an ion exchange resin (Amberlite IR-120) and evaporated *in vacuo*. The resulting oily residue was acetylated with pyridine and Ac_2O in the usual manner to give a crystalline substance. Recrystallization from EtOH-n-hexane afforded 94 mg of pentaacetate **34** as colourless prisms, m.p. 98–99°. $[\alpha]_D^{26}$ −52·9° (c=0·97, $CHCl_3$); IR (Nujol): 1740, 1240–1210 cm^{-1}; NMR ($CDCl_3$): 9·02 (3H, d, J=6 c/s, C_8–Me), 7·94–7·99 (15H, 5×OAc), 6.30 (5H, m, C_3, C_{11} and C_5–H) (Found: C, 55·67; H, 6·61. $C_{26}H_{38}O_{13}$ requires: C, 55·91; H, 6·85%).

Dihydro-7-epiloganin tetraacetate (**35**)

A soln of **23** (262 mg) in AcOH (10 ml) was shaken with H_2 at 40° for 22 h in the presence of a catalyst prepared by the reduction of 180 mg of PtO_2. The catalyst was filtered off and the filtrate was evaporated to dryness. The resulting colourless syrup was crystallized from EtOH-n-hexane to afford 235 mg of **35** as fine colourless needles, m.p. 150–151°. $[\alpha]_D^{30}$ −50·6° (c=0·77, $CHCl_3$); IR (Nujol): 3400–3150, 1740; NMR ($CDCl_3$): 8·89 (3H, d, J=6 c/s, C_8–Me), 6·34 (3H, s, COOMe), 6·21 (2H, m, C_3–H) (Found: C, 53·85; 6·55. $C_{25}H_{36}O_{14}$ requires: C, 53·56; H, 6·48%).

Dihydro-7-epitosylloganin tetraacetate (**36**)

A soln of **35** (276 mg) and tosyl chloride (360 mg) in pyridine (3 ml) was stood overnight at room temp and then poured into ice water. The resulting crystalline substance was collected and recrystallized from EtOH to give 194 mg of fine colourless needles, m.p. 145–146°. $[\alpha]_D^{30}$ −60·0° c=0·60, $CHCl_3$); NMR

($CDCl_3$): 9·05 (3H, d, $J=7$ c/s, C_8-Me), 7·55 (3H, s, aromatic Me), 6·35 (3H, s, COOMe), 2·64, 2·22 (4H, AB quartet, $J=8$ c/s, aromatic H) (Found: C, 53·61; H, 6·23. $C_{32}H_{42}O_{16}S$ requires: C, 53·78; H, 5·93%).

Reduction of Dihydro-7-epitosylloganin tetraacetate (**36**) *with* LAH

A soln of **36**(190 mg) in THF (5 ml) was added dropwise to a suspension of LAH (250 mg) in ether (10 ml) with stirring and the mixture was heated under reflux for 4 h. After decomposition of the excess reagent with AcOEt, satd aq Na_2SO_4 was added to the reaction mixture and a white ppt formed. The soln was decanted off and the residue was triturated repeatedly with EtOH. The ethanolic soln was neutralized on Amberlite IR-120 and evaporated *in vacuo* to give colourless syrup which was acetylated in the usual way. The resulting pale yellow syrup was chromatographed on silica gel (5 g) eluting first with light petroleum (4 ml) and then light petroleum-ether (1:1 v/v; 10 ml) and 1 ml fractions of eluate were collected. Fractions Nos 7–9 gave a colourless syrup which was cryatallized from MeOH–H_2O. Recrystallization from $CHCl_3$-n-hexane yielded 14 mg of colourless prisms, m.p. 97–99°. $[\alpha]_D^{25}$ −45·0° (c=0·39, $CHCl_3$) (Found: C, 56·13; H, 7·10. $C_{26}H_{38}O_{13}$ requires: C, 55·91; H, 6·85%).

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