Tetrahedron. Vol. 25, pp. 2233 to 2239. Pergamon Press 1969. Printed in Great Britain

CONSTITUENTS OF SOLIDAGO SPECIES—I[1]

THE CONSTITUTION AND STEREOCHEMISTRY OF DITERPENOIDS FROM *SOLIDAGO CANADENSIS* L.

T. ANTHONSEN

Department of Chemistry, Norway Institute of Technology, Trondheim, Norway

and

P. H. MCCABE, R. MCCRINDLE and R. D. H. MURRAY

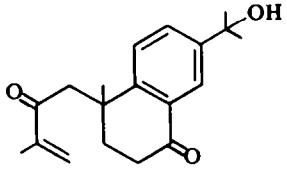
Department of Chemistry, University of Glasgow, Glasgow W.2.

(*Received in the UK* 23 *December* 1968; *Accepted for publication* 1 *January* 1969)

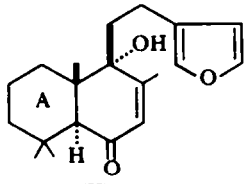
Abstract—The constitution and stereochemistry of solidagenone II and the epimeric spiro ethers III from *Solidago canadensis* L. are deduced from their spectroscopic and chemical properties.

IN 1947 Houston and Burrell isolated[2] a diterpenoid from the roots of *Solidago canadensis* L. and reported the m.p. of the primary crystals as 89–90°, raised to 131–132° on recrystallisation. They deduced the correct molecular formula, $C_{20}H_{28}O_3$, and found that the compound failed to form carbonyl derivatives. A recent spectroscopic investigation[3] of the higher melting compound led to the proposal of a structure I which has been shown[1a] to be untenable. In this paper the constitution and stereochemistry of this compound II, for which we have proposed[1b] the name solidagenone, is established. We also record the isolation from these roots of a sharp-melting (108–110°) mixture of ethers III epimeric at C-13 which is readily converted into solidagenone.

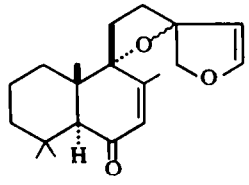
The constitution and stereochemistry of solidagenone (as II) can be deduced from the following chemical and spectroscopic evidence. The β-substituted furan ring



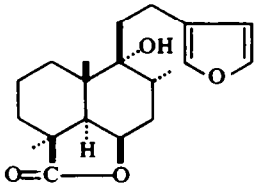
(I)



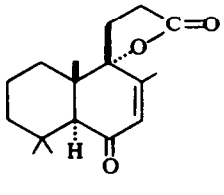
(II)



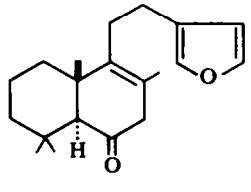
(III)



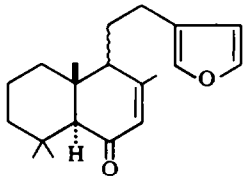
(IV)



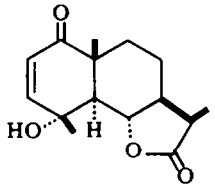
(V)



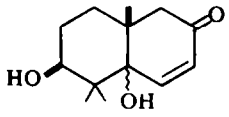
(VI)



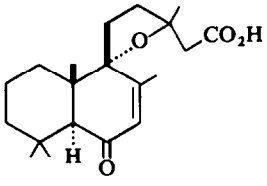
(VII)



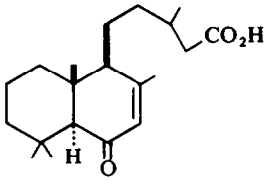
(VIII)



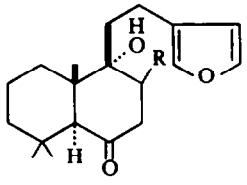
(IX)



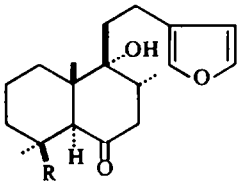
(X)



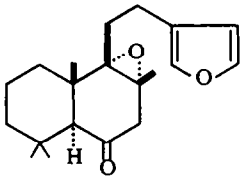
(XI)



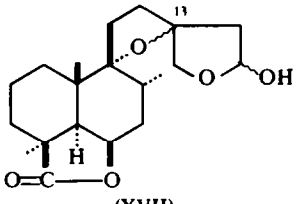
(XII): R = βCH_3
(XIII): R = αCH_3



(XIV): R = CHO
(XV): R = $CH(SCH_2)_2$



(XVI)



(XVII)

is indicated by the IR (ν_{max} 1502 *w* and 873 *s* cm^{-1}), NMR (τ 2·63 and 2·73, 2α-H; τ 3·67, 1β-H) and mass (*m/e*, 81 and 95) spectra and colour tests (see Experimental Section). The carbonyl absorption at 1678 cm^{-1} in the IR suggests the presence of an αβ-unsaturated ketone, although in the UV the enone absorption is masked in a broad composite band, λ_{max} 223 nm (ε 10,000). However a narrow band, λ_{max} 234 nm (ε 9800), results when the furan absorption of a similar compound, marrubiin[4] IV, λ_{max} 212 nm (ε 5300) is subtracted. The derived maximum is consistent with structure II since the γ-hydroxyl group should have[5–7] a hypsochromic effect. The methyl group on the double bond resonates as a doublet at τ 7·98 in the NMR spectrum and its coupling (J = 1·3 cps) to the α-vinyl proton at τ 4·27 (broad *s*) has been confirmed by double irradiation experiments. The presence of a hydroxyl group is suggested by the IR absorption at 3611 (free) and 3567 (OH—π) cm^{-1} and confirmed by NMR data, a concentration-dependent peak at about τ 8 (—O*H*, *s*) disappearing when the sample is shaken with D_2O. Furthermore, this hydroxyl group is tertiary since there is no resonance attributable to a proton of the type $H—\overset{|}{\underset{|}{C}}OH$ and the hydroxylic proton appears as a singlet at τ 4·98 in dimethyl sulphoxide solution.[8] The NMR also discloses three quaternary C-methyl groups (τ 9·01, 8·85 and 8·82) and a one proton singlet at τ 7·27 is attributed to H-5.

The following observations suggest that the locations of the hydroxy group and the furan ring in solidagenone and in marrubiin are identical. First, the interaction of these two groups is apparent in the IR of the diterpenoids both of which show absorption arising from an intramolecular bonded (OH—π) hydroxyl group.[4a] Second, both diterpenoids have peaks at *m/e* 81 and *m/e* 95 (fission of C-11, C-12 and C-9, C-11 bonds respectively) and the unusual feature[9] for compounds of this type of a mass peak, M, more intense than the M-18 peak. The steric relationship of these two functional groups in solidagenone was convincingly demonstrated by the formation of the γ-lactone V, m.p. 143–144°, ν_{max} 1783 and 1681 cm^{-1}, by oxidation of solidagenone with chromic acid in acetic acid.

The location of the hydroxyl group on the γ-carbon atom of the enone system inferred (*vide supra*) from the position of the UV maximum was confirmed by conversion of solidagenone with zinc in acetic acid, sodium amalgam in ethanol or lithium in ammonia into the βγ-unsaturated ketone VI, m.p. 78–79°, $[\alpha]_D$ +139°, which is readily transformed into the Δ^7 isomer VII, m.p. 58–59°. Analogous reductions have been reported for vulgarin[7] VIII and the hydroxy-enone[5] IX. A biogenetically plausible structure for solidagenone II (without stereochemistry) could be advanced on the basis of the above evidence and bearing in mind the presence[6] of 6-oxogrindelic acid X in a member of the *Grindelia* genus (*G. robusta*), a close relative of the *Solidago* genus.

The structure readily accommodates the following data. The presence of an intense M-124 peak in the mass spectrum, indicating scission[9] (C-5, C-6 and C-9, C-10) of a normal terpenoid ring *A* which bears no oxygen substituents, is explained. Further, the failure to form derivatives of the tertiary hydroxyl group and the sterically hindered ketone (cf. 6-oxogrindelic acid X and 6-oxocativic acid[10] XI) is expected as is the formation of the saturated ketone solidaganone XII, m.p. 110–111°, on lithium aluminium hydride reduction. Finally, the benzene-induced shifts[11,12] of the C-4 methyl groups in solidaganone (−0·09 and −0·11 ppm) accord with the presence of a 6-ketone.

In an effort to confirm the structure proposed for solidagenone we attempted to convert both it and marrubiin into the dihydrosolidagenone XIII. This compound, m.p. 89–90°, was prepared from marrubiin via the ketoaldehyde[4a] XIV by reduction of the derived oily thioacetal XV with Raney nickel in acetone. We have not yet found conditions whereby solidagenone can be reduced directly to compound XIII. The dihydro-derivative, solidaganone XII, isolated from lithium aluminium hydride or catalytic reduction has[11] an axial methyl group at C-8. However, dehydration of the ketol XIII with phosphoryl chloride in pyridine furnished the βγ-unsaturated ketone (VI), m.p. 77–79°, $[\alpha]_D$ +132°, already prepared from solidagenone (*vide supra*). This confirms the structure of solidagenone and provides the absolute configurations at C-5 and C-10.

The configuration at the remaining asymmetric centre (C-9) was derived as follows. The βγ-enone VI with *m*-chloroperbenzoic acid in chloroform gave one furan—containing epoxide XVI, m.p. 54–55°, which was smoothly isomerised to solidagenone with β-napthalenesulphonic acid in refluxing benzene. Formation of an α-epoxide and thus ring opening to a 9α-hydroxyl group can be predicted on the basis of earlier work[13] with analogous compounds. However, any uncertainty as to the orientation of the epoxide ring was removed by reduction of the compound with lithium alu-

minium hydride which is known to produce trans-diaxial opening of this function. As expected, the product after oxidation to the 6-ketone was the dihydrosolidagenone XIII. This not only convincingly settles the configuration at C-9 in solidagenone and thus allows the assignment of a constitution and stereochemistry to the compound II but also adds further support to the already overwhelming evidence adduced[4] for the stereochemistry at C-8 and C-9 in marrubiin IV.

Solidagenone may well be an artefact. In our hands, concentration of a light petroleum extract of *S. candensis* L. resulted in the deposition of a crystalline material, m.p. 108–110°, which contained no solidagenone (TLC). Further concentration of the mother liquors gave small amounts of solidagenone which significantly could also be obtained in high yield from the material m.p. 108–110° for example by refluxing an ethanolic solution, dissolution in chloroform for several hours or chromatography over alumina. The constitution III of this crystalline material can be deduced from its NMR spectrum (see Fig. 1 for assignments) when taken in conjunction with its ready transformation into solidagenone. It is interesting to note that a mixture of hemiacetals XVII (epimeric at C-13) co-occurs with marrubiin in *Marrubium vulgare*. Indeed, it appears possible that compounds of the type III and XVII may be intermediates in the biogenesis of diterpenoids of the labdane class which bear a furan ring on the side chain and a hydroxyl group at C-9.

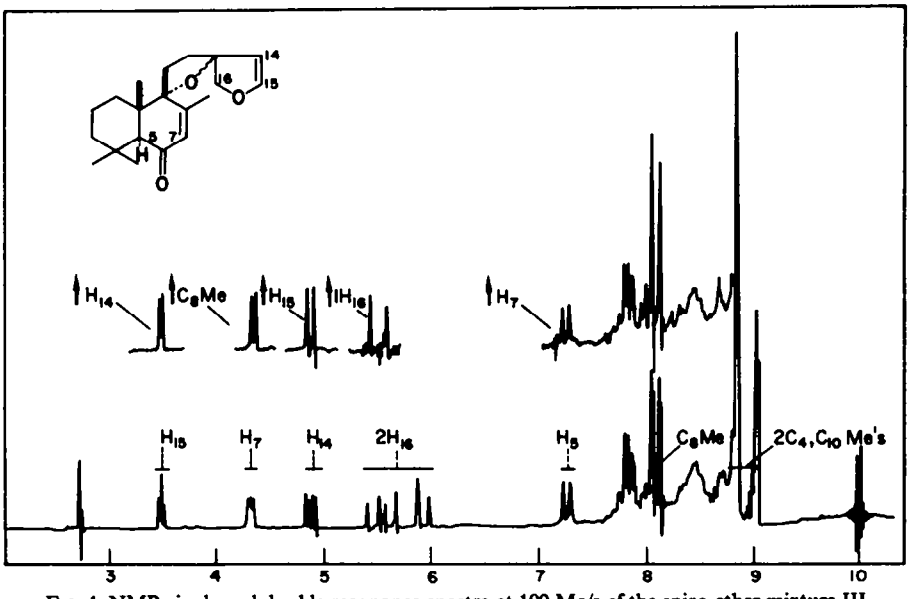


FIG. 1. NMR single and double resonance spectra at 100 Mc/s of the spiro-ether mixture III.

EXPERIMENTAL

M.ps are uncorrected and were determined on a Kofler hot-stage apparatus. Specific rotations refer to $CHCl_3$ solns. Woelm Grade I alumina, deactivated to the appropriate grade according to Brockmann, was used for chromatography. For analytical and preparative thin-layer chromatography (TLC), chromatoplates were spread with Kieselgel G (Merck). Light petroleum was of b.p. 40–60° unless otherwise stated. Microanalyses were by Mr. J. M. L. Cameron, Glasgow. Infrared solution spectra were recorded on a Unicam SP100 Mark II or Perkin–Elmer 225 or 257 spectrophotometer. Nuclear magnetic resonance

spectra were run on the Perkin–Elmer R-10 and the Varian Associates HA100 spectrometers in $CDCl_3$ (unless otherwise stated) using approx. 0·3 M solutions and tetramethylsilane as internal standard. Mass spectra were run on an A.E.I. MS9 or MS12 instrument.

Isolation of diterpenoids II *and* III *from* Solidago canadensis *roots*

Dried, finely powdered roots (108 g) of *S. canadensis* were continuously extracted with light petroleum for 4 hr. The concentrated extract, on standing, deposited large yellow prisms (2·2 g), m.p. 101–106°. Twice crystallised from light petroleum this formed colourless prisms of the *spiro-ether mixture* III, m.p. 108–110°. (Found: C, 75·8; H, 8·6. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%); ν_{max} (CCl_4) 1677 cm^{-1}; λ_{max} 210 (log ε 3·97) and 232 nm (4·00); see Fig. 1 for NMR spectrum. The mother liquors after removal of the yellow prisms were further concentrated and furnished solidagenone II as an amorphous deposit (0·6 g) which crystallised from ether–light petroleum as colourless needles, m.p. 131–133°. (Found: C, 75·9; H, 8·8. Calc. for $C_{20}H_{28}O_3$: C, 75·9; H, 8·9%); $[\alpha]_D$ −15·2 (*c* 1·0); ν_{max} (CCl_4) 3611, 3567 and 1678 cm^{-1}; λ_{max} 223 nm (log ε 4·03); NMR signals at τ 9·01, 8·85, 8·82 (all, s, 3H; quaternary CH_3's), 7·98 (d, 3H; J = 1·3 c/s; C-8 CH_3), 7·98 (t, 2H; J = 8 c/s; C-11), 7·30 (t, 2H; J = 8 c/s; C-12), 7·27 (s, 1H; C-5), 4·26 (diffuse q, 1H; J = 1·3 c/s; C-7), 3·67, 2·73, 2·63 (all, m, 1H; furan protons). The residue of this light petroleum extract, a pale brown oil (4·7 g), was chromatographed over silica gel (120 g). Fractions eluted with ether–light petroleum (2:3) furnished a further quantity of solidagenone (700 mg).

Conversion of the epimeric ethers III into solidagenone II

The mixture of ethers (III) was quantitatively converted into solidagenone by (a) heating in refluxing EtOH for 4 hr, (b) dissolution in $CHCl_3$ (for 24 hr) or (c) chromatography in $CHCl_3$ over alumina (Grade III; neutral). The solidagenone was identified in each case by IR, NMR, m.p., mixed m.p. and TLC.

Colour test for the β-furan in solidagenone

Solidagenone on TLC when sprayed with Ehrlich's reagent or AcOH–H_2SO_4 and warmed gently gave pink and red-brown spots respectively.

Oxidation of solidagenone with chromic acid in acetic acid

Solidagenone (445 mg) in glacial AcOH (11 ml) was treated at 20° for 50 hr with CrO_3 (1·3 g) in water–AcOH (2·5 and 6·5 ml respectively). The acetic acid was removed *in vacuo*, water added and the mixture extracted with EtOAc. The organic layer was washed successively with water, aqueous Na_2CO_3 and water, dried and the solvent evaporated. The residual colourless oil (160 mg) was purified by preparative TLC [ether–light petroleum (3:2)] and afforded the γ-*lactone V* which crystallised from ether–light petroleum as needles, m.p. 143–144°. (Found: C, 74·0; H, 8·6. $C_{17}H_{24}O_3$ requires C, 73·9; H, 8·75%); ν_{max} (CCl_4) 1783 and 1681 cm^{-1}; λ_{max} 231 nm (log ε 4·10); NMR signals at τ 8·98 (s, 3H; quaternary CH_3), 8·84 (s, 6H; 2 quaternary CH_3's), 8·09 (d, 3H; J = 1 c/s; C-8 CH_3), 7·26 (s, 1H; C-5), 4·21 (q, 1H; J = 1 c/s; C-7).

Formation of the βγ-enone VI *from solidagenone*

(a) *With lithium in liquid ammonia.* Solidagenone (100 mg) and anhydrous ether (20 ml) were added separately to a stirred solution of Li (20 mg) in liquid NH_3 (80 ml). After 30 min NH_4Cl (1 g) was added and the solvents were allowed to volatise. The residue was shaken with water–ether (40 ml and 100 ml respectively) and the organic layer washed with 1NHCl and water and dried. Removal of solvent gave the crude product (97 mg), which was chromatographed over alumina (Grade I; neutral; 10 g). Elution with $CHCl_3$–C_6H_6 (1:9) furnished the *βγ-enone* VI (28 mg) which crystallised from ether–light petroleum as colourless needles, m.p. 78–79° (Found: C, 79·8; H, 9·5. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%); ν_{max} (CCl_4) 1718 cm^{-1}; ν_{max} (KBr disc) 1706 cm^{-1}; λ_{max} 204 nm (log ε 4·13); $[\alpha]_D$ +139° (*c* 1·0); NMR signals at τ 9·05, 9·00, 8·74 (all, s, 3H; quaternary CH_3's), 8·34 (s, 3H; C-8 CH_3), 3·68, 2·71 and 2·60 (all, m, 1H; furan protons).

(b) *With zinc in acetic acid.* AnalaR Zn powder (500 mg) was added in portions over 30 min to a stirred solution of solidagenone (400 mg) in refluxing glacial AcOH (10 ml). The solvent was removed *in vacuo* and the residue extracted with ether. The product crystallised spontaneously and when recrystallised from ether–light petroleum gave the βγ-enone VI (320 mg), m.p. 77–79°.

(c) *With sodium amalgam in ethanol.* Solidagenone (105 mg) and Na–Hg (5%; 500 mg) were stirred in EtOH at 20° for 15 hr. The EtOH was removed under vacuum at 20° and the reaction mixture extracted with ether. The extracts were washed with water, dried and the solvent was evaporated. The crystalline product (93 mg) was separated into two components by preparative TLC. The upper band gave the βγ-enone VI (38 mg) and the lower, starting material (44 mg).

9-Deoxysolidagenone

The βγ-enone VI (58 mg) was chromatographed over alumina (Grade I; basic; 4 g). Early fractions, C_6H_6–$CHCl_3$ (19:1), contained starting material (6 mg) while fractions eluted with C_6H_6–$CHCl_3$ (9:1) yielded the isomeric αβ-*enone* VII (40 mg), which formed colourless needles, m.p. 58–59°, from pentane. (Found: C, 80·1; H, 9·4. $C_{20}H_{28}O_2$ requires: C, 80·0; H, 9·4%); ν_{max} (CCl_4) 1675 cm^{-1}; λ_{max} 215 (log ε 3·80) and 240 nm (4·03); NMR signals at τ 9·18, 8·89, 8·86 (all, *s*, 3H; quaternary CH_3's), 8·06 (*d*, 3H; J = 1 c/s; C-8 CH_3), 4·22 (*m*, 1H; C-7), 3·69, 2·71 and 2·61 (all, *m*, 1H; furan protons).

8-*Episolidaganone* XIII

The keto-aldehyde[4a] XIV (380 mg) and ethane dithiol (0·5 ml) were dissolved in anhydrous ether (20 ml) containing freshly distilled BF_3-etherate (4 ml). After 30 hr at 20° the reaction mixture was diluted with ether (40 ml) and washed with 1N NaOH (5 × 50 ml) and water (2 × 50 ml) and dried. Removal of solvent gave a crude product (240 mg) which was chromatographed over alumina (Grade I; neutral; 20 g). $CHCl_3$–C_6H_6 (3:7) eluted the oily keto-thioacetal XV (148 mg); NMR signals at τ 8·99 (*d*, 3H; J = 8 c/s, C-8 CH_3), 8·94, 8·72 (both *s*, 3H; quaternary CH_3's), 6·92 [*m*, 4H; $(SCH_2)_2$], 4·78 (*s*, 1H; SCHS), 3·79, 2·82 and 2·70 (all, *m*, 1H; furan protons). The thioacetal was reduced with acetone-deactivated Ra nickel (2 g) in refluxing AnalaR acetone (20 ml) for 1 hr. The product (130 mg), recovered from the Ra nickel by Soxhlet extraction, was chromatographed over alumina (Grade III; neutral; 12 g). Fractions eluted with C_6H_6 after further purification by preparative TLC (ether–light petroleum; 3:7) gave the *hydroxy-ketone* XIII (98 mg), which crystallised from ether–light petroleum as colourless flakes, m.p. 89–90°. (Found: C, 75·6; H, 9·3. $C_{20}H_{30}O_3$ requires: C, 75·4; H, 9·5%); ν_{max} (CCl_4) 3628, 3588 and 1711 cm^{-1}; λ_{max} 207 nm (log ε 3·79); NMR signals at τ 9·09, 9·02, 8·77 (all, *s*, 3H; quaternary CH_3's), 8·99 (*d*, 3H; J = 8 c/s; C-8 CH_3), 7·20 (*s*, 1H; C-5), 3·73, 2·77 and 2·67 (all, *m*, 1H; furan protons). The methyl resonances shifted progressively in solutions containing increasing percentages of C_6H_6 to final values (in 100% C_6H_6) of τ 9·27, 8·83, 8·55 and 9·34 respectively

Dehydration of the hydroxy-ketone (XIII)

The hydroxy-ketone XIII (32 mg) was treated with phosphoryl chloride (0·5 ml) in refluxing pyridine (12 ml) for 6 hr. Work-up afforded an oil (30 mg) which was purified by preparative TLC (ether–light petroleum; 1:9; two developments). From the upper (lower $\Delta^{9(11)}$-isomer) of two barely separated bands the Δ^8-enone VI (7 mg) was recovered. It crystallised from ether–light petroleum as needles, m.p. 77–79°, $[\alpha]_D$ +132° (*c* 0·4) and was identical [mixed m.p. (78–79°), IR, NMR, mass spectrum] with the product from Zn–AcOH reduction of solidagenone.

Epoxidation of the βγ-*enone* VI

m-Chloroperbenzoic acid (88 mg) in AnalaR $CHCl_3$ (10 ml) was added to a solution of the Δ^8-enone VI (100 mg) in the same solvent (25 ml). After 35 min at 20° the reaction mixture was filtered through a short alumina column (Grade I; basic) and the recovered product adsorbed in a preparative chromatoplate. Development twice with ether–light petroleum (2:3) gave two major bands. From the lower, starting material (32 mg) was recovered, while the upper furnished the *epoxide* XVI (40 mg), which when further purified by sublimation (at 0·2 mm) had m.p. 52–55°. (Found: C, 75·6; H, 8·6. $C_{20}H_{28}O_3$ requires: C, 75·9; H, 8·9%); ν_{max} (CCl_4) 1714 cm^{-1}; NMR signals at τ 8·98 (*s*, 6H; 2 quaternary CH_3's), 8·80, 8·72 (both, *s*, 3H; quaternary CH_3's), 3·73, 2·78 and 2·66 (all *m*, 1H; furan protons).

Conversion of the epoxide XVI *into solidagenone*

A saturated solution of naphthalene-2-sulphonic acid in C_6H_6 was added to a solution of the epoxide (32 mg) in the same solvent (45 ml). After 10 min at 80° the solvent was removed and the reaction mixture filtered in $CHCl_3$ through a short column of alumina (Grade I, basic). The eluate contained (TLC) mainly two compounds which were separated by preparative TLC (ether–light petroleum; 3:7; developed twice). Of the two major bands, the upper gave starting material XVI (12 mg) and the lower solidagenone II, (16 mg), m.p. 131–132°, identified by mixed m.p., TLC, IR and NMR.

Conversion of the epoxide XVI *into* 8-*episolidaganone* XIII

The epoxide XVI (44 mg) was treated with $LiAlH_4$ (200 mg) in refluxing dry ether (15 ml) for 8 hr. Work-up with saturated Na_2SO_4 afforded an oil (42 mg) which was oxidised with CrO_3 (60 mg) in pyridine (10 ml) for 14 hr. MeOH (1 ml) and then an EtOAc–water mixture (4:1, 50 ml) was added and the suspension

filtered through celite. The organic layer was washed with 1N HCl (3 × 20 ml) and water and dried. Removal of solvent *in vacuo* gave an oil (31 mg) which was purified by preparative TLC (ether–light petroleum; 3:7). The major component (18 mg) was 8-episolidaganone XIII which crystallised from ether–light petroleum and had m.p. 89–90°, identified by TLC, mixed m.p., IR, and NMR.

Acknowledgements—We thank Mrs. S. L. Hunter, Ayr for a supply of *Solidago canadensis*, the Science Research Council for a maintenance award (to P.H.M.) and the Norway Institute of Technology for a Fellowship (to T.A.).

REFERENCES

[1] Preliminary communications:
[a] T. Anthonsen, *Acta Chem. Scand.* **20**, 904 (1966);
[b] T. Anthonsen, P. H. McCabe, R. McCrindle and R. D. H. Murray, *Chem. Commun.* 740 (1966);
[c] *Idem*, *Acta Chem. Scand.* **21**, 2289 (1967).
[2] F. G. Houston and R. C. Burrell, *Arch. Biochem.* **16**, 299 (1948).
[3] H. Gerlach, *Pharmazie* **20**, 523 (1965).
[4] [a] R. A. Appleton, J. W. B. Fulke, M. S. Henderson and R. McCrindle, *J. Chem. Soc.* (C), 1943 (1967);
[b] D. M. S. Wheeler, M. Wheeler, M. Fetizon and W. H. Castine, *Tetrahedron* **23**, 3909 (1967);
[c] L. Mangoni and M. Adinolfi, *Gazz. Chim. Ital.* **98**, 122 (1968).
[5] T. G. Halsall, W. J. Rodewald and D. Willis, *J. Chem. Soc.* 2798 (1959).
[6] L. Mangoni and M. Bellardini, *Gazz. Chim. Ital.* **92**, 983 (1962).
[7] T. A. Geissman and G. A. Ellestad, *J. Org. Chem.* **27**, 1855 (1962).
[8] O. L. Chapman and R. W. King, *J. Am. Chem. Soc.* **86**, 1256 (1964).
[9] C. R. Enzell and R. Ryhage, *Ark. Kemi* **23**, 367 (1965).
[10] T. G. Halsall and M. Moyle, *J. Chem. Soc.* 1324, (1960).
[11] T. Anthonsen, P. H. McCabe, R. McCrindle and R. D. H. Murray, to be published.
[12] J. D. Connolly and R. McCrindle, *Chem. & Ind.* 379 (1965); D. H. Williams and N. S. Bhacca, *Tetrahedron* **21**, 2021 (1965).
[13] L. Mangoni and M. Adinolfi, *Gazz. Chim. Ital.* **97**, 66 (1967).