Tetrahedron. Vol. 26, pp. 3091 to 3097. Pergamon Press 1970. Printed in Great Britain

CONSTITUENTS OF SOLIDAGO SPECIES—II[1]

REACTIONS OF SOLIDAGENONE, THE MAJOR DITERPENOID FROM *SOLIDAGO CANADENSIS* L.

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and

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(*Received in UK* 18 *March* 1970; *Accepted for publication* 26 *March* 1970)

Abstract—Some reductions and rearrangements of solidagenone (**1**) are described. These transformations substantiate the structure and stereochemistry previously deduced for **1**.

IN THE course of our studies of the diterpenoid, solidagenone (**1**), we have encountered several reactions which, although not essential for a logical derivation of the constitution and stereochemistry of the compound, substantiate our earlier conclusions[1] and are in themselves interesting chemical transformations.

Reductions

Reduction of solidagenone with LAH gave under mild conditions predominantly the saturated ketone, solidaganone (**2**), also obtained by catalytic hydrogenation, while more vigorous reduction provided solidagan-6β-ol (**3**) as the major product. The axial orientation of the secondary OH group in **3** was deduced from NMR evidence;[2] the half band width (~9 Hz) of the signal at τ 5·53 is consistent with the C-6 proton experiencing one equatorial–equatorial coupling and two equatorial–axial couplings. The facile dehydration of **3** to **4** on reaction with methanesulphonyl chloride in pyridine is confirmatory evidence for the antiparallel arrangement of the secondary OH group and the C-5 hydrogen.

The reduction of **1** is stereoselective; there is no evidence for the formation of the C-8 epimer (**5**)[1] of solidaganone. The orientation of the C-8 Me group in these ketones, axial in **2** and equatorial in **5**, has been determined by observing the chemical shifts of the C-8 and C-10 Me groups in both ketones and in the axial alcohols (**3** and **6**). The assignments of the various tertiary Me resonances were made by determining the NMR spectra of **2** and **5** in $CDCl_3$ and in C_6H_6, with utilisation of the plane rule,[3] and of the derived deutero compounds (**6** and **7**) (Tables 1–3). On the assumption that ring B has a chair conformation, symmetry considerations would predict nearly identical chemical shift changes for an 8β Me group (Axial) and the axial C-10 Me group when the 6-ketone is converted to the 6-β alcohol.[4] The results (Tables 2 and 3) clearly demonstrate that the C-8 Me group in solidaganone is axial. However, in solidaganone, the chemical shift difference for the

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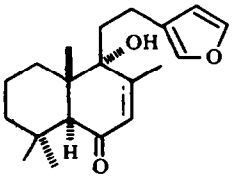
C-8 Me is less than that of the C-10 Me which might suggest that ring B is distorted from a pure chair. This is not unexpected bearing in mind the 1,3-diaxial interactions involved.

Reduction[1] of solidagenone with lithium in liquid ammonia or zinc in acetic acid proceeded in a different manner[5] with loss of the tertiary OH group giving the βγ-unsaturated ketone (**8**).



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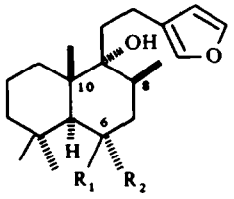
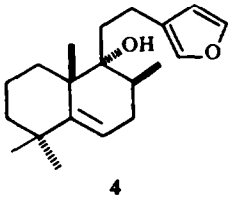


2: $R_1 + R_2 = O$
3: $R_1 = OH$, $R_2 = H$



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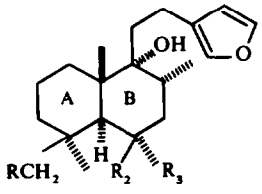
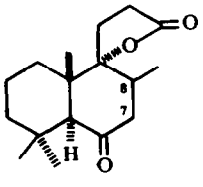
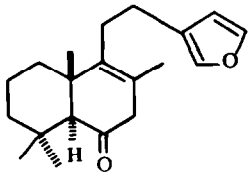


5: $R_1 = H$, $R_2 + R_3 = O$
6: $R_1 = D$, $R_2 = OH$, $R_3 = H$
7: $R_1 = D$, $R_2 + R_3 = O$



9:7,8-dehydro
10: 8β-Me
11: 8α-Me



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One explanation for the stereoselectivity of the LAH reduction of solidagenone is that initially the reagent reacts with the axial C-9 tertiary OH function forming a complex which delivers a hydride ion internally to C-8 from the α-face. In support of this theory there is no evidence for the production of either of the Δ^7-enols which would result from direct attack of the reagent on the CO group. The axial orientation of the secondary alcohol in **3** indicates a preference for hydride attack at C-6 from the α-face, a consequence of the steric influence of the axial Me groups in ring A.[6] It is likely that steric hindrance to reagent approach may also account for the stereoselectivity encountered during the catalytic hydrogenation of **1**. In this context, it is perhaps significant that

catalytic hydrogenation of the enone-lactone (**9**) should afford both C-8 epimeric keto-lactones (**10** and **11**). Here the bulk of the lactone ring projects towards the α-side of the molecule thus adsorption of this face on to the catalyst surface might be expected to be less efficient.

Rearrangements

The unique positional and stereochemical relationship of the tertiary OH group, furan ring and enone system of solidagenone gave rise to several interesting products when solidagenone was treated with *p*-toluenesulphonic acid in refluxing aqueous methanol. After 1 hr, with ~85% of starting material still unreacted, only one compound (**12**), formally a dehydration product, was formed. When, after 18 hr, about half of **1** had reacted, two major products, mainly **12**, some **13**, and several minor products were present. On complete reaction of solidagenone (90 hr) at least ten furan-containing products, including **14**, were present with **13** now being the major constituent (~65%).

Rearrangement product **12** contains the enone system of **1**; the vinyl Me Group resonates as a doublet at τ 8·06 and its coupling (J = 1·4 Hz) to the olefinic proton at τ 3·85 has been confirmed by double irradiation experiments. It possesses three tertiary Me groups (τ 8·67, 8·67, 8·73) and a β-substituted furan (τ 2·69, 2·83, 3·81) while strong M-94 and M-95 ions in the mass spectrum indicate[7] the presence of the grouping —CH_2·CH_2—  . Moreover, the UV maximum at 246 nm (ε 13800) is consistent with the compound having a cross-conjugated dienone system.[8] The formation of **12** from **1** (Scheme I) provides additional evidence for the *trans* anti-parallel arrangement of the OH group, C-10 Me, and ketone-labilised hydrogen at C-5 in solidagenone, the rearrangement presumably being initiated by protonation, then elimination, of the tertiary OH group.

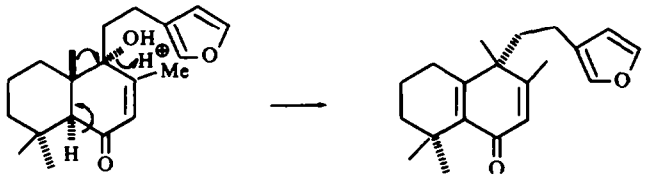
As the acid-catalysed reaction proceeded, **13** was produced at the expense of **12**. Significantly **13** was the only product formed when pure **12** was resubjected to the reaction conditions. This new compound differs from its precursor in having four tertiary Me groups (τ 8·72, 8·75, 8·80, 8·88), a 2,3-disubstituted furan ring (two 1 H doublets, J = 2·5 Hz, at τ 2·84 and 3·95), and no other olefinic protons. Two one-proton doublets at τ 7·27 and 7·47 (J = 16 Hz) are ascribed to two geminal hydrogens adjacent to a CO grouping (presumably at C-7). The derivation of **13** is presumed to proceed (Scheme II) via protonation of the CO group followed by condensation between the electron deficient centre at C-8 and the reactive α-position of the furan ring.

It is possible to come to a tentative conclusion regarding the stereochemistry of the B,C-ring fusion in **13**. Since the formation of **12** from **1** involves a 1,2-shift of the C-10 Me group, the side chain at C-9 (in **12**) must have an α configuration. From an examination of molecular models it can be seen that the orientation of the side chain which allows maximum overlap of the π orbitals on C_8 and C_{15} in the transition state is that in which the furan ring lies below the plane of ring B. Thus at least from a kinetic viewpoint, the conversion of **12** to **13** would be expected to lead to a *cis* fusion of rings B and C.

The most polar of the minor components of the acid-catalysed reaction was a methoxy-ketone for which structure **14** is tentatively proposed. The β-substituted furan ring (τ 2·56, 2·65 and 3·65) is intact and three tertiary Me groups (τ 8·80, 8·84 and 9·12) are present. The mass spectral ions at *m/e* 81 and *m/e* 249 (M-81) are consistent with the furan ring possessing an attached methylene group,[7] while the complex two

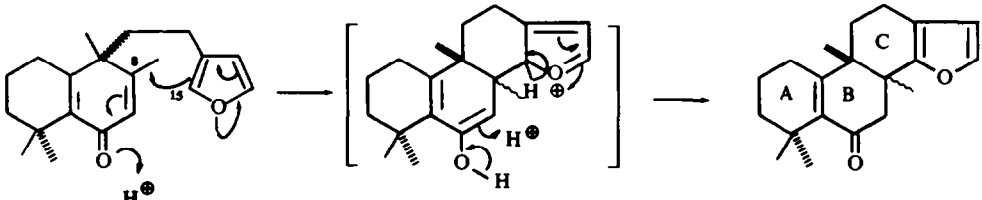
hydrogen multiplet between τ 7·2 and 7·7 for the methylene protons suggests the presence of the grouping —CH_2CH_2—  . IR (ν_{max} 1682 and 1627 cm^{-1}) and UV data (λ_{max} 253 nm, ε 8000) are indicative of a fully substituted enone in **14**, as is the absence of any vinyl proton resonance.

Formally, structure **14** can be derived from the protonated form of **1** (Scheme III) via an allylic addition-elimination followed by a protropic shift. This would require that the enone substituents are a Me (τ 8·05) and a OMe (τ 6·36) group which is in agreement with the NMR data. However, the appearance of the UV maximum at a shorter wavelength than expected[9] for an α-methoxy-enone remains unexplained.



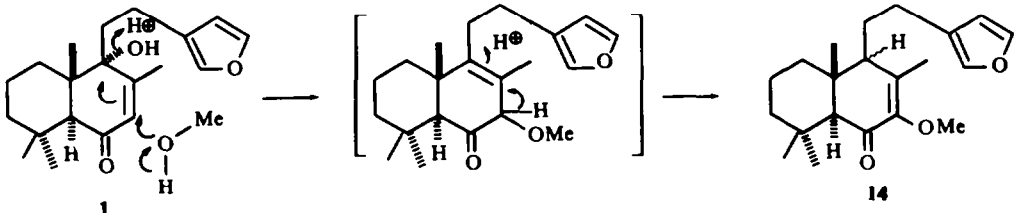
1 **12**

Scheme I



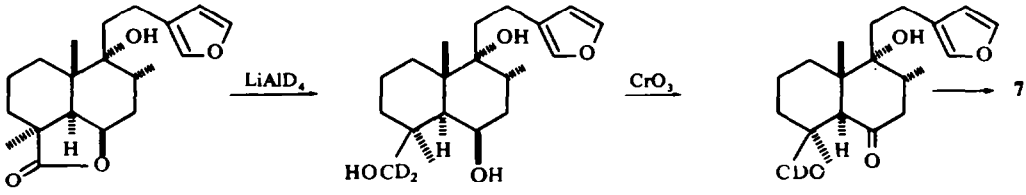
12 **13**

Scheme II



1 **14**

Scheme III



Scheme IV

TABLE 1. METHYL RESONANCES OF KETONES 2 AND 5

		Chemical shift τ $CDCl_3$	Chemical shift τ C_6H_6	Chemical shift difference (ppm)
Ketone 2	C-8	8·92	9·17	+0·25
	C-4 Axial	8·78	8·53	−0·25
	C-4 equatorial	9·05	8·88	−0·17
	C-10	9·00	9·13	+0·13
Ketone 5	C-8	8·99	9·34	+0·35
	C-4 axial	8·77	8·55	−0·22
	C-4 equatorial	9·02	8·83	−0·19
	C-10	9·09	9·27	+0·18

TABLE 2. METHYL RESONANCES OF SOLIDAGANONE (2) AND THE AXIAL ALCOHOL (3)

	Chemical shift τ 3	2	Chemical shift difference (ppm)
C-8	8·65	8·92	+0·27
C-4 axial	8·78	8·78	±0·00
C-4 equatorial	9·01	9·05	+0·04
C-10	8·62	9·00	+0·38

TABLE 3. METHYL RESONANCES OF 8-EPISOLIDAGANONE-19-d_1(7) AND THE AXIAL ALCHOHOL(6)

	Chemical shift τ 6	7	Chemical shift difference (ppm)
C-8	9·06	9·00	−0·06
C-4 axial	8·73*	8·77*	+0·04
C-4 equatorial	9·03	9·03	±0·00
C-10	8·70	9·09	+0·39

* deuteromethyl resonance (2H)

EXPERIMENTAL

For general experimental details, see Part I.[1] Alumina (Grade I) was employed for column chromatography.

Reduction of solidagenone with lithium aluminium hydride

(a) Solidagenone[1] (1 g) and LAH (203 mg) in anhyd ether (40 ml) were kept at room temp for 25 hr. Reduction was terminated by the dropwise addition of satd Na_2SO_4aq and the suspension was dried, filtered and evaporated. The crude product (920 mg) was chromatographed over alumina (neutral, 90 g). Fractions eluted with chloroform–benzene (1:4) to (9:11) contained *solidaganone* 2 (450 mg), needles, m.p. 110–111° (from ether–light petroleum). (Found: C, 75·2; H, 9·3. $C_{20}H_{30}O_3$ requires: C, 75·4; H, 9·5%);

$\gamma_{max}^{CCl_4}$ 1713, 1621, 3578 cm^{-1}; γ_{max}^{KBr} 1690 cm^{-1}; λ_{max} 207 nm, ε 6300; NMR signals at τ 9·05, 9·00, 8·78 (all *s*, 3 H; Quaternary $CH_3'S$), 8·92 (*d*, 3H; J = 8 Hz; C-8 CH_3), 7·00 (*s*, 1H; C-5), 3·71, 2·76, 2·63 (all *m*, 1H; furan protons). The Me resonances shifted progressively in solns containing increasing percentages of C_6H_6 to final values (in 100% C_6H_6) of τ 8·88, 9·13, 8·53, and 9·17 respectively.

(b) In an alternative procedure, solidagenone (555 mg) in THF (30 ml) was refluxed for 1 hr with excess LAH. The oily product, isolated as above, was chromatographed over alumina (neutral, 40 g). Elution with chloroform–benzene (1:1) gave a mixture (100 mg) of **2** and **3**, while continued elution gave fractions (300 mg) containing the above compounds and solidagan-6α-ol. On preparative TLC of the later fractions in ether–light petroleum (3:7), the axial alcohol (**3**) partially separated as the higher R_f front of a broad band. The tail of this band contained solidaganone and a small amount of what may be solidagan-6α-ol; NMR signals at τ 9·00, 8·69, 8·38 (all, *s*, 3H), 8·74 (*d*, 3H; J = 8 Hz), 5·78 (*m*, 1H; C-6), 3·71, 2·75, 2·65 (all, *m*, 1H; furan protons). *Solidagan-6β-ol* (3) (120 mg) eluted from the band front, crystallized from ether–light petroleum as prisms, m.p. 101–102°. (Found: C, 75·0; H, 10·0. $C_{20}H_{32}O_3$ requires: C, 75·0; H, 10·1%); NMR signals at τ 9·01, 8·77, 8·62 (all, *s*, 3H; quaternary $CH_3'S$), 8·65 (*d*, 3H; J = 8 Hz; C-8 CH_3), 5·62 (*m*, 1H; C-6), 3·81, 2·86, 2·75 (all, *m*, 1H; furan protons).

Catalytic hydrogenation of solidagenone

Solidagenone (82 mg) in EtOH (8 ml) and triethylamine (2·5 ml) was hydrogenated over 10% Pd-C for 15 min. Freed from catalyst and solvent, the oily mixture (87 mg) was adsorbed on silica (TLC). Development in $CHCl_3$—MeOH (49:1) gave two concentrated bands, the less polar of which furnished **2** (55 mg) while the lower band contained a mixture of compounds in which hydrogenation of the furan ring had taken place.

Hydrogenation of the enone–lactone (**9**)

The enone–lactone[1] (110 mg) in EtOH (20 ml) was hydrogenated for 20 min over Adams catalyst. Filtration and removal of solvent gave an oily mixture (100 mg) of mainly two compounds which were separated by preparative TLC in ether–light petroleum (4:1) (two developments). The less polar compound was the *keto-lactone* **11** (25 mg) needles, m.p. 109–110° (from ether–light petroleum). (Found: C, 73·6; H, 9·6. $C_{17}H_{26}O_3$ requires: C, 73·4; H, 9·4%); $\gamma_{max}^{CCl_4}$ 1781 (lactone), 1717 cm^{-1} (ketone); NMR signals at τ 9·09, 9·02, 8·79 (all, *s*, 3H; quaternary $CH_3'S$), 9·04 (*d*, 3H; J = 8 Hz; C-8 CH_3), 7·71, 7·35 (both, *m*, 1H; C-7), 7·50 (*s*, 1H; C-5). The more polar product was the isomeric *keto-lactone* **10** (45 mg) needles, m.p. 146–148° (from ether–light petroleum). (Found: C, 73·4; H, 9·2%); $\gamma_{max}^{CCl_4}$ 1782 (lactone), 1716 cm^{-1} (ketone); NMR absorption at τ 9·05, 9·02, 8·78 (all, *s*, 3H; quaternary $CH_3'S$), 8·89 (*d*, 3H; J = 8 Hz; C-8 CH_3), 7·70, 7·20 (both, *m*, 1H; C-7), 7·48 (*s*, 1H; C-5). The latter compound was identical (mixed m.p. TLC, IR and NMR) to the major product of chromic acid-acetic acid oxidation of **2**.

Oxidation of solidaganone (**2**) *with chromic acid in acetic acid*

Solidaganone (270 mg) in AcOH (6 ml) was reacted for 50 hr with a soln of CrO_3 (708 mg) in water (1·2 ml) and AcOH (3·6 ml). The AcOH was removed under reduced press and the residue, after dilution with water (100 ml), was extracted with ether. The oily product (120 mg) was purified by preparative TLC in chloroform to give **10**, m.p. 148–149°.

Dehydration of solidaganol (**3**)

Methanesulphonyl chloride (0·5 ml) was added over ½ hr to an ice-cooled soln of solidaganol (760 mg) in dry pyridine (4 ml). After shaking for 1 hr, water was added and the product extracted into ether. Work up gave a brown oil which was absorbed on alumina. Elution with ether–light petroleum (1:4) gave solidag-5-ene, m.p. 87° (Found: M, 302·2243, $C_{20}H_{30}O_2$ requires M, 302·2246), $\gamma_{max}^{CHCl_3}$ 1501 and 873 cm^{-1}.

Preparation of the deuterated compounds (**6** and **7**)

Details of the conversion of marrubiin to **5** have been reported.[1] The analogous interconversion (Scheme IV) employing LAD in the initial step has given *ketone* **7**. (Found: M, 319·2259. $C_{20}H_{29}DO_3$ requires: 319·2258). The position of deuteration was clear from the absence of the appropriate resonances[1] of each of the intermediate compounds.

Ketone **7** (54 mg) in anhyd ether was refluxed for 2 hr with excess LAH. The crude product after workup was chromatographed over alumina (neutral). A fraction (27 mg) eluted with $CHCl_3$–benzene (1:9) was

distilled at 100–110° at 0·01 mm to give **6** as a clear, viscous oil. (Found: C, 74·9; H, 10·2. $C_{20}H_{31}DO_3$ requires: C, 74·7; H. 9·7; D, 0·6%).

Acid-catalysed rearrangement

Solidagenone (1 g) in MeOH (20 ml) was refluxed for 18 hr with aqueous *p*-toluenesulphonic acid (10 ml; 85 mg/ml). After evaporation of MeOH under reduced press, the resulting emulsion was extracted with ether and the separated ethereal layer washed with water, dried, and evaporated. The residual oil was absorbed on preparative chromatoplates which were eluted with ether–light petroleum (1:1). The separated bands gave, in order of decreasing chromatoplate mobility, a colourless oil (30 mg); the *enone* **13** (40 mg), prisms m.p. 99–100° (from light petroleum). (Found: C, 80·65; H, 8·95. $C_{20}H_{26}O_2$ requires: C, 80·5, H, 8·8%), $\gamma_{max}^{CHCl_3}$ 1663, 1568, 1502, and 889 cm^{-1}, λ_{max}^{EtOH} 246 nm, ε 10,800; the *methoxy-enone* **14** (7 mg), prisms m.p. 89–90° (from light petroleum). (Found: C, 76·05; H, 9·25. $C_{21}H_{30}O_3$ requires: C, 76·3; H, 9·15%), $\gamma_{max}^{CCl_4}$ 1682, 1627, 1500, and 872 cm^{-1}, λ_{max}^{EtOH} 209, ε 7600 and 253 nm, ε 8000; and the *dienone* **12** (225 mg), prims m.p. 85–86° (from ether–light petroleum). (Found: C, 80·6; H, 8·9. $C_{20}H_{26}O_2$ requires: C, 80·5; H, 8·8%); $\gamma_{max}^{CHCl_3}$ 1662, 1613, 1500, 882, and 873 cm^{-1}, λ_{max}^{EtOH} 246 nm, ε 13,800.

In another experiment where solidagenone (400 mg) in MeOH (60 ml) was refluxed for 90 hr with aqueous *p*-toluenesulphonic acid (15 ml) with work up as above, **13** (251 mg); **14** (21 mg); and **12** (95 mg) were isolated.

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