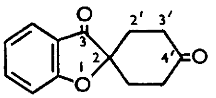
954. *The Preparation of (±)-α- and (±)-β-Grisan-3 : 4′-diol and the Resolution of the α-Isomer.*

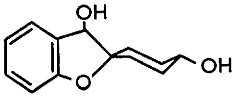
By P. McCloskey.

Stepwise reduction of grisan-3 : 4′-dione with sodium borohydride has yielded (±)-α- and (±)-β-grisan-3 : 4′-diol by way of α- and β-4′-hydroxy-grisan-3-ones. The (±)-α-diol has been resolved into optical antipodes and the (+)-α- and the (+)-β-diol have been shown to be metabolites of grisan-3 : 4′-dione in the broad bean (*Vicia faba* L.).

In studies[1] on the translocation of certain grisan derivatives in the broad bean (*Vicia faba* L.), a crystalline dextrorotatory grisan-3 : 4′-diol (cf. II, III) was isolated from the shoots of plants which had been grown for several days in a dilute aqueous solution of grisan-3 : 4′-dione (I). A diol of identical ultraviolet absorption and similar optical rotation was isolated from the residual solution used for growth (from which all the dione had disappeared) and, in low yield sufficient only for spectral examination, from the plant roots, but the infrared spectra of the three materials were significantly different, which suggested that the specimens were possibly mixtures of stereoisomers. This at first appeared to be supported by the wide melting ranges of the specimens; later, however, it was found that melting behaviour in this series is uncertain.



(I)



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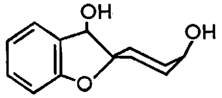

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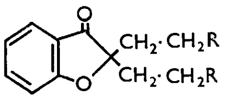

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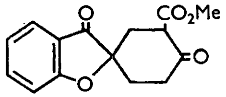

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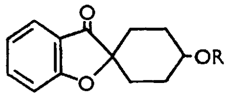

(VI)

Conversion of grisan-3 : 4′-dione (I) into the diol introduces an asymmetric centre at position 3, and the possibility of geometrical isomerism at position 4′ (the molecule has a plane of symmetry through this second centre). The 4′-hydroxyl group may thus be *trans* or *cis* to the 2 : 3-bond, and since this bond will be equatorial in the preferred conformation the most probable structures for the stable (α) and less stable (β) form of (±)-grisan-3 : 4′-diol are (II) and (III) in which the 4′-hydroxyl group is equatorial and axial respectively.

Grisan-3 : 4′-diol was obtained as a mixture of stereoisomers by reduction of grisan-3 : 4′-dione (I) which had been synthesised by dicyanoethylation of coumaranone, conversion of the dicyano-compound (IV; R = CN) into the dimethyl ester (IV; R = CO_2Me) by treatment with methanolic hydrochloric acid, Dieckmann cyclisation of this ester, and acid hydrolysis of the β-keto-ester (V).

Reduction of grisan-3 : 4′-dione with lithium aluminium hydride yielded a solid mixture of isomeric diols which, as transpired, contained a large proportion of the α-isomer but was not readily separated into the components by fractional crystallisation or chromatography on alumina. Both processes were difficult to follow because the material crystallised poorly, yielding solids of ill-defined melting behaviour. However, the diol mixture was oxidised selectively at the 3-position by chromic oxide–pyridine, giving in high yield a mixture of the 4′-hydroxygrisan-3-ones (VI; R = H) as indicated by the ultraviolet absorption [$\lambda_{max.}$ 250, 325 mμ (log ε 4·0, 3·7)] [the diol has $\lambda_{max.}$ 281, 288 mμ (log ε 3·5, 3·4)]. The glassy product did not crystallise but was separated into two different ketols by fractional crystallisation of the 3 : 5-dinitrobenzoates. Hydrolysis of these derivatives afforded

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[1] Crowdy, Green, Grove, McCloskey, and Morrison, *Biochem. J.*, in the press.

the pure ketols, the main product, considered to be that derived from the α-diol, being termed α and the minor β; both ketols then crystallised readily.

These ketols were more satisfactorily prepared by selective partial reduction of grisan-3 : 4′-dione with sodium borohydride. In ice-cold aqueous methanol the 4′-carbonyl group could be virtually titrated with aqueous sodium borohydride whereas reduction of the 3-carbonyl group was relatively slow under these conditions. Crystallisation of the product gave almost pure α-ketol and a residue from which, after conversion into the mixed dinitrobenzoates, the pure β-derivative was separated by fractional crystallisation. By this procedure the α- and the β-ketol were obtained in yields of 85% and 8% respectively, a ratio of stable to less stable forms rather higher than that previously obtained from unhindered *cyclo*hexanones by reduction with sodium borohydride in aqueous methanol.[2,3]

Reduction of the α-ketol with excess of borohydride gave (±)-α-grisan-3 : 4′-diol, regarded as (II), which appeared to crystallise as a racemic mixture since its infrared spectrum (solid) was identical with that of the optically active material isolated from the bean shoots. This result, which suggested that the natural product might be pure (+)-α-grisan-3 : 4′-diol, was fortunate as it was impossible to compare the spectra in solution because of the slight solubility of the diols in all the useful spectral solvents.

Attempts to resolve the inactive α-diol into optical antipodes were at first unsuccessful, *e.g.*, by chromatography of the diol on a relatively large column of " activated " D-lactose,[4] chromatography of the oily bis-(−)-menthyloxyacetates on alumina, and preparation of salts of the hydrogen phthalates and 3-nitrophthalates with active bases. The last method, in which an attempt was made to confine esterification to the relatively unhindered 4′-position by the use of one equivalent of phthalic anhydride and to inhibit polymerisation by the choice of pyridine as solvent,[5] gave only ill-defined and mostly gummy derivatives.

It seemed that resolution employing fractional crystallisation was more likely to succeed if the diastereoisomeric mono-derivatives of the diol could be obtained uncontaminated with bis-derivatives. This was done by preparing the α-4′-(−)-*N*-menthylphthalamic ester [6] [VI; R = $CO{\cdot}C_6H_4{\cdot}CO{\cdot}NH$-(−)-menthyl] and reducing the keto-group of this well-defined crystalline compound by sodium borohydride, though this led to some cleavage of the ester linkage. Fractional crystallisation, etc., of the resultant mixture of diastereoisomeric α-3-hydroxygrisan-4′-yl (−)-*N*-menthylphthalamates gave the pure (+)- and (−)-diastereoisomers (see p. 4736 for details), and hydrolysis yielded (+)- and (−)-α-grisan-3 : 4′-diols (II), having $[\alpha]_D$ ±73° in reasonable agreement with that of the natural diol obtained from the plant shoots ($[\alpha]_D$ + 79° in a determination using 1·5 mg.).[1] Both enantiomorphs melted at *ca.* 205°, a value retained by the (−)-isomer on rapid recrystallisation from benzene–acetone; in general, however, attempts to recrystallise this high-melting modification led to a crystalline product which melted much lower, over a wide range, possibly owing to a combination of polymorphism and the formation of viscous melts.

Reduction of the β-ketol with borohydride gave (±)-β-grisan-3 : 4′-diol, regarded as (III), which was not resolved. Infrared examination of the inactive diol, which also apparently crystallised as a conglomerate, indicated that this product was present in the natural diol isolated from the bean roots and from the residual treating solution, and it was then shown that a synthetic mixture containing almost equal quantities of the (±)-α- and (±)-β-diol had an infrared spectrum virtually identical with that of the natural diol from these two sources. This fact, considered together with the specific rotation of the material obtained from the residual treating solution ($[\alpha]_D$ + 68·5°),[1] leaves little doubt that the diols present in the mixture are both dextrorotatory.

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[2] Dauben, Fonken, and Noyce, *J. Amer. Chem. Soc.*, 1956, **78**, 2579.
[3] Beckett, Harper, Balon, and Watts, *Chem. and Ind.*, 1957, 663.
[4] Prelog and Wieland, *Helv. Chim. Acta*, 1944, **27**, 1132.
[5] Levene and Mikeska, *J. Biol. Chem.*, 1927, **75**, 587.
[6] Human and Mills, *J.*, 1949, S 77.

EXPERIMENTAL

M. p.s are corrected unless otherwise stated. Microanalyses are by Messrs. W. Brown and A. G. Olney, of these laboratories, and R. Rothwell (Imperial Chemical Industries Limited, Dyestuffs Division).

The preparations leading to grisan-3 : 4′-dione were carried out in collaboration with Dr. J. R. Bartels-Keith, of these laboratories, and Dr. W. H. Davies (Imperial Chemical Industries Limited, Dyestuffs Division).

2 : 2-*Di-2′-cyanoethylcoumaranone*.—Coumaranone [7] (13·4 g.) and potassium *tert.*-butoxide (1·1 g.) in dioxan (30 ml.) were stirred vigorously at 15—23° during addition (20 min.) of acrylonitrile (10·6 g.). Stirring was continued for 5 hr. and the mixture then acidified with 2N-hydrochloric acid (5 ml.), poured into water (100 ml.), and extracted with ether. Concentration of the extract afforded prisms of 2 : 2-*di-2′-cyanoethylcoumaranone* (10·6 g.), having m. p. 83·5—84·5° after recrystallisation from ether (Found: C, 70·1; H, 5·4; N, 11·5. $C_{14}H_{12}O_2N_2$ requires C, 70·0; H, 5·0; N, 11·7%).

Chromatography on alumina in benzene–methanol (99 : 1) of the residual red gum obtained by evaporation of the mother-liquor yielded a further quantity (0·7 g.) of product, eluted as a pink band fluorescing blue in ultraviolet light.

Boiling the dinitrile with 5N-sodium hydroxide for 2½ hr. yielded 2 : 2-*di-2′-carboxyethylcoumaranone*, m. p. 137—138° (from water) (Found: C, 60·45; H, 5·1. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%). The *diethyl ester*, obtained by heating the acid in ethanol containing sulphuric acid (6% w/w), formed crystals, m. p. 27—28°, from ether (Found: C, 64·8; H, 6·55. $C_{18}H_{22}O_6$ requires C, 64·7; H, 6·6%).

2 : 2-*Di-(2-methoxycarbonylethyl)coumaranone*.—A mixture of 2 : 2-di-2′-cyanoethylcoumaranone (59·1 g.) in water (9 ml.), and methanol (250 ml.) saturated with hydrogen chloride, was set aside at room temperature for 2 hr. (protected against atmospheric moisture) and then heated at 60°. After 45 min. the precipitate of ammonium chloride was filtered off and washed with dry methanol. The combined filtrate and washings were boiled under reflux for 2¼ hr., set aside at room temperature overnight, poured into water (1 l.), and extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate, dried, and evaporated and the product was twice distilled, to yield 2 : 2-*di-(2-methoxycarbonylethyl)coumaranone* (63·5 g.), b. p. 166—168°/0·4 mm. (Found: C, 62·9; H, 5·9. $C_{16}H_{18}O_6$ requires C, 62·7; H, 5·9%). Continuous extraction with ether of the aqueous mother-liquor afforded a further quantity (4·4 g.) of the crude ester.

Methyl (±)-3 : 4′-*Dioxogrisan-3′-carboxylate*.—Sodium (3·85 g.) was powdered in dry toluene (300 ml.) and 2 : 2-di-(2-methoxycarbonylethyl)coumaranone (43·5 g.) in toluene (160 ml.) containing methanol (0·5 ml.) added with vigorous stirring during 1 hr., the mixture being heated to boiling during 30 min. After an initial lag the sodium was rapidly consumed and replaced by a yellowish-brown powder in a reaction which reached maximum velocity towards the end of the addition period, at which point heating was withdrawn for several min. A further portion of toluene (100 ml.) was added, and stirring and heating were continued for 11 hr., after which the mixture was set aside overnight, then poured into water (500 ml.) containing 2N-sulphuric acid (85 ml.) and extracted with ether. The extract was washed with sodium hydrogen carbonate solution, dried, and evaporated to a yellowish solid (35·8 g.), m. p. 117—123°. Crystallisation from light petroleum (b. p. 40—60°)–ether (2 : 1) yielded prisms of the *grisan ester*, m. p. 122·5—124° (Found: C, 65·85; H, 5·1. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·15%).

Grisan-3 : 4′-*dione*.—The above β-keto-ester (31·55 g.) was heated under reflux with dioxan (80 ml.), water (80 ml.), and concentrated hydrochloric acid (80 ml.), nitrogen being passed through the mixture and the exit gases occasionally tested for carbon dioxide (barium hydroxide). Evolution of carbon dioxide being negligible after 7 hr., the mixture was cooled and extracted with ether, and the extract washed with water and sodium hydrogen carbonate solution, dried, and evaporated to yield an orange gum (24·2 g.) which readily solidified. The combined crude product (43·5 g.) from several experiments was crystallised from ether, yielding prisms of *grisan*-3 : 4′-*dione* (16·4 g.), m. p. 89·5—90·5° (Found: C, 72·35; H, 5·65. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%), $\lambda_{max.}$ (in ethanol) 250, 328 mμ (log ε 4·0, 3·7). Evaporation of the mother-liquor and distillation of the gummy residue (b. p. 128—129°/0·5 mm.) gave an oil which afforded a further quantity (18 g.) of crystalline product, m. p. 89—90·5° (from ether). The

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[7] Fries and Pfaffendorf, *Ber.*, 1910, **43**, 214; Mameli, *Gazzetta*, 1926, **56**, 759.

2 : 4-*dinitrophenylhydrazone* had m. p. 230—231° (from dioxan–ethanol) (Found: C, 57·75; H, 4·2; N, 14·1. $C_{19}H_{16}O_6N_4$ requires C, 57·6; H, 4·0; N, 14·15%).

Reduction of Grisan-3 : 4′-*dione with Lithium Aluminium Hydride.*—Grisan-3 : 4′-dione (5·4 g.) in dry ether (250 ml.) was stirred vigorously under reflux and treated with lithium aluminium hydride (1 g.) in four portions added at intervals of 15 min. After 3½ hr. the mixture was cooled at 0°, treated with ice until the excess of reagent had been decomposed, and then shaken with N-hydrochloric acid (175 ml.) and more ether (total ca. 1 l.) until all the solid had dissolved. After separation the ether solution was washed with saturated aqueous sodium hydrogen carbonate (10 ml.), dried, and evaporated, yielding a slightly gummy solid (5·44 g.). The ether-washed product (4·52 g.), a mixture of (±)-α- and (±)-β-grisan-3 : 4′-diol in which the former predominated as shown by infrared absorption, had m. p. 167—174°.

α- *and* β-4′-*Hydroxygrisan*-3-*one.*—(a) *By reduction of grisan*-3 : 4′-*dione.* Grisan-3 : 4′-dione (3·48 g.) in methanol (20 ml.) at 0° was treated dropwise with sodium borohydride (81%; 0·25 g.) in water (to 10 ml.). The reagent was at first rapidly consumed but after 7·55 ml. of the solution (equivalent to slightly more than that required for the reduction of one carbonyl group) had been added during 20 min. the excess of borohydride was sufficient to bleach a weak alcoholic solution of magenta in *ca.* 1 min. and persisted for a further 10 min. (at 0°) but had disappeared after 15 min. The mixture was then diluted with water and extracted with ether. Recovery gave a gum (3·47 g.) which readily crystallised when warmed with a little ether. Fractional crystallisation of the product, first from ether, and later from ether containing increasing quantities of light petroleum (b. p. 40—60°), yielded α-4′-*hydroxygrisan*-3-*one* (2·68 g.), m. p. 105·5—106·5° after further recrystallisation from ether (Found: C, 71·2; H, 6·4. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·5%), $\lambda_{max.}$ (in ethanol) 249, 324·5 mμ (log ε 3·98, 3·70). The 3 : 5-*dinitrobenzoate* crystallised as needles, m. p. 221—222°, from acetone (Found: C, 58·1; H, 4·2; N, 6·8. $C_{20}H_{16}O_8N_2$ requires C, 58·25; H, 3·9; N, 6·8%). The α-*naphthylurethane* formed needles, m. p. 176—177°, from ethanol (Found: C, 73·9; H, 5·4; N, 3·6. $C_{24}H_{21}O_4N$ requires C, 74·4; H, 5·5; N, 3·6%). The *acetyl derivative* formed leaflets, m. p. 132—133°, from light petroleum (b. p. 40—60°)–ether (1 : 1) (Found: C, 69·4; H, 6·2. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%).

The mother-liquor was evaporated and the gummy residue (0·78 g.) in dry benzene (10 ml.) and pyridine (1 ml.) was treated with 3 : 5-dinitrobenzoyl chloride (0·9 g.) in benzene (5 ml.) during 5 min. with shaking. The mixture was warmed on the water-bath for 30 min., then cooled and diluted with benzene and water. The benzene layer was washed, dried, and evaporated, yielding a slightly gummy solid (1·25 g.). Crystallisation from benzene (20 ml.) yielded β-3-*oxogrisan*-4′-*yl* 3 : 5-*dinitrobenzoate* (0·33 g.) as needles having m. p. 262—263° after further crystallisation from benzene (Found: C, 58·5; H, 4·3; N, 6·8. $C_{20}H_{16}O_8N_2$ requires C, 58·25; H, 3·9; N, 6·8%). Continued fractional crystallisation of the dinitrobenzoate mixture from benzene, and later from acetone, afforded the α-dinitrobenzoate (0·56 g.) and a further quantity of the β-dinitrobenzoate (0·2 g.).

The β-dinitrobenzoate (1·27 g.) was heated under reflux with potassium hydroxide (0·365 g.) in methanol (10 ml.) for 1 hr., then diluted with water (100 ml.) and extracted with ether (6 × 100 ml.). Recovery gave a gum (0·68 g.) which crystallised from ether yielding prisms of β-4′-*hydroxygrisan*-3-*one*, m. p. *ca.* 66—85° raised to 88·5—89·5° after 3 hours' heating at 78°/0·1 mm. followed by ½ hr. at 95—100°/0·1 mm. (Found, after heating: C, 71·6; H, 6·5. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·5%), $\lambda_{max.}$ (in ethanol) 249, 325 mμ (log ε 3·97, 3·70). The *acetyl derivative* formed prisms, m. p. 145—146°, from light petroleum (b. p. 40—60°)–ether (1 : 1) (Found: C, 69·5; H, 6·2. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%).

(b) *By oxidation of grisan*-3 : 4′-*diol.* Grisan-3 : 4′-diol (2·2 g.; mixture of isomers obtained by reduction of grisan-3 : 4′-dione with lithium aluminium hydride) was added rapidly with shaking to a suspension of the complex prepared from chromium trioxide (2·0 g.) in pyridine (20 ml.). After being shaken for 10 min. whilst the temperature rose slightly and the suspended complex was replaced by a brown amorphous powder, the mixture was set aside for 22 hr., then diluted with water and extracted with ether (6 × 125 ml.). The extract was washed with 2N-hydrochloric acid and saturated aqueous sodium hydrogen carbonate, dried, and evaporated to a glass (2·1 g.) which crystallised rapidly when seeded with α-4′-hydroxygrisan-3-one. Crystallisation from ether afforded α-4′-hydroxygrisan-3-one (0·72 g.) and a gummy residue which was converted into dinitrobenzoate and worked up as under (*a*), eventually yielding α-3-oxogrisan-4′-yl 3 : 5-dinitrobenzoate (1 g.), m. p. 216—218°, the β-derivative (0·27 g.), m. p. 259—261° after further crystallisation, and a mixture (0·5 g.) containing both derivatives.

(±)-α-*Grisan*-3 : 4′-*diol*.—α-4′-Hydroxygrisan-3-one (5·3 g.) in methanol (10 ml.) at 0° was treated with sodium borohydride (81%; 0·7 g.) in water (3 ml.). In a few minutes the mixture became warm and crystals were deposited. After being kept overnight at 0° the mixture was filtered and the solid rinsed with cold methanol and ether, affording (±)-α-*grisan*-3 : 4′-*diol* (4·77 g.), m. p. 175·5—180·5°, softening at 171° (Found: C, 71·3; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%), $\lambda_{max.}$ (in ethanol) 281, 288 mμ (log ε 3·49, 3·44). Dilution of the filtrate with water, extraction with ether, and recovery gave a further quantity (0·51 g.) of product, m. p. 169—173°, softening at 141°. Recrystallisation of the first crop afforded balls of opaque solid, m. p. 148—158° (cloudy melt), from benzene, or, from methanol, prisms which softened slowly above 171°, became partially opaque on continued heating, and gave a clear melt at 199°.

α-3-*Oxogrisan*-4′-*yl* (−)-N-*Menthylphthalamate*.—α-4′-Hydroxygrisan-3-one (2·18 g.) and phthalic anhydride (1·48 g.) were heated in dry pyridine (5 ml.) on the steam-bath for 4 hr. The mixture was cooled, diluted with cold N-hydrochloric acid, and extracted with ether. The extract was washed with 18% hydrochloric acid (3 × 10 ml.) and water (3 × 10 ml.), dried, and evaporated to a gum (3·67 g.). This product in dry benzene (5 ml.) was treated with freshly purified thionyl chloride (1·3 g.) in benzene (5 ml.), and the mixture set aside overnight at room temperature, then refluxed for 15 min. and evaporated under reduced pressure, affording a gum (3·8 g.) which was at once redissolved in benzene (5 ml.) and treated with pyridine (1 ml.) in benzene (2 ml.) followed by (−)-menthylamine (1·7 g.) in benzene (3 ml.). On addition of the base the mixture became warm and crystals were deposited. The mixture was set aside for 3 hr., then refluxed for 15 min., cooled, diluted with benzene, and shaken successively with 2N-hydrochloric acid, water, and saturated aqueous sodium hydrogen carbonate, dried, and evaporated, to yield a slightly gummy solid (4·5 g.). Recrystallisation from benzene (15 ml.) afforded pale yellow crystals (3·6 g.) of α-3-*oxogrisan*-4′-*yl* (−)-N-*menthylphthalamate*, $[\alpha]_D$ −29° (*c* 1·12 in ethanol), m. p. 210—210·5° after further crystallisation from ether (Found: C, 73·9; H, 7·55; N, 2·7. $C_{31}H_{37}O_5N$ requires C, 73·9; H, 7·4; N, 2·8%). Concentration of the mother-liquor and dilution with ether gave a second crop of slightly crude material (0·24 g.).

(+)- *and* (−)-α-3-*Hydroxygrisan*-4′-*yl* (−)-N-*Menthylphthalamate*.—Preliminary experiments indicated that the quality and yield of the product of this reduction depended rather critically on the conditions. The best results were obtained as follows: α-3-Oxogrisan-4′-yl (−)-*N*-menthylphthalamate (300 mg.) in methanol (10 ml.) at 0° was treated with sodium borohydride (25 mg.) with shaking. The mixture was then set aside overnight at 0°. Solutions from twelve such experiments were combined, diluted with 0·1N-hydrochloric acid, and extracted with ether, the extract being washed with water, dried, and evaporated to a gummy solid (3·52 g.) which was boiled with a little ether, cooled at 0°, and filtered. This gave a mixture of the diastereoisomeric α-3-hydroxygrisan-4′-yl (−)-*N*-menthylphthalamates (1·88 g.), m. p. 197—200°.

Six recrystallisations of this material from benzene yielded (−)-α-3-*hydroxygrisan*-4′-*yl* (−)-N-*menthylphthalamate* (0·49 g.), m. p. 218—219°, $[\alpha]_D$ − 57° (*c* 0·9 in ethanol) (Found: C, 73·8; H, 8·0; N, 2·6. $C_{31}H_{39}O_5N$ requires C, 73·6; H, 7·8; N, 2·8%). A further quantity (total 0·78 g.) of the same diastereoisomer was obtained during subsequent fractionation the progress of which was, however, difficult to follow at first because of the occasional separation of a solvated, sparingly soluble, voluminous crystalline solid, m. p. 136—141° (gas evolution) followed by resolidification and remelting at *ca*. 190—194°, $[\alpha]_D^{20}$ −24° (*c* 1·0 in ethanol) after drying at 80° for 45 min. Recrystallisation of such material from fresh solvent led to a first crop of unsolvated (−)-diastereoisomer of reasonably good quality.

As no solvent could be found to reverse the relative solubilities of the two diastereoisomers the fractionation was continued in benzene. Concentration of the mother-liquor five times, with removal of intermediate crops of solid mixtures, yielded a solution which showed a positive rotation. Evaporation yielded a gum (293 mg.) which crystallised from ether to yield needles (194 mg.) of (+)-α-3-*hydroxygrisan*-4′-*yl* (−)-N-*menthylphthalamate*, m. p. 185—186°, $[\alpha]_D^{21}$ +10° (*c* 1·1 in ethanol) or +19° (*c* 1·0 in benzene) (Found: C, 73·5; H, 8·1; N, 3·2%). On repeated crystallisation of this compound from ether its m. p. at first rose to 186·5—187·5°, then fell to 178—184°, and finally rose to 188—190° whilst the specific rotation remained virtually constant ($[\alpha]_D$ +10°, +11°, +10°, in ethanol).

The residue (1·65 g.) obtained by evaporation of the original mother-liquor was chromatographed on alumina (50 g.) in ether. Elution with ether (total 150 ml.) yielded a gum (437 mg.), crystallisation of which from light petroleum (b. p. 40—60°)–ether gave prisms (314 mg.), m. p. 108—109°, of (−)-*N*-menthylphthalimide, identified by undepressed m. p. on admixture with authentic material. Subsequent fractions, eluted at first with ether but later with ether containing acetone (0·25%), yielded a solid (300 mg.), m. p. 146—175° raised to 160—178° on crystallisation from ether, $[\alpha]_D^{20}$ −5° (ethanol), identified as α-grisan-3 : 4′-diol by comparison of infrared spectra. Elution was completed by means of benzene–acetone (199 : 1, changing to 99 : 1) and yielded a gum (900 mg.) which, after dissolution in benzene and separation of an unidentified solid (277 mg.), m. p. 182—184°, $[\alpha]_D$ −12° (in benzene), showed a positive rotation, and was again chromatographed on alumina (50 g.) in benzene. Elution with benzene–acetone (95 : 5) yielded solid fractions (total 454 mg.), m. p. 180—185°, which were combined and crystallised from ether, affording (+)-α-3-hydroxygrisan-4′-yl (−)-*N*-menthylphthalamate (287 mg.), $[\alpha]_D$ +21° (in benzene), $[\alpha]_D$ +11° (in ethanol), m. p. 187·5—189° undepressed on admixture with the specimen obtained previously.

(+)-α-*Grisan*-3 : 4′-*diol*.—(+)-α-3-Hydroxygrisan-4′-yl (−)-*N*-menthylphthalamate (170 mg.) was heated under reflux for 1 hr. with 2N-potassium hydroxide (2 ml.). After cooling, the mixture, in which oily crystals were suspended, was diluted with a little water which dissolved the oil, cooled at 0°, and filtered, yielding leaflets (50 mg.) of (+)-α-*grisan*-3 : 4′-*diol*, m. p. 203—205°, $[\alpha]_D^{21}$ +73° (*c* 1·0 in ethanol) (Found: C, 71·15; H, 7·2. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). After recrystallisation from benzene–acetone the product, of unchanged rotation, melted gradually between 170° and 202°. The infrared spectrum was identical with that of (±)-α-grisan-3 : 4′-diol (above), the (−)-α-diol (below), and material isolated from the shoots of plants of the broad bean which had been grown on an aqueous solution of grisan-3 : 4′-dione.[1]

(−)-α-*Grisan*-3 : 4′-*diol*.—Hydrolysis of (−)-α-3-hydroxygrisan-4′-yl (−)-*N*-menthylphthalamate under the same conditions afforded leaflets of (−)-α-*grisan*-3 : 4′-*diol*, $[\alpha]_D^{20}$ −73° (*c* 0·8 in ethanol), m. p. 206—207° from benzene–acetone (Found: C, 70·55; H, 7·3%). Further crystallisation from benzene caused a depression in m. p., affording needles which softened *ca.* 190°, melting mainly 192—198°.

(±)-β-*Grisan*-3 : 4′-*diol*.—β-4′-Hydroxygrisan-3-*one* (253 mg.) in methanol (0·5 ml.) and water (0·2 ml.) at 8° was treated with sodium borohydride (35 mg.). The mixture, in which crystals of ketol had separated, was gently shaken and became homogeneous after 5 min. Almost immediately crystals separated. After being kept overnight at 4° these were filtered off and washed with cold water, yielding leaflets (235 mg.) of (±)-β-*grisan*-3 : 4′-*diol*, m. p. 171—175°, softening 169° (Found: C, 70·9; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%), $\lambda_{max.}$ (in ethanol) 281, 287·5 mμ (log ε 3·51, 3·46). Recrystallisation yielded clusters of prisms, m. p. 131—139°, from benzene, or prisms, m. p. 168—176°, softening at 156°, from methanol–water (1 : 2).

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