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TERPENOIDS—LXI

CONVERSION OF EUDESMOL TO DI- AND TETRAHYDROCOSTOL*

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Abstract—Dihydro-β-eudesmol (IV), obtained by catalytic hydrogenation of β-eudesmol (II), on pyrolysis via the benzoate gives dihydro-β-selinene (V). Its epoxyderivative (VI) is converted on treatment with acetic acid to the hydroxy acetate (VII), the benzoate of which on pyrolysis, followed by saponification, affords dihydrocostol (XI), converted by hydrogenation to tetrahydrocostol (XII). The alcohol (XI) is not identical with agarol to which the same stereoformula has been assigned previously. These results would necessitate a re-examination of the structure and stereochemistry of agarol which has already been undertaken.

EUDESMOL, probably is the most well-known sesquiterpene of the selinanic group. It usually occurs as a mixture of two isomers,[1a,b] α- and β-eudesmols (I and II). Another isomer, γ-eudesmol (III), is produced when the hydrochloride of α or β eudesmol is treated with base.[1a] It has also been recently reported to occur in nature.[2,3]

Hydrogenation of the three isomeric eudesmols with platinum oxide in glacial acetic acid has been reported to give a single dihydro product[1a] (IV). Recently it has been shown that a mixture of α and β-eudesmols on hydrogenation with Pd—C in methanol–acetic acid gives a C_4-epimeric mixture of dihydroeudesmols.[4] However, hydrogenation with PtO_2 in methanol gives pure dihydroeudesmol[4] (IV). β-eudesmol (II) on hydrogenation should give pure dihydro-β-eudesmol (IV) as a result of attack of hydrogen preferentially from the less hindered side which has been confirmed during the present investigation. The stereochemistry of dihydro-β-eudesmol has been rigorously established as represented by the formula[5,6] (IV).

In connection with work in a related area we were in possession of some β-eudesmol obtained in the pure form by fractional distillation[1b] and chromatography.[1a] It seemed worthwhile to convert it through a few simple reactions to a product represented by the structure XI, previously assigned to agarol, isolated from agarwood oil.[7,8] It was also evident that the compound XI obtained synthetically could be

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[1] [a] F. J. McQuillin and J. D. Parrack, *J. Chem. Soc.* 2973 (1956); [b] E. Von Rudloff, *Chem. & Ind.* 743 (1962).

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[8] T. C. Jain, Ph.D. thesis, Agra University (1960).

hydrogenated to tetrahydrocostol (XII), giving further support to the known absolute configuration of the same and that of the parent alcohol costol (XIV) itself.[9a,b]

For this purpose dihydro-β-eudesmol (IV) was prepared by hydrogenation of pure β-eudesmol using PtO_2 in methanol. The purity of the product was ascertained by GLC and the properties were in agreement with those reported.[4] Dihydro-β-eudesmol was converted to the benzoate which was pyrolysed at 230° under reduced pressure to furnish pure (98%, GLC) dihydro-β-selinene (V). The IR spectrum of V shows characteristic strong bands at 1645 and 887 cm^{-1} due to the end-methylene double bond. The hydrocarbon (V) should have the same stereochemistry as dihydro-β-eudesmol (IV), as pyrolysis of the benzoate to the olefin should not cause any change in the stereochemistry of the ring juncture and the isopropenyl side chain should necessarily remain β-oriented.

Treatment of dihydro-β-selinene (V) under controlled conditions with perbenzoic acid gives epoxy-dihydro-β-selinene (VI), ν_{max} 2688, 909, 859 cm^{-1} (epoxide). On keeping the epoxide in glacial acetic acid at room temperature smooth cleavage takes place to furnish the hydroxy-acetate (VII). The structure VII for the hydroxy acetate is preferred to the alternative structure VIII on the basis of the ease of saponification and the difficulty experienced for acetylation. A small amount of the aldehyde (IX), formed by acid catalysed isomerization of the epoxide, was characterized as the semicarbazone which is identical with that of tetrahydrocostal, previously not reported in the literature.

The easiest way to effect the elimination of the tertiary hydroxyl group of the hydroxy acetate (VII) in the desired direction is pyrolysis of the benzoate. Using milder conditions than employed for dihydroeudesmol the benzoate of the acetoxy alcohol is converted to the required acetate (X) showing characteristic IR absorption, ν_{max} 1640, 890, 1736 and 1253 cm^{-1}. Saponification followed by chromatography furnishes the synthetic alcohol (XI) with characteristic IR bands at ν_{max} 3400, 1037 (primary hydroxyl group), 1647, 903 cm^{-1} (end-methylene double bond). In addition, from the earlier fractions of chromatography, small amounts of a conjugated diene was also isolated with λ_{max} 238 mμ (ε 19,720), 243 mμ (21,800), 248 mμ (20,710) and 254 mμ (15,000) and ν_{max} 2755, 1618, 886 and 826 cm^{-1}. On the basis of these spectral data[10] the diene has been assigned the heteroannular structure XIII.

The synthetic alcohol (XI) on hydrogenation gives the dihydro compound (XII) whose IR spectrum is identical with that of authentic tetrahydrocostol prepared by the hydrogenation of costol. The optical rotations are also comparable. Thus these transformations lend further support to the previously established stereochemistry of costol (XIV) and tetrahydrocostol[9a,b] (XII).

The same structure and absolute stereochemistry as represented by the synthetic alcohol (XI) has been previously assigned to agarol isolated from the oil of agarwood. The IR spectrum of natural agarol differs remarkably from that of the synthetic alcohol, which undoubtedly has the correct stereochemistry as in the formula XI. In conformity with their identical stereochemistry, the specific rotations of tetrahydrocostol (XII, +14·5°), dihydro-β-eudesmol (IV, +18·4°), dihydro-β-selinene (V, +19·3°), epoxy-dihydro-β-selinene (VI, +17·1°) and selinane (XV, +19·2°)

[9] [a] V. Benes'ova, V. Sy'kora, V. Herout and F. Sorm, *Chem. & Ind.* 363 (1958);
[b] *Coll. Czech. Chem. Commun.* **24**, 2365 (1959).

[10] L. Dorfmann, *Chem. Revs.* **53**, 47 (1953).

follow the same pattern with comparable values. Against this, the reported specific rotation of natural agarol (−21·8°) does not compare in sign with these values, which should not be the case, if agarol possesses the absolute stereochemistry as in XI. The positive specific rotation (+16·6°) reported for dihydroagarol[7,8] also

under a stream of N_2 for 5 hr, during which time the solution became gradually red and clear. After cooling, the MeOH was removed *in vacuo* to afford the residue which was dissolved in ice-water (40 ml). The resulting aqueous solution was extracted with ether to thoroughly remove the ether soluble material. The aqueous layer was filtered, acidified with conc. HCl and extracted with ether. The ether layer was washed with NaCl aq, dried and the ether removed to afford a crude crystalline product, m.p. 81–85° (658 mg, 69%) which was recrystallized from n-hexane to give colorless needles, m.p. 89–91° after drying (P_2O_5) overnight. $[\alpha]_D^{19}$ +1·50° (*c*, 15 in EtOH), p% 4·0. $IR_{\nu C=O}$ 1722 cm^{-1}. (Found: C, 64·88; H, 5·95. Calc. for $C_9H_{10}O_2$: C, 65·05; H, 6·07%).

Methyl-(O-phenylglyoxyl)-reserpate (VIII) *hydrochloride*. To a solution methyl reserpate (IV; 2·5 g, 6·03 mmoles) in dry pyridine (30 ml), phenylglyoxylic acid chloride (2·3 ml) was added under ice-cooling, during which time the solution exothermically turned red. The mixture was allowed to stand at a room temp for 4 days to become a red brown solution, which was concentrated to a volume of 5 ml *in vacuo*, and this was poured onto ice water (50 ml). The resulting mixture was made basic with $NaHCO_3$ and extracted with chloroform. The chloroform was removed to leave a pale red caramel which was rather unstable. So the caramel was dissolved in chloroform, to which was added 5% HCl to precipitate the hydrochloride in a powdered form. Yield, 2·76 g (78·5%). The crude hydrochloride was recrystallized from 90% EtOH to yield pale yellow sandy crystals, m.p. 218–219° (dec.), $[\alpha]_D^{22}$ −57·2° (*c*, 0·58 in AcOH). $IR_{\nu C=O}$ 1732, 1725, 1683 cm^{-1}. (Found: C, 61·80; H, 6·08; N, 4·59. $C_{31}H_{34}N_2O_7 \cdot HCl \cdot H_2O$ requires: C, 61·94; H, 6·20; N, 4·66%).

Methyl (O-atrolactyl)-reserpate (IX). To an ethereal solution of MeMgI prepared from Mg (338 mg, 13·9 mmoles), MeI (1·975 g, 13·9 mmoles) and absolute ether (40 ml), was added a solution of the foregoing ester (VIII; 1·9 g, 3·48 mmoles) (being freed from the hydrochloride with ammonia) in tetrahydrofuran (40 ml), during which time the white precipitate appeared immediately. Stirring was continued and the temp allowed to rise to room temp in 15 min. The mixture was refluxed at 60–70° for an additional 3 hr, and poured onto ice-water (50 ml) containing NH_4Cl (12 g). The resulting mixture was worked up in the same manner as in the case of VI to give a pale red caramel (IX; 1·497 g, 76·6%) as a crude product. $IR_{\nu OH}$ 3380, $IR_{\nu C=O}$ 1725 cm^{-1}.

Atrolactic acid (VIIb). The foregoing ester (1·44 g, 2·56 mmoles) was dissolved in methanol (17·5 ml), to which was added a solution of KOH (1 g) in H_2O (2·5 ml). The whole mixture was refluxed under a stream of N_2 for 5 hr. Worked up in the same way as that of VIIa, there was obtained the crude acid (VIIb; 270 mg, 63·5%), m.p. 80–84°, which was recrystallized from n-hexane to afford colorless needles, m.p. 88–90°, $[\alpha]_D^{19}$ − 9·78° (*c*, 6·5 in EtOH), p % 25·9. $IR_{\nu OH}$ 3410, $IR_{\nu C=O}$ 1722 cm^{-1}.

Yohimbone (XIX). Yohimbone (XIX) was prepared according to the procedure described by Witkop.[24] M.p. 301–303° (dec.). Yield, 49·4%. $IR_{\nu C=O}$ 1703 cm^{-1}.

Epiyohimbol (XX). To a suspension of the foregoing yohimbone (XIX; 4 g, 13·6 mmoles) in EtOH (300 ml) was added $NaBH_4$ (2 g). The mixture became clear in ca. 30 min, and was allowed to stand for 2 hr, occasionally shaking. The EtOH was removed *in vacuo*, and water (150 ml) was added to the residue. The deposited crystals were collected by filtration, washed with water, dried and recrystallized from 80% MeOH to afford 3·3 g (82%) of colorless needles (XX), m.p. 254° (dec.), $[\alpha]_D^{24}$ −76° (*c*, 0·51 in MeOH). $IR_{\nu OH}$ 3300, $IR_{\nu C-O}$ 1020 cm^{-1}.

17α-*Chloroyohimbone* (XXI). To a solution of the foregoing epiyohimbol (XX; 3·3 g, 11 mmoles) in pyridine (40 ml) was added $POCl_3$ (11 ml) under ice-cooling, and the resulting mixture refluxed at 130° for 2 hr, during which time the color of the solution turned red. The solvent was removed *in vacuo* to leave the residue, which was poured into ice water containing $NaHCO_3$ to separate red brown crystals. The crude material collected by filtration was dissolved in MeOH and treated with active charcoal. The MeOH was removed, and the residue on recrystallization from MeOH furnished colorless needles (XXI; 2·111 g, 61%), m.p. 179–182°. $[\alpha]_D^{26}$ −60·7° (*c*, 0·28 in EtOH). (Found: C, 72·94; H, 7·62; N, 8·82; Cl, 11·18. $C_{19}H_{23}N_2Cl$ requires: C, 72·48; H, 7·36; N, 8·90; Cl, 11·26%).

Δ^{17}-*Yohimbene* (XXII). A solution of 17α-chloroyohimbane (XXI; 1·2 g, 3·8 mmoles) in colliding

and the relevent fractions repeatedly chromatographed over neutral alumina and sublimed to furnish GLC pure β-eudesmol, m.p. 80–81° $(\alpha)_D^{27}$ +58·03°, ν_{max} 3333, 1645, 1190, 1136, 960, 919, 888 and 858 cm^{-1}. Lit.[1a] m.p. 75·5–76°, $(\alpha)_D$ +63·8° for β-eudesmol. It showed a single peak in the GLC.

Dihydro-β-eudesmol (IV). Pure β-eudesmol (15 g) was hydrogenated in absolute methanol (300 ml) using PtO_2 (500 mg) at atm. press. till absorption was complete (24 hr). The catalyst was filtered off, solvent removed and the residue sublimed (80–83°/0·3 mm) to furnish an analytical specimen, m.p. 83–84°, $(\alpha)_D^{27}$ +18·58° (*c*, 5·1); negative tetranitromethane test. It was 95% pure by GLC (Found: C, 80·08; H, 12·49. $C_{15}H_{26}O$ requires: C, 80·37; H, 12·59%). Lit.[4] m.p. 85·5–86°, $(\alpha)_D^{25}$ +18·1° (*c*, 2·16; $CHCl_3$).

Benzoate of dihydro-β-eudesmol. Dihydro-β-eudesmol (V, 10 g) in dry pyridine (25 ml) was mixed with benzoyl chloride (10 ml) and left at room temp for 2 days. The contents were diluted with ice-cold water (200 ml) and extracted with ether (3 × 50 ml). The combined ether extracts were washed with dil. HCl, dil. Na_2CO_3aq and water, dried and solvent removed to furnish the crude benzoate which was chromatographed over neutral alumina (gr. II, 500 g) to furnish the benzoate (14·3 g), b.p. 180°/0·2 mm, n_D^{28} 1·5250 (Found: C, 80·17; H, 9·63. $C_{22}H_{32}O_2$ requires: C, 80·48; H, 9·75%).

Dihydro-β-selinene (V). Pure dihydro-β-eudesmol benzoate (14·g) in a distillation flask with a wide arm was pyrolysed by heating in an oil bath at 230° at 110 mm press. for 40 min. The small amount of material which distilled over was combined with the material in the flask, taken up in ether (100 ml) and washed with dil. NaOH aq and water, dried and solvent removed to furnish the crude material which was chromatographed over neutral alumina (gr. I, 500 g). Pet. ether (500 ml) eluted dihydro-β-selinene (V, 8·4 g) which was found to be 98% pure by GLC; b.p. 115°/4 mm $(\alpha)_D^{27}$ +19·3°, n_D^{27} 1·4958; ν_{max} 1645 (m) 888 (s) cm^{-1} (Found: C, 87·10; H, 12·41. $C_{15}H_{26}$ requires: C, 87·38; H, 12·62%).

Epoxy-dihydro-β-selinene (VI). Dihydro-β-selinene (V, 7·0 g) was mixed in the cold with a chloroform solution of perbenzoic acid (150 ml, 0·63 N). The reaction was followed by titration of aliquots at intervals against standard thiosulphate solution and when a little more than 1 equiv. was consumed (18 hr), the chloroform solution was washed with dil. Na_2CO_3 aq and water, dried and solvent removed to furnish the epoxide (7·23 g) which was directly used in the next step. An analytical specimen showed, b.p. 135°(bath)/0·7 mm, $(\alpha)_D^{28}$ +16·93° (*c*, 14·0); ν_{max} 2688 (w), 909 (m), 859 (m) cm^{-1} (epoxide) (Found: C, 81·31; H, 11·63. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

The acetoxy-alcohol (VIIa). The epoxide (VI, 6 g) was mixed with glacial acetic acid (20 ml) and left at room temp for 24 hr. Excess acetic acid was removed under red. press., the residue taken up in ether, washed with Na_2CO_3aq and water, dried and solvent removed to furnish the crude product (7·3 g) which was chromatographed over neutral alumina (gr.II, 200 g). Pet. ether (1·5 l) eluted unreacted epoxide (0·55 g). Pet. ether–benzene (70 ml, 1:1) eluted material (0·265 g) which from its IR spectrum, ν_{max} 1733, 2772 (aldehyde) and semicarbazone, m.p. 197–98°, was identified as tetrahydrocostal. Mixed m.p. with an authentic specimen* (*vide infra*) showed no depression. Fractions 3 and 4 eluted with the same solvent mixture (2X100 ml, 4·22 g) had identical IR spectra and comparable specific rotations (+7·57° and +6·92°) and were combined and distilled to furnish an analytical specimen of the acetoxy-alcohol (VIIa) as a viscous oil, b.p. 152°(bath)/0·3 mm, $(\alpha)_D^{27}$ +7·32° (*c*, 18·3); sap. value 164 (calc. 173·2); ν_{max} 3425(s), 1145(m), 1044 (s), 1730 (s), 1250 (s) cm^{-1}. (Found: C, 72·08; H, 10·49. $C_{19}H_{32}O_4$ requires: C, 72·30; H, 10·71%). Saponification with alcoholic potash gave the corresponding diol, an oil, b.p. 150°(bath)/0·35 mm, ν_{max} 3460 (s), 1050 (s) cm^{-1}; $(\alpha)_D^{27}$ +9·29° (*c*, 9·3) (Found: C, 75·2; H, 11·39. $C_{15}H_{28}O_2$ requires: C, 75·01; H, 11·67%).

The acetoxy-benzoate (VIIb). The acetoxy-alcohol (VIIa, 4·1 g) in dry pyridine (11 ml) was mixed with benzoyl chloride (5 ml) and left at room temp for 2 days. The product was worked up as usual and chromatographed over neutral alumina (gr.II, 150 g) and eluted with pet. ether–benzene (1:1) to furnish the acetoxy-benzoate (VIIb, 5·4 g) whose IR spectrum showed complete absence of hydroxyl group and was directly used in the next step.

Pyrolysis of the acetoxy-benzoate (VIIb). The acetoxy-benzoate (5·3 g) was pyrolysed for 20 min at 220° and 30 mm press. and completely distilled over at a lower press. The distillate which was contaminated with benzoic acid was saponified by refluxing with excess alcoholic potash (50 ml, 10%)

* Authentic specimen was kindly supplied by Mr. A. S. Bawdekar of our laboratory who prepared tetrahydrocostal by oxidizing costol with MnO_2, followed by hydrogenation.

for 1 hr, as the IR spectrum of an aliquot freed from benzoic acid by chromatography showed that the pyrolysis had proceeded in the desired direction. The product was worked up as usual to furnish the crude alcohol (2·73 g) which was chromatographed over neutral alumina (gr.II, 70 g).

Fraction I eluted with pet. ether (150 ml) was a hydrocarbon (860 mg) which was further purified by chromatography to furnish the conjugated diene (XIII), b.p. 120°(bath)/3·5 mm, $(\alpha)_D^{26}$ +80·18° (*c*, 2·7), n_D^{26} 1·5250; λ_{max} 238 mμ, (ε 19,720), 243 mμ (21,800), 248·5 mμ (ε 20,710) and 254 mμ, (ε 15,000); ν_{max} 2755(w), 1618(w), 1647(m), 886(s), 820(m), 762(s) cm^{-1}. (Found: C, 88·01; H, 11·62. $C_{15}H_{24}$ requires: C, 88·24; H, 11·76%). Fractions 2 and 3 (390 mg) eluted with pet. ether (500 ml) were not further investigated.

Fractions 4, 5 and 6 (690 mg) containing the required alcohol (XI) and eluted with pet. ether–benzene (500 ml, 1:1) had comparable IR spectra. Ether (200 ml) eluted mostly polymeric material which was distilled to furnish more alcohol (290 mg). The combined materials were mixed and rechromatographed over neutral alumina (gr.II, 30 g).

Fractions 1 and 2 eluted with pet. ether–benzene (2X50 ml; 1:1, 224 mg) showed $(\alpha)_D^{27}$ +1·53 and +6·3° and were presumably impure alcohol. The latter three fractions eluted with pet. ether–benzene (3X75 ml, 1:1, 472 mg) having identical optical rotations and IR spectra were combined and distilled to furnish the synthetic alcohol (XI, 430 mg), b.p. 105°(bath)/0·2 mm, n_D^{26} 1·5133 $(\alpha)_D^{26}$ +11·55°; ν_{max} 3400, 1037 (primary hydroxyl group), 1647, 903 cm^{-1} (end methylene double bond). The purity as estimated from GLC was 95%. It gave only a liquid 3,5-dinitrobenzoate (Found: C, 80·89; H, 11·63. $C_{15}H_{26}O$ requires: C, 81·08; H, 11·71%).

Hydrogenation of the synthetic alcohol (XI). The synthetic alcohol (XI, 150 mg) in methanol (20 ml) was stirred with PtO_2 (20 mg, pre-reduced) in an atm. of H_2. Absorption ceased after 1·12 equivs H_2 were absorbed. The dihydro-alcohol purified by chromatography over neutral alumina (gr.II, 5 g) showed b.p. 103°(bath)/0·2 mm and $(\alpha)_D^{27}$ +12·6° (*c*, 6·8). Its IR spectrum was identical with that of an authentic sample of tetrahydrocostol (Found: C, 80·65; H, 12·64. $C_{15}H_{28}O$ requires: C, 80·37; H, 12·59%).

Tetrahydrocostol (XII). Authentic costol isolated from costus root oil was hydrogenated to tetrahydrocostol with PtO_2 in absolute methanol and purified by chromatography. The authentic sample showed $(\alpha)_D^{27}$ +14·5° (*c*, 12), (Found: C, 80·81; H, 12·53. $C_{15}H_{28}O$ requires: C, 80·37; H, 12·59%).