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CHEMISTRY OF TERMINALIA SPECIES—IX*

THE STRUCTURE OF METHYL ANHYDRO TOMENTOSATE

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Abstract—Methyl triacetyltomentosate by loss of water (1 mole) with $POCl_3$–pyridine yields methyl anhydrotomentosate which is not identical with methyl dehydroarjunolate. The anhydro compound yields a molecule of formaldehyde in OsO_4–$Pb(OAc)_4$ oxidation, establishing an exocyclic double bond, probably situated at C-20 through a methyl shift. It suffers facile catalytic reduction to give methyl dihydroanhydrotomentosate which resembles methyl asiatate in m.p., m.m.p., and lactonization but a comparison of their IR spectra reveals that probably inversion at C-19 has taken place during the Wagner–Meerwein methyl rearrangement.

The dehydration of methyl triacetyltomentosate (I, R = Ac) with $POCl_3$–pyridine, recorded earlier, takes place in a manner different from the course noticed with methyl siaresinolate by Barton *et al.*[2] Instead of methyl dehydroarjunolate (II), an isomeric compound, named methyl anhydrotomentosate (III), is formed by loss of a molecule of water. This compound retains half a molecule of water even after careful purification over chromatographic alumina, azeotropic distillation with sodium-dry benzene and drying at 110° at 0·1 mm. Its reactions suggest the presence of an exocyclic double bond (tetranitromethane—prominent yellow) which is readily reduced with Pt–H_2 under ordinary pressure and temperature, to methyl dihydroanhydrotomentosate (V; tetranitromethane—very pale yellow).

The position of the double bond is established by the following series of reactions:

The action of osmium tetroxide on methyl triacetylanhydrotomentosate (IV) yields a glycol (VI) which on oxidation with lead tetra-acetate yields formaldehyde detected by the formation of a dimedone derivative. The resulting compound is a ketone (VII) with strong absorption at 1705 cm^{-1} characterstic of a cyclohexanone unit in the molecule[3] and the peak at 1740 cm^{-1} in the IR spectrum corresponds to a carbomethoxyl group.

Unequivocal evidence for the presence of a cyclohexanone ring system in VII was provided by $LiALH_4$ reduction of methyl tomentosate (I, R = H) to $2\alpha,3\beta,19\beta,23,28$-pentahydroxy-lean-12-en (VIII) and the corresponding 3,23-isopropylidene-2,28-diacetyl derivative (IX) was subjected to dehydration with $POCl_3$–pyridine as in methyl triacetyltomentosate (I, R = AC). The product (X) exhibited a prominent yellow colour with tetranitromethane in accordance with the behaviour of III. During

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* Part VIII: *J. Ind. Chem. Soc.* **40**, 311, 1963.

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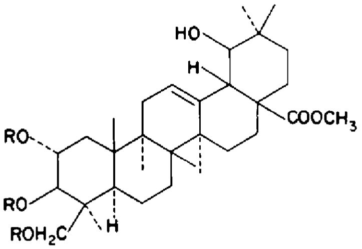
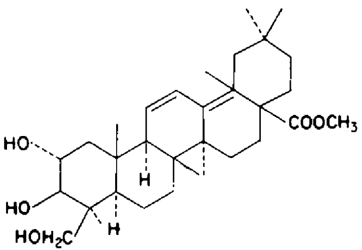
[1] L. R. Row and G. S. R. S. Rao, *Tetrahedron Letters* No. 4, 129 (1962).

[2] D. H. R. Barton, C. J. W. Brookes and N. J. Holness, *J. Chem. Soc.* 278 (1951).

[3] J. R. Ames, J. L. Beaton, A. Bowes and E. R. H. Jones, *J. Chem. Soc.* 1905 (1954).



I



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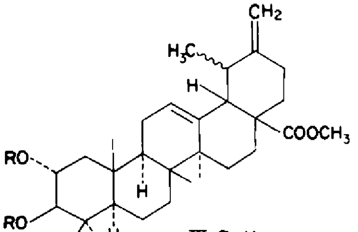
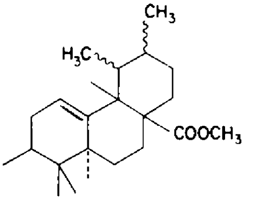
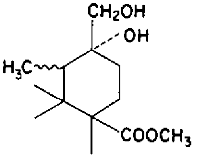


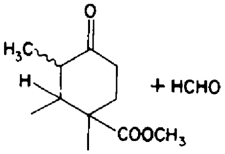
III R = H
IV R = Ac



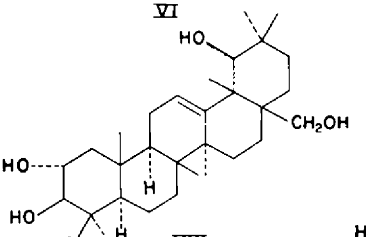
V



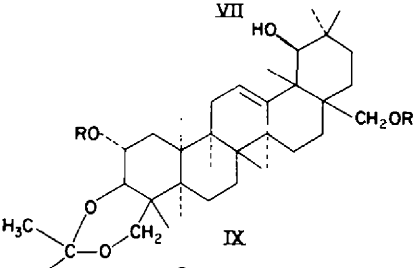
VI



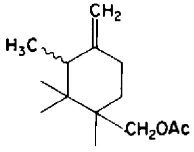
VII



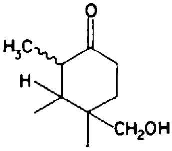
VIII



IX



X



XI

osmium tetroxide–lead tetra-acetate oxidation, X yields formaldehyde and XI, m.p. 198–200° $(\alpha)_D^{30°}$ +41°, which has a prominent C=O peak at 1704 cm^{-1} characteristic of a cyclohexanone ring system.[3] The UV absorption at λ_{max}^{EtOH} 281 mμ (log ϵ 3·988) supports characterization of the molecule as in XI.

The formation of formaldehyde from X and the presence of a cyclohexanone ring system in VII and XI is possible only if the double bond in III is exocyclic as in taraxasterol (XII).[3,4] Like taraxastene (XIII) or ψ-taraxastene,[3,4] IV gives rise to an α,β-unsaturated aldehyde (XIV) (λ_{max}^{EtOH} 251 mμ, log ϵ 4·41) when refluxed with selenium dioxide in glacial acetic acid.

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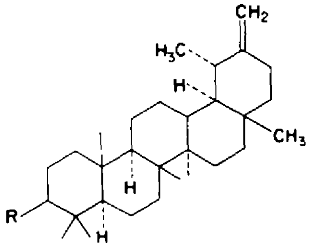
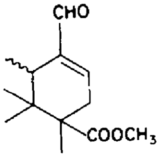
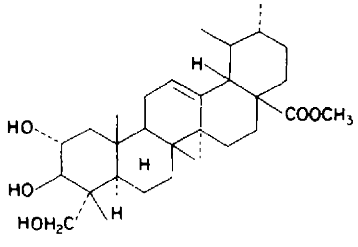
[4] G. Lardelli, Hs. K. Krüsi, O. Jeger and L. Ruzicka, *Helv. Chim. Acta* **31**, 1815 (1949).



XII R=OH
XIII R=H



XIV



XV

The exocyclic double bond in III could have been formed during dehydration involving the 19-hydroxyl of methyl tomentosate (I) and involving a 1,2-methyl shift as shown in chart 1-A.

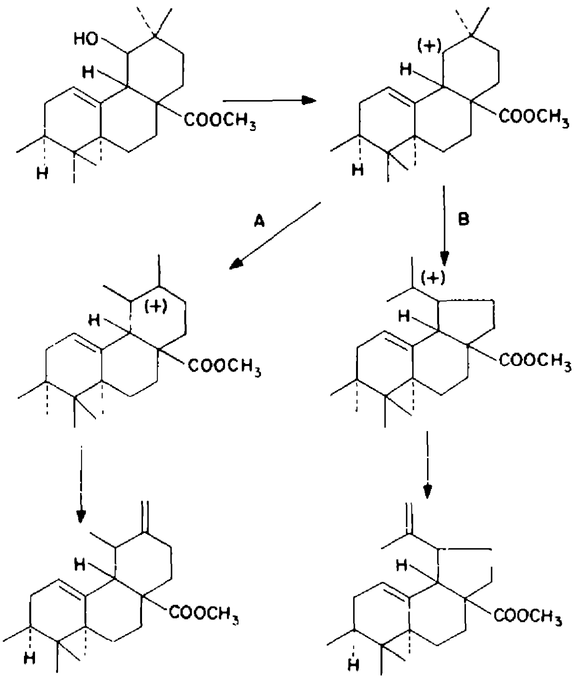


Chart 1

The formation of an α,β-unsaturated aldehyde (XIV) during oxidation of IV as well as the formation of a cyclohexanone ring system during the OsO_4–$Pb(OAC)_4$ oxidation definitely suggests that the methyl shift is not accompanied by a ring contraction (route B[5]). The methyl anhydrotomentosate may, therefore, be formulated as methyl 19(?)-methyl-20-methylene-2α,3β,23-trihydroxyurs-12-en-28-oate (III).

If no inversion takes place at C-19 during the methyl shift, V, obtained by the Pt–H_2 reduction, should be a derivative of ursolic acid in which it has been established beyond doubt that D/E rings are *cis* locked (18β-17β) with 19β-20α-Me groups[6] and should be formulated as methyl 2α-3β-23-trihydroxyurs-12-en-28-oate (XV), identical with methyl asiatate (XV), a dihydroxyursolic acid isolated from *Centella asiatica.*[7]

A comparison with an authentic sample of methyl asiatate was made possible by a kind gift of a specimen by Dr. T. G. Halsall. Like methyl asiatate, the former does not undergo lactonization with HBr–HOAC at room temperature even after 48 hr unlike any hydroxyoleanolic acid. The optical rotations of both are quite close, as well as their melting points. A mixed melting point is undepressed leading to the only probable conclusion that methyl dihydroanhydrotomentosate is identical with methyl asiatate (XV). However, their IR spectra, although quite similar, are not absolutely identical. It is probable, therefore, that the methyl dihydroanhydrotomentosate possesses the epimeric configuration at C19 as a result of inversion during methyl shift. Such inversion at the migration terminus during Wagner-Meerwein rearrangements are fairly common.[8]

EXPERIMENTAL

M.ps are uncorrected. Optical rotations were measured in chloroform unless otherwise stated and the UV absorption spectra recorded in ethanol. The compounds described were all purified by chromatographic adsorption on alumina and before analysis, dried at 100°/0·2 mm for 6 hr.

Methyl triacetylanhydrotomentosate (IV)

Compound I[9] (1·5 g) in dry pyridine (25 ml) was treated dropwise with freshly distilled $POCl_3$ (4 ml). The solution was heated under reflux on an oil bath for 4 hr, cooled and diluted with ice cold water. It was extracted with ether and the extract dried and distilled to remove the solvent. The pale yellow residue (300 mg) in benzene (25 ml) was passed over a column of chromatographic alumina and eluted with benzene–ether (4:1; 200 ml). The eluate was distilled and the residue crystallized from pet. ether (b.p. 40–60°) to give IV as pale yellow microcrystalline powder: m.p. 126–28°. (Found: C, 70·02; H, 8·42. $C_{37}H_{54}O_8$, $\frac{1}{2}H_2O$ requires: C, 69·92; H, 8·66%).

Methyl anhydrotomentosate (III)

Compound IV was refluxed with 2N methanolic KOH on water bath for 3 hr and the product (III) isolated by pouring the solution into water, was crystallized from methanol as colourless needles; m.p. 198–200° depressed to 160–168° by admixture with methyl dehydroarjunolate; $(\alpha)^{30}_{D}$, +30° (*c*, 1·5). (Found in a sample dried at 110° at 10 mm: C, 72·67; 73·01; H, 9·65; 9·80. $C_{31}H_{48}O_5$,$\frac{1}{2}H_2O$ requires: C, 73·08; H, 9·63%). (Sample dried at 150° in Pregl's heater at 150°: C, 73·55; H, 9·88%, loss 1·2%. $\frac{1}{2}H_2O$ requires 1·8%).

Oxidation of methyl triacetylanhydrotomentosate with selenium dioxide

Isolation of 20-*aldehyde* (XIV). Compound IV (500 mg) in glacial acetic acid (50 ml) was refluxed with SeO_2 (600 mg) for 1 hr. The metallic Se was removed by filtration and the product isolated by

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[5] L. Ruzicka, A. Randowski, J. Norymberski and O. Jeger, *Helv. Chim. Acta* **29**, 210 (1946).

[6] E. J. Corey and E. W. Cantrell, *J. Amer. Chem. Soc.* **80**, 499 (1958).

[7] P. Boiteau, A. Buzas, E. Lederer and J. Polonsky, *Bull. Soc. Chim.* **31**, 46 (1949).

[8] D. J. Cram, *Steric Effects in Organic Chemistry* (Edited by M. S. Newman) p. 260 (1956).

[9] L. R. Row and G. S. R. S. Rao, *Tetrahedron* **18**, 827 (1962).

dilution with water. It was deacetylated by hydrolysis with 2N methanolic KOH and the product (XIV) crystallized from ether as colourless needles (350 mg.) m.p. 240–242°, $(\alpha)_D^{29}$, $-174{\cdot}3°$ (*c*, 1·2). λ_{max}^{EtOH} 251 mμ (log ε, 4·4). (Found: C, 72·52; H, 9·62. $C_{31}H_{47}O_6$ requires: C, 72·45; H, 9·24%).

Reaction of methyl triacetylanhydrotomentosate with osmium tetroxide–lead tetra-acetate

Isolation of 20-*ketone* (VII). Compound IV (1·5 g) in dry ether (100 ml) was treated with an ethereal solution of OsO_4 (500 mg) and the mixture, after 4 days at room temp, attained a deep violet colour. The solvent was removed and the osmic acid complex decomposed by refluxing the brown residue with benzene (20 ml), mannitol (2 g) and KOH aq. (30 ml, 4%) on a water for 3 hr. The liquid was reduced to a small volume (red. press., poured into water (100 ml), extracted with ether and the dried ether extract on removal of the solvent deposited the diol (250 mg) which resisted crystallization. It was dissolved in chloroform (4 ml) and glacial acetic acid (20 ml) and then treated with lead tetra-acetate (2·4 g). The resulting solution was left overnight at room temp, briefly heated to 60° and poured into water. The aqueous solution was steam distilled and the distillate (50 ml) collected in aqueous alcoholic dimidone solution (1%) which deposited fine needles m.p. 186–187° undepressed with authentic formaldehyde dimedone derivative.

The aqueous extract (after steam distillation) was extracted with ether, and the dried ether extract deposited a gum on evaporation. It was deacetylated by refluxing for 2 hr with 2N alcoholic KOH and the product purified by chromatography on alumina. It was purified from methanol as pale yellow crystals, m.p. 180–182°, $\lambda_{max}^{CHCl_3}$ 1740 cm⁻¹, 1705 cm⁻¹. (Found: C, 70·26; H, 8·81. $C_{30}H_{44}O_6$,-$\frac{1}{2}H_2O$ requires: C, 70·72; H, 8·84%).

2,19,28-*Trihydroxy*-3,23,0,0-*isopropylidineolean*-12-*ene* (IX, R=H)

The 2,3,19,23,28-pentahydroxyolean-12-ene[9] (m.p. 280–282°) (500 mg) in dry acetone (50 ml) was treated with 3 drops conc. HCl and kept overnight. The pale yellow isopropylidene derivative was purified by passing over chromatographic alumina (30 g) and fractionally eluted with methanol–ether (1:1). Careful crystallization from anhydrous acetone-benzene gave an amorphous powder, m.p. 240° with softening at 170°. $(\alpha)_D^{30°}$, $+23{\cdot}9°$ (*c*, 0·98). (Found: C, 74·32; H, 10·43. $C_{33}H_{54}O_5$ requires: C, 74·71; H, 10·19%).

Acetylation with Ac_2O–pyridine at room temp for 24 hr yielded a diacetate which did not solidify.

Action of $POCl_3$-*pyridine on the diacetyl derivative of* 3,23,0,-*isopropylidenepentol*

Isolation of 20-*keto compound* (XI). The liquid diacetate (200 mg) was refluxed with $POCl_3$–pyridine for 4 hr, poured into water and worked up in the usual way. The crude material (tetranitromethane—deep yellow) was treated with OsO_4 (100 mg) in dry ether (100 ml). After 4 days the OsO_4-complex was decomposed by refluxing with benzene (20 ml), mannitol (4 g) and KOH aq. (20 ml, 4%) for 3 hr. The benzene was removed (red. press.) and the residual liquid extracted with ether. The dry ether extract on removal of the solvent gave the glycol in the form of a liquid (120 mg) which was directly treated with chloroform (4 ml) and lead tetra-acetate (1 g) in glacial acetic acid (20 ml). After 12 hr at room temp, the mixture was steam distilled. The distillate was treated with 1% aqueous alcoholic dimedone solution. After a few min, pale yellow needles separated out, m.p. 184–186° undepressed by dimedone-formaldehyde derivative.

The residue after steam distillation was extracted with ether. The dry ether extract deposited a pale yellowse mi-solid which was refluxed with 8% methanolic KOH. After removal of methanol, it was acidified and the product worked up in the usual way by chromatographic purification. It crystallized from anhydrous acetone–petrol b.p. (40–60°) as colourless micro prismatic crystals. m.p. 196–198° $(\alpha)_D^{30°}$, $+41°$ (*c*, 0·720), $\lambda_{max}^{CHCl_3}$ 1704 cm⁻¹; UV λ_{max}^{EtOH} 281 mμ (log ε 3·988). (Found in a sample dried at 1·0 mm at 100°: C, 74·28; H, 9·58. $C_{33}H_{50}O_5$ requires: C, 74·7; H, 9·73%).

Catalytic reduction of methyl anhydrotomentosate

Methyl dihydroanhydrotomentosate (V). Methyl anhydrotomentosate (250 mg) was shaken with hydrogen in the presence of Adams catalyst, 1 mole H_2 (12 ml) was absorbed rapidly. The reduced compound (250 mg) after repeated chromatography over alumina deposited a solid which crystallized from methanol as colourless needles m.p. 215–216°, with sintering at 198° unchanged by authentic sample of methyl asiatate $(\alpha)_D^{30°}$, $+58°$ (*c*, 0·82). (Found: C, 72·19; H, 9·89. $C_{31}H_{50}O_5$, $\frac{1}{2}H_2O$

requires: C, 72·80; H, 9·98%). With tetranitromethane, only a very pale yellow colour was observed.

The triacetyldihydroanhydrotomentosate (acetic anhydride–pyridine) crystallized from acetone–pet. ether as fine needles; m.p. 126–8°; $(\alpha)_D^{80°}$, +11·9° (c, 1·02).

Attempted lactonization

Methyl dihydroanhydrotomentosate (100 mg) was treated with HBr (66% 10 ml) and acetic acid (10 ml). After 2 days, the product was worked up in the usual way and crystallized from methanol in colourless needles; m.p. 214–216° unchanged by the parent compound.

Acknowledgements—It is a pleasure to thank Profs. T. G. Halsall, Oxford for a sample of methyl asiatate, T. R. Seshadri, Delhi University and N. V. Subba Rao, Osmania University for the IR and UV spectra recorded in this paper. Two of us (G. S. R. S. and T. S. R.) wish to express their grateful thanks to C.S.I.R. and Government of India respectively for fellowships.