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TERPENOIDS AND RELATED COMPOUNDS—XXI[1]

THE STRUCTURES AND STEREOCHEMISTRY OF PUTRANJIVIC ACID AND PUTRANJIC (PUTRIC)* ACID

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Abstract—The structures IIIa and IVa suggested for putranjic and putranjivic acids respectively have been confirmed by the synthesis of methyl putranjivate (IVb) from friedel-3-ene (IX). Putranjic acid has been shown to have *S*-configuration (IIIa) at C_2.

We have reported the isolation and structure elucidation of two new friedelin derivatives, putranjivadione (I)[2] and roxburgholone (II)[3] besides the isolation of friedelin and friedelanol from the trunk bark of *Putranjiva roxburghii*. From the acidic fraction of the trunk bark of the plant Garg and Mitra[4, 5] and Seshadri *et al.*[6, 7] independently isolated an acid, named putranjic (putric) acid* for which both groups suggested the 3,4-seco-friedelin structure (IIIa) on the basis of physical data and chemical transformations. From the leaves of *P. roxburghii* Seshadri *et al.*[8] isolated another acid named putranjivic acid and suggested[9] the structure IVa. These authors[7] also established the relationship between these two acids by transforming each into V. Recently Garg and Mitra[10] isolated yet another acid, named roxburghonic acid from the leaves of the plant and suggested the structure VI. The root bark of *P. roxburghii* has been shown[8b] to contain friedelin, putranjivadione (I), roxburgholone (II) and methyl putranjate (IIIb).

Although the structures of putranjic acid (IIIa)[5, 7] and putranjivic acid (IVa)[9] have been based on NMR and mass spectrometric data, neither of these two acids has been compared with any derivative of friedelin and consequently no assignment could be made regarding the configuration of any asymmetric centre in these acids. In the present communication we report the synthesis of methyl putranjivate (IVb) from friedel-3-ene (IX) thus confirming the suggested structure and establishing the configuration at all asymmetric centres in putranjivic acid (IVa). Since putranjic acid (IIIa) has been correlated with putranjivic acid (IVa), our synthesis also confirms the structure of the former acid and establishes the stereochemistry at all centres except C_2. We show in this communication that C_2 of putranjic acid (IIIa) has the *S*-configuration.

Methyl friedelonate[11] (VII) was the starting material for the synthesis of methyl putranjivate (IVb). As during the formation of VII other products were formed, its purification was difficult and the yield was low. Hence we attempted to prepare VII from the diol VIIIa which had also been previously prepared.[12] from friedel-3-ene (IX)

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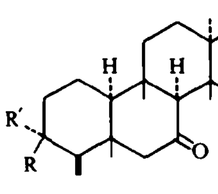
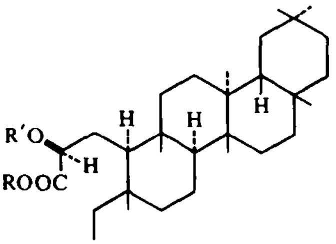
* The name putranjic acid is used in this communication.

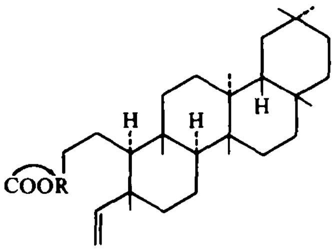
CHART I



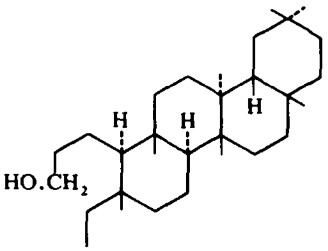
I, $^{R'}_{R}{>}= O$
II, R' = OH, R = H



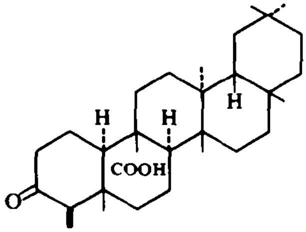
IIIa, R = R' = H
b, R = Me, R' = H
c, R = Me, R' = CS·SMe



IVa, R = H
b, R = Me



V

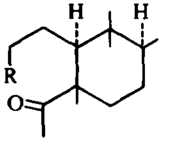


VI

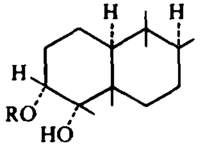
by treatment with osmium tetroxide. By slight modification of this method, we obtained the diol VIIIa, which formed a monoacetate (VIIIb). The NMR spectra of VIIIb shows signals due to the eight tertiary Me groups between δ 0·8 to 1·12 ppm. A three proton sharp singlet due to the acetoxy Me group at C_3 appears at δ 2·05 ppm. A pair of doublets appears around δ 4·88 ($J = 12$ cs) and δ 4·98 ppm ($J = 6$ cs) indicating that the C_3 proton is axially oriented or β. Consequently the acetoxy group at C_3 in the acetate (VIIIb) is equatorial or α-oriented. It is known[13] that hydroxylation of an olefin with osmium tetroxide passes through an osmate ester and can give only a *cis*-glycol system. Hence the hydroxyl group at C_4 in the glycol (VIIIa) or its monoacetate 'VIIIb) is axial or α-oriented.

If the assignment of the above configuration is correct then treatment of VIIIb with phosphorus pentachloride should yield by molecular rearrangement to either glut-5(10)-enyl 3α-acetate (X) or glut-5-enyl 3α-acetate (XI) or both. As no molecular rearrangement took place, the only product isolated in good yield was the enol acetate (XII), which furnished friedelin on base hydrolysis. This was not surprising since in the nonsteroid conformation of Ring A, the β-hydrogen at C_3 and the α-hydroxyl at C_4 are in *anti-peri-planer* orientation necessary for the elimination of a molecule of water. This is also direct evidence for the assigned configuration of the glycol system (VIIIa).

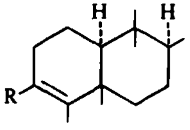
CHART II



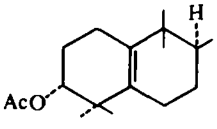
VII, R = COOMe
XIII, R = CHO
XIV, R = COOH



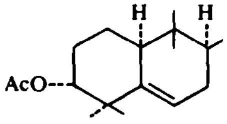
VIIIa, R = H
b, R = Ac



IX, R = H
XII, R = OAc



X



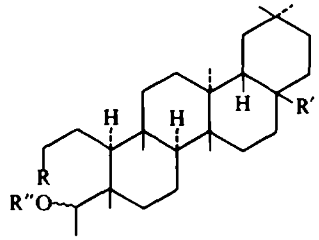
XI

An attempt to cleave the *cis*-diol (VIIIa) with sodium metaperiodate failed probably due to the low solubility of the diol in dioxan. The cleavage was however carried out with lead tetraacetate and the crude ketoaldehyde (XIII) obtained as a gum. It was oxidised to the acid (XIV) and the latter esterified to methyl friedelonate (VII).

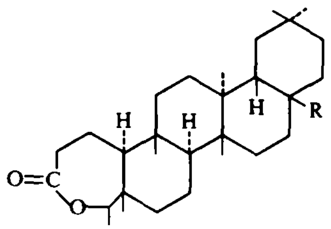
On reduction methyl friedelonate (VII) yielded a mixture (TLC) which by chromatography could be resolved into two components. The less polar component was the epimeric mixture of the desired hydroxyester (XV), m.p. 252–256° with softening at 160°. The IR spectrum shows peaks at 1725 cm^{-1} (COOMe) and 3500 cm^{-1} (OH). The more polar component, $C_{30}H_{54}O_2$, m.p. 212–214° shows the absence of any carbomethoxy peak but has a broad peak at 3400 cm^{-1} due to a hydrogen bonded OH group. Obviously it was the diol (XVI). Govindachari *et al.*[14] reported the isolation of a triol (XVII) by the sodium borohydride reduction of apetalactone (XVIII).

We expected that dehydration of the hydroxyester (XV) would yield methyl putranjivate (IVb), but when the epimeric mixture of the hydroxyester (XV) was treated with phosphorus oxychloride a crystalline solid, $C_{31}H_{52}O_2$, m.p. 108–110°, $[\alpha]_D$ − 3·9° was obtained which was not methyl putranjivate (IVb). The IR spectrum shows peaks at 1745 cm^{-1} (COOMe) and 910 cm^{-1} (tetrasubstituted olefinic linkage). Therefore, a molecular rearrangement had taken place through the dichlorophosphate derivative (XIX) and the final product had the structure XX). The NMR spectrum supports this structural assignment. The six tertiary Me groups gave signals in the

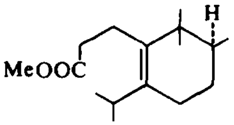
CHART III



XV, R = COOMe, R′ = Me, R″ = H
XVI, R = CH_2OH, R′ = Me, R″ = H
XVII, R = R′ = CH_2OH, R″ = H
XIX, R = COOMe, R′ = Me, R″ = $POCl_2$
XXI, R = COOMe, R′ = Me, R″ = CS·SMe



XVIII, R = CH_2OH



XX

region from δ 0·95 to 1·21 ppm. The presence of a methylene group adjacent to a carbomethoxy group was indicated by a two proton multiplet around δ 2·38 ppm. The carbomethoxy Me signal appeared as a three proton singlet at δ 3·75 ppm. The signals at δ 1·42 and 1·48 ppm were attributed to the two isopropyl Me groups deshielded by the olefinic linkage. Further there was no signal for olefinic proton.

Finally the desired elimination was successfully carried out by Chugaev reaction.[15] The hydroxyester (XV) was converted into the crude methyl xanthate (XXI)[16] which on pyrolysis furnished methyl putranjivate (IVb) identical (mixed m.p., TLC and IR) with natural methyl putranjivate from *P. roxburghii.*

This synthesis also settled the structure and stereochemistry of putranjic acid (IIIa) except the absolute configuration at C_2. It has been reported[16, 17] that the circular dichroism of the xanthates of asymmetric α-hydroxyacids can be utilised for the assignment of configuration at the α-carbon atom. The sign of the Cotton effect curve due to the $n \rightarrow \pi^*$ transition of the C=S moiety of the xanthates of α-hydroxyacids in the region around 350–360 mμ is dependent on the configuration of the asymmetric carbon atom bearing the xanthate group. Thus methyl putranjate (IIIb) was converted to the xanthate (IIIC), which showed a positive Cotton effect CD curve around 360 mμ. Hence C_2 of methyl putranjate has the *S*-configuration as represented in the structure (IIIb).

EXPERIMENTAL

All m.ps are uncorrected. The light petroleum used had b.p. 60–80° unless otherwise stated. Rotations were measured in chloroform. TLC was carried out on silica gel G (E. Merck).

Friedel-3-ene (IX), m.p. 252–254° (TLC single spot) was prepared following the method of Courtney *et al.*[19]

Friedelana-3α,4α-diol (VIIIa).[12] A soln of IX (1·56 g) and OsO_4 (1 g) in pyridine (40 ml) and ether (20 ml) was refluxed for 26 hr. The solvent was removed under reduced pressure to yield a pink residue, which was dissolved in benzene (35 ml) and 95% EtOH (35 ml) and the soln was refluxed for 6 hr after the addition of a soln of mannitol (6·3 g) and KOH (6·3 g) in 95% EtOH (35 ml) and H_2O (15 ml). The mixture was diluted with ether after cooling and the ether layer was washed with H_2O, dried (Na_2SO_4) and evaporated to give a solid, which was chromatographed over a column of silica gel (30 g). Elution with light petroleum gave the starting material (IX) in a very small amount. Further elution with a mixture of benzene and $CHCl_3$ (1:1) yielded a solid which on crystallisation from light petroleum furnished VIIIa (1·25 g), m.p. 235–237°, $[\alpha]_D + 16°$ (TLC single spot).

3-*α-Acetoxy, 4α-hydroxyfriedelane* (VIIIb).[12] The diol VIIIa (0·5 g) was acetylated with Ac_2O (5 ml) and pyridine (5 ml) to furnish after crystallization from acetone pure VIIIb (0·38 g), m.p. 250–252°, $[\alpha]_D - 4·4°$ (TLC single spot). (Found: C, 78·14: H, 11·19. Calc for $C_{32}H_{54}O_3$: C, 78·56: H, 11·18%): IR Peaks at 3600 cm^{-1} (OH) and 1740 and 1245 cm^{-1} (acetoxy): NMR. See Introduction.

Δ^3-*Enolacetate of friedelin* (XII). The monoacetate VIIIb (0·2 g) was added to a suspension of PCl_5 (0·2 g) in dry light petroleum, b.p. 40–60° (20 ml) with shaking. The soln became clear after 35 min, when hot H_2O was added. The mixture was diluted with ether and worked up as usual. The crude solid was charomatographed over a column of alumina (15 g deactivated with 0·9 ml of 10% aq AcOH). Elution with a mixture of light petroleum and benzene (4:1) gave a solid which on crystallization from moist acetone yielded XII, m.p. 238–240°, $[\alpha]_D + 5·8°$ (TLC single spot). (Found: C, 78·77: H, 11·30. $C_{32}H_{52}O_2$, H_2O requires: C, 78·86: H, 11·18%).

Hydrolysis of the enolacetate (XII)

Friedelin. A mixture of XII (0·07 g), benzene (3 ml), 10% MeOH-KOH (2 ml) was refluxed for 4 hr. The crude solid (0·6 g) was chromatographed over activated alumina (7 g). Elution with a mixture of light petroleum and benzene (4:1) furnished a solid, which on crystallization from a mixture of $CHCl_3$ and acetone gave friedelin, m.p. 258–260°, identical (mixed m.p., TLC and IR) with an authentic specimen.

Oxidation of the diol (VIIIa) *with lead tetraacetate*

Methyl friedelonate (VII).[11] Lead tetraacetate (1·5 g) was added to a soln of VIIIa (1·2 g) in dry benzene (150 ml) with stirring for 3 hr. The mixture was diluted with H_2O and the brown ppt was extracted with ether. The ether soln was washed with H_2O, dried (Na_2SO_4) and evaporated to yield a gum, which on chromatography over a column of silica gel (25 g) yielded XIII as a viscous mass (1·3 g) which could not be crystallised. The gum (1·3 g) in acetone (100 ml) was treated with Jone's chromic acid reagent[19] prepared from CrO_3 (4·2 g), conc H_2SO_4 (2·5 ml) and H_2O (20 ml). The crude acid (XIV: 1·1 g) was esterified by treatment with an ethereal soln of CH_2N_2 (from 1·2 g of nitrosomethylurea). The crude methyl ester was chromatographed over a column of alumina (25 g deactivated with 1·5 ml of 10% aq AcOH). Elution of the column with a mixture of light petroleum and benzene (4:1) furnished a solid, which on crystallization from MeOH afforded VII (0·6 g), m.p. 156–158°, $[\alpha]_D \pm 0°$ (lit[11] m.p. 155–157°, $[\alpha]_D -2°$) TLC single spot). (Found: C, 78·89: H, 10·88. Calc. for $C_{31}H_{52}O_3$: C, 78·76: H, 11·09%).

Sodium borohydride reduction of methyl friedelonate (VII)

Hydroxyester (XV) *and diol* (XVI). A soln of VII (0·5 g) in pyridine (30 ml) was added to a suspension of $NaBH_4$ (0·25 g) in cold MeOH (15 ml) containing a drop of N NaOH. The mixture was allowed to stand at room temp for 72 hr and then worked up to yield a partially crystalline mass which showed two spots in TLC and was chromatographed over a column of silica gel (20 g). Elution with a mixture of light petroleum and benzene (1:4) afforded a solid (0·17 g), which on crystallization from light petroleum gave XV as an epimeric mixture, m.p. 252–256° with softening at 160° (TLC single spot). (Found: C. 78·67; H, 11·49. $C_{31}H_{54}O_3$ requires: C, 78·42: H, 11·47%): IR. See Introduction.

Further elution of the column with a mixture of benzene and ether (4:1) furnished another solid (0·07 g), which on crystallisation from acetone gave XVI, m.p. 212–214°, $[\alpha]_D + 2·4°$ (TLC single spot). (Found: C, 80·55: H, 11·99. $C_{30}H_{54}O_2$ requires: C, 80·65: H, 12·18%): IR. See Introduction.

Treatment of the hydroxyester (XV) *wfth phosphorus oxychloride*

Rearranged unsaturated ester (XX). $POCl_3$ (1 ml) was carefully added with shaking to a cold soln of XV (0·1 g) in pyridine (12 ml). The mixture was shaken for 5 min and allowed to stand in an ice bath for 4 hr and then overnight at room temp. It was carefully poured into crushed ice and worked up to give a gum (0·09 g), which was chromatographed over a column of silica gel (6 g). Elution with a mixture of benzene and light petroleum (1:4) furnished a solid, which on crystallization from MeOH yielded (XX), m.p. 108–110°, $[\alpha]_D$ – 3·9° (positive tetranitromethane test and TLC single spot). (Found: C, 81·33; H, 11·25. $C_{31}H_{52}O_2$ requires: C, 81·52; H, 11·48%): IR and NMR. See Introduction.

Chugaev reaction with the hydroxy ester (XV)

Methyl putranjivate (IVb). A soln of XV (0·3 g) in dry thiophene free benzene (60 ml) was added to a suspension of pulverized Na (0·6 g) in benzene (10 ml) and the mixture was refluxed for 5 hr. CS_2 (5 ml) was added and the mixture was refluxed for 5 hr. Then MeI (6 ml) was added and the mixture was refluxed for 5 hr, cooled and filtered. The filtrate was evaporated under vacuum to afford crude XXI (0·28 g) as a partially crystalline solid.

The crude XXI was heated at 220° for 2 hr and then at 300° for 5 hr under 20 mm pressure. The partially crystalline distillate (0·15 g) was chromatographed over a column of silica gel (8 g). Elution with a mixture of light petroleum and benzene (4:1) furnished a solid (0·06 g), which on crystallization from MeOH afforded IVb, m.p. 128–130° identical (mixed m.p., TLC and IR) with an authentic specimen.

Preparation of the xanthate of methyl putranjate (IIIc)

A soln of IIIb (1·0 g) isolated from the bark of *P. roxburghii*[4] in dry thiophene free benzene (120 ml) was added to a suspension of NaH (1·2 g) in benzene (10 ml) and the mixture was refluxed for 6 hr. CS_2 (15 ml) was added and the mixture refluxed for 5 hr. Then MeI (12 ml) was added and the mixture was refluxed for 5 hr. After usual work up IIIc was obtained as an amorphous solid, m.p. *ca* 105°d which showed a positive Cotton effect of low intensity in the CD curve in the region 345–360 mμ.

λ	θ
360–345	+ 41·4°
340–338	+ 21·0°
331	– 7·0°
325	+ 17·3°
320	– 17·3°
316	+ 10·4°
275	– 621·0°
250	– 141·0°

Acknowledgements—We are highly indebted to Prof. Carl Djerassi for the CD curve, to Prof. K. H. Overton and Dr. Nitya Nand for the N.M.R. spectra and to Prof. D. K. Banerjee, Prof. J. N. Chatterjea and Dr. S. C. Pakrashi for the I.R. spectra. We are also indebted to Messrs East India Pharmaceutical Works Ltd., Calcutta for the award of a Research Scholarship to one of us (A.K.D.).

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