BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 46, 569—572 (1973)

Putranjic Acid. Synthesis and Stereostructure

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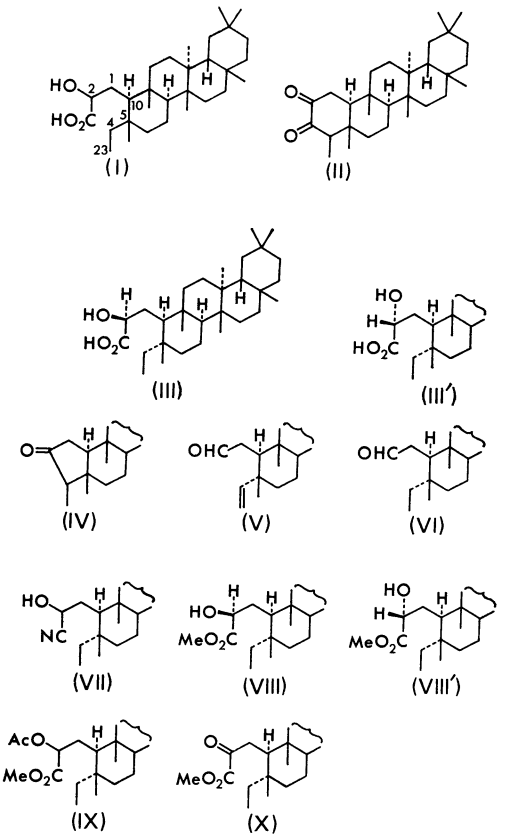
(Received July 6, 1972)

Putranjic acid, isolated from *Putranjiva roxburghii* has been synthesized from friedelane-2,3-dione and has been shown to be (2S)-2-hydroxy-3,4-seco-friedelan-3-oic acid.

Several friedelin derivatives have been isolated from stem-bark, leaves and seeds of *Putranjiva roxburghii* (Euphorbiacea).[1-10] From the acidic fraction of the stem-bark of the plant, Garg and Mitra[1,5] and Seshadri *et al.*[6,8] independently isolated putranjic acid[11] and putric acid, respectively, which were found to be the same triterpene monohydroxy-acid, 2-hydroxy-3,4-seco-friedelan-3-oic acid (I).

1) H. S. Garg and C. R. Mitra, *Phytochemistry*, **7**, 2053 (1968).
2) a) G. R. Chopra, A. C. Jain, and T. R. Seshadri, *Curr. Sci.*, **37**, 301 (1968); *Chem. Abstr.*, **69**, 93685q (1968). b) G. R. Chopra, A. C. Jain, T. R. Seshadri, and G. R. Sood, *Indian J. Chem.*, **8**, 776 (1970); *Chem. Abstr.*, **74**, 1024a (1971).
3) P. Sengupta, A. K. Chakraborty, A. M. Duffield, L. J. Durham, and C. Djerassi, *Tetrahedron*, **24**, 1205 (1968).
4) P. Sengupta and J. Mukherjee, *ibid.*, **24**, 6259 (1968).
5) H. S. Garg and C. R. Mitra, *Tetrahedron Lett.*, **1969** 231.
6) G. R. Chopra, A. C. Jain, and T. R. Seshadri, *Curr. Sci.*, **38**, 101 (1969); *Chem. Abstr.*, **70**, 106704t (1969).
7) G. R. Chopra, A. C. Jain, and T. R. Seshadri, *Indian J. Chem.*, **7**, 1179 (1969); *Chem. Abstr.*, **72**, 67139g (1970).
8) G. R. Chopra, A. C. Jain, and T. R. Seshadri, *Indian J. Chem.*, **8**, 401 (1970); *Chem. Abstr.*, **73**, 45626g (1970).
9) H. S. Garg and C. R. Mitra, *Planta Med.*, **19**, 352 (1971); *Chem. Abstr.*, **75**, 20688g (1971).
10) H. S. Garg and C. R. Mitra, *Phytochemistry*, **10**, 865 (1971).
11) In this paper, we use the name putranjic acid, which was first given by Garg and Mitra to the acid.

The structure of putranjic acid[5,8] has been deduced from spectral and chemical data, although no direct comparison with friedelin derivatives has been made. Thus, the configuration of any asymmetric center in this acid has been left undetermined. In a preliminary communication,[12] we have reported the synthesis of putranjic acid from friedelane-2,3-dione (II). The complete stereostructure of putranjic acid has been shown to be (2S)-2-hydroxy-3,4-seco-friedelan-3-oic acid (III). Detailed experimental data are given below.[13]



Friedelane-2,3-dione (II)[14] was subjected to benzylic acid rearrangement by refluxing with potassium hydroxide in diethylene glycol. The resulting hydroxy-acid was treated with lead tetraacetate in acetic acid to give norfriedelin (IV),[15] which was shown to contain its epimer by glc examination. On treatment with base, the mixture afforded pure norfriedelin (IV). Thus the alkaline unstable component would probably be 4α-methyl epimer of IV.

Norfriedelin (IV) was irradiated with a high pressure mercury lamp in *n*-hexane and converted into 5α-vinyl-10β-formylmethyl-des-A-friedelane (V),[16] which on catalytic hydrogenation gave 5α-ethyl-10β-formylmethyl-des-A-friedelane (VI).[8] The saturated aldehyde (VI) was identical with a product which had been obtained by photoreaction of friedelin.[17]

The saturated seco-aldehyde (VI) was converted into its cyanohydrin derivative (VII), which was further hydrolyzed with hydrochloric acid and acetic acid. On treatment with diazomethane, the reaction products gave two hydroxy-esters (VIII and VIII') and an acetoxy-ester (IX). The hydroxy-esters (VIII and VIII') were separated by silica gel column chromatography into VIII [mp 176.5—177.0°C, $[\alpha]_D^{25}$ −2.0° ($CHCl_3$)] and VIII' [mp 133—134°C, $[\alpha]_D^{25}$ +2.5° ($CHCl_3$)]. The hydroxy-ester (VIII) was identical with methyl putrate (methyl putranjate,[1] mp 176°C, $[\alpha]_D$ −23.5°; methyl putrate,[8] mp 175—176°C, $[\alpha]_D$ −8.3°) with respect to mp, IR, NMR, MS, and tlc. There are some discrepancies between our optical rotation values and those reported by two Indian groups. The disagreements depend on the purity of the samples and on the accuracy of measurement.

The acetoxy-ester (IX) was hydrolyzed with potassium hydroxide and treated with diazomethane to give a mixture of VIII and VIII'. This shows that the acetoxy-ester (IX) consists of an epimeric mixture. The total yields of VIII and VIII' were 23.9 and 21.0%, respectively, from the saturated seco-aldehyde (VI).

Oxidation of VIII and VIII' with the Jones reagent gave the same keto-ester (X) [mp 153°C]; the spectral data were identical with those of methyl oxoputranjate[5] (methyl oxoputrate[8]).

The hydroxy-esters (VIII and VIII') were hydrolyzed with potassium hydroxide in ethanol to give hydroxy-acids, (III) [mp 227.0—227.5°C, $[\alpha]_D^{35}$ +19° ($CHCl_3$)] and (III') [mp 240.0—241.5°C, $[\alpha]_D^{35}$ −1.0° ($CHCl_3$)], respectively. The hydroxy-acid (III) was identical

Table

Acid		$[\alpha]_{Acid}$	$[\alpha]_{Me\text{-}ester}$	$[\alpha]_{Acid} - [\alpha]_{Me\text{-}ester}$
Lactic[18]	S	+ 3.82°	− 8.25°	+12.07°
	R	− 2.26°	+ 7.46°	− 9.72°
Leucic[19,20]	S	+19.4°	−12.5°	+31.9°
	R	−19.4°	+19.2°	−38.6°
I	S	+19° (III)	− 2.0° (VIII)	+21°
	R	− 1.0° (III')	+ 2.5° (VIII')	− 3.5°
Putranjic[1]	S	+ 1°	−23.5°	+24.5°
Putric[8]	S	+21.3°	− 8.3°	+29.6°

12) R. Aoyagi, E. Furukori, Y. Moriyama, T. Tsuyuki, and T. Takahashi, *Chem. Lett.*, **1972**, 451.

13) Sengupta *et al.* recently established the configurations of all asymmetric centers in putranjivic acid (3,4-seco-friedel-4(23)-en-3-oic acid) by synthesis of methyl putranjivate from friedel-3-ene through a lengthy pathway [P. Sengupta and A. K. Dey, *Tetrahedron*, **28**, 1307 (1972)]. The synthesis indicates the establishment of configurations of putranjic acid except C-2 position. The configuration at C-2 of putranjic acid was determined as S by CD measurement of its xanthate; This result is in line with our conclusion.

14) V. V. Kane and R. Stevenson, *J. Org. Chem.*, **25**, 1394 (1960).

15) L. Ruzicka, O. Jeger, and P. Ringnes, *Helv. Chim. Acta*, **27**, 972 (1944).

16) R. Aoyagi, T. Tsuyuki, and T. Takahashi, This Bulletin, **43**, 3967 (1967).

17) F. Kohen, A. S. Samson, and R. Stevenson, *J. Org. Chem.*, **34**, 1355 (1969); R. Stevenson, T. Tsuyuki, R. Aoyagi, and T. Takahashi, This Bulletin, **44**, 2567 (1971).

18) I. Heilbron ed., "Dictionary of Organic Compounds," Vol. 4, 1994 (1965), Maruzen, Tokyo.

19) C. G. Baker and A. Meister, *J. Amer. Chem. Soc.*, **73**, 1336 (1951).

20) C. Fuganti and D. Ghirngheli, *Gazz. Chim. Ital.*, **99**, 316 (1969).

with natural putranjic acid with respect to mp, IR and optical rotation (putranjic acid,[1] mp 218—220°C, $[\alpha]_D$ +1°; putric acid,[8] mp 220—222°C, $[\alpha]_D$ +21.3°). The mixture with an authentic sample showed no melting point depression. While the optical rotation values of these two natural products did not coincide, our value was almost the same as that of Seshadri's group.

Optical rotations of some α-hydroxy carboxylic acids bearing methylene group in β-position and those of their methyl esters are listed in the Table. As a rule, the differences ($\Delta=[\alpha]_{Acid}-[\alpha]_{Me\text{-}ester}$) are positive in *S*-configuration and negative in *R*-configuration. The configuration at C-2 of putranjic acid should therefore be of *S*-configuration. Consequently putranjic acid is shown to be (2*S*)-2-hydroxy-3,4-seco-friedelan-3-oic acid; that is 10β-[(2*S*)-2-carboxy-2-hydroxy]ethyl-5α-ethyl-des-A-friedelane (III).

Experimental[21]

Isolation of Friedelane-2,3-dione (II). The "cork smoker wash solid"[22] was washed with acetone to remove the dark colored impurities and extracted with benzene below 15°C. Evaporation of the benzene gave a dark brown solid, to which hot acetone was added and heated for a while under reflux. The hot suspension was filtered. On cooling the filtrate gave a crude crystal, a 1:1 mixture of friedelin and friedelane-2,3-dione, which was dissolved in benzene and passed through a column of alumina. Friedelane-2,3-dione (II),[14] eluted with ethyl acetate, was crystallized from the same solvent, and showed mp 271—272°C. The content of II was about 30% based on the starting material.

Norfriedelin (IV) from II. A suspension of II (10 g) in diethylene glycol (250 ml) was heated under reflux with potassium hydroxide (10 g) for 4.5 hr under a nitrogen atmosphere. After cooling, water (1 l) was added. Precipitates were collected on a filter paper and washed with water. The dried precipitates were dissolved in acetic acid (1.5 l) and lead tetraacetate (24 g) was added to the solution, which was stirred for two days at room temperature. After destroying the excess lead tetraacetate with ethylene glycol (20 ml), the acetic acid was evaporated to give crude norfriedelin. The product gave one spot on tlc, but was shown to contain a small amount of its C-4 methyl epimer by glc examination (column; Diasolid H-523, 250°C, retention time 31.4 and 28.8 min, respectively). The epimeric mixture was treated with alkali to afford pure norfriedelin with a longer retention time. Recrystallization from acetone gave 6.0 g of norfriedelin (IV),[15] mp 240.5—241.5°C, ν_{max} (Nujol) 1735 cm^{-1}, M^+ 412.

5α-Vinyl-10β-formylmethyl-des-A-friedelane (V) from IV. Norfriedelin (IV, 997 mg) was irradiated with a high pressure mercury lamp in *n*-hexane (700 ml) for 45 hr under an argon atmosphere at room temperature. The reaction products were separated by silica gel column chromatography and an aldehyde fraction was collected and crystallized from acetone to afford 236 mg of 5α-vinyl-10β-formylmethyl-des-A-friedelane (V),[16] mp 162.5—163.5°C, ν_{max} (Nujol) 2700, 1713, 1660, 1000, and 903 cm^{-1}, M^+ 412, NMR ($CDCl_3$) δ 9.70 (t, J=2—3 Hz, -CHO).

5α-Ethyl-10β-formylmethyl-des-A-friedelane (VI) from V. The unsaturated seco-aldehyde (V, 600 mg) was dissolved in ethanol (60 ml) and hydrogenated in the presence of 10% Pd-C (14 mg) for 1 hr at room temperature. The usual treatment and recrystallization from ether gave 5α-ethyl-10β-formylmethyl-des-A-friedelane (VI,[8] 57.4 mg) as needles, mp 181.0—181.5°C, ν_{max} (Nujol) 2720 and 1708 cm^{-1}, no absorption of double bond, M^+ 414, NMR ($CDCl_3$) δ 9.70 (t, J=2—3 Hz, -CHO).

Methyl Putranjate (VIII) and Its Epimer (VIII') from VI. Saturated aldehyde (VI, 50 mg) was dissolved in ethanol (50 ml) and acetic acid (5 ml), and a solution of potassium cyanide (300 mg) in water (1 ml) was added dropwise under stirring at room temperature. The reaction mixture was further stirred for 12 hr and extracted with ether, and the ethereal extract was washed with water. Cyanohydrin (VII) was separated from the starting material (VI) by silica gel column chromatography. Without further purification, it was dissolved in a mixture of acetic acid (30 ml) and concentrated hydrochloric acid (3 ml). This was heated under reflux for 1 hr and after the usual work-up the reaction product was treated with diazomethane in ether and chromatographed on silica gel (50 g) to give three compounds. Fractions, first eluted with benzene, gave 13.6 mg of *O*-acetyl-ester (IX), ν_{max} (Nujol) 1750, 1225, 1078, and 1058 cm^{-1}, M^+ 516, NMR (CCl_4) δ 3.76 (s, $-COOCH_3$), 2.11 (s, $-OCOCH_3$). This fraction gave one spot on tlc.

A second product was collected by further elution of the same solvent. On recrystallization from methanol–water, 3.3 mg of VIII' was obtained, mp 133—134°C, $[\alpha]_D^{25}$ +2.5° (*c* 1.0, $CHCl_3$), ν_{max} (Nujol) 3520, 1708, 1065, and 1025 cm^{-1}, Found: C, 78.16; H, 11.22%. Calcd for $C_{31}H_{54}O_3$: C, 78.42; H, 11.47%. M^+ 474 (the fragmentation pattern was the same as that of VIII), NMR (CCl_4) δ 3.78 (s, $-COOCH_3$).

Further elution with the same solvent gave methyl putranjate (VIII). Recrystallization from methanol–water gave 6.0 mg of VIII, mp 176.5—177.0°C, $[\alpha]_D^{25}$ −2.0° (*c* 0.80, $CHCl_3$), ν_{max} (Nujol) 3530, 1730, and 1100 cm^{-1}, Found: C, 78.21; H, 11.48%. Calcd for $C_{31}H_{54}O_3$: C, 78.42; H, 11.47%. M^+ 474, NMR (CCl_4) δ 3.78 (s, $-COOCH_3$), 3.95 (t, J=5.5 Hz, -CHOH).

Acetoxy-ester (IX, 13.6 mg) was hydrolyzed with potassium hydroxide (20 mg) in ethanol (30 ml) at 40°C for 4 hr. The hydrolysate was treated with diazomethane in ether and separated by silica gel chromatography to give VIII (5.9 mg) and VIII' (7.2 mg) after recrystallization. Thus, the total yields of methyl putranjate (11.9 mg) and its epimer (10.9 mg) were 23.9 and 21.1%, respectively, based on the saturated aldehyde (VI).

Putranjic Acid (III) and Its Epimer (III') from VIII and VIII'. Methyl putranjate (VIII, 50 mg) and potassium hydroxide (10 mg) in ethanol (30 ml) were warmed at 40°C for 4 hr. The acid, after being acidified with hydrochloric acid, was extracted with ether and recrystallized from methanol–water, giving 47.5 mg of putranjic acid (III), mp 227.0—227.5°C, $[\alpha]_D^{35}$ +19° (*c* 0.38, $CHCl_3$) ν_{max} (Nujol) 3520 and 1720 cm^{-1}.

The epimeric acid (III', 35 mg) was obtained from VIII' (40 mg) by the same procedure, mp 240.0—241.5°C, $[\alpha]_D^{35}$ −1.0° (*c* 0.38, $CHCl_3$), ν_{max} (Nujol) 3430 and 1703 cm^{-1}.

Methyl Putranjate (VIII) from Putranjic Acid (III). To putranjic acid (18 mg) in ether (10 ml) was added diazomethane in ether. After evaporation the residue was chromatographed and recrystallized from methanol–water to

21) All melting points were determined on a hot block and uncorrected. IR and mass spectra were measured using Hitachi EPI-G2 and Hitachi RMU-6 spectrometers. NMR spectra were taken on a Hitachi Model R-24 NMR spectrometer at 60 MHz, using TMS as an internal standard. Tlc was carried out on silica gel G (E. Merck).

22) R. Stevenson, *J. Org. Chem.*, **26**, 2142 (1961).

yield methyl putranjate (VIII, 16 mg). Mp, IR, and tlc were identical with those of the authentic sample.

By the same procedure the epimeric acid (III') was converted into the ester (VIII').

Methyl Oxoputranjate (X) from VIII and VIII'. Methyl putranjate (VIII, 11.0 mg) was dissolved in acetone at 0—5°C and the Jones reagent (7 ml) was added dropwise with stirring for 1.5 hr. The reaction mixture was extracted with ether and the ethereal extract was washed with water. Distillation of the solvent and recrystallization from methanol gave methyl oxoputranjate (X, 10.0 mg) as white needles, mp 153°C, ν_{max} (Nujol) 1750, 1730, and 1083 cm^{-1}, Found: C, 78.52; H, 10.83%. Calcd for $C_{31}H_{52}O_3$: C, 78.76; H, 11.09%. NMR (CCl_4) δ 3.80 (s, $-COOCH_3$), 2.65 (q, $-CO-CH_2-$), 1.88 (t, J=6 Hz, C-10 H).[23]

The epimeric hydroxy-ester (VIII') gave the same oxidation product (X) by the same reaction procedure.

The authors wish to thank Professor T. R. Seshadri for the generous gift of the authentic sample of methyl putrate, and Professor C. R. Mitra for the authentic sample of putranjic acid. The authors are also grateful to the Ministry of Education for a grant-in-aid.

23) Lit. methyl oxoputranjate,[5] mp 148—149°C, NMR δ 1.9 (t, J=5.5 Hz, 1H), 2.75 (q, J=5.5 and 4.5 Hz, 2H: methyl oxoputrate, mp 152—154°C, $[\alpha]_D$ +24.0°, ν_{max} (KBr) 1760 cm^{-1}, NMR (CCl_4) δ 3.82, 2·67 (q), 1.9 (t, J=5 Hz).