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LEWIS ACID CATALYSED REARRANGEMENT OF TRITERPENOIDS

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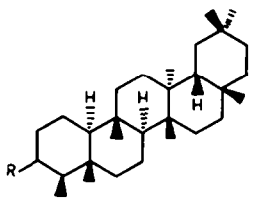
Abstract—From the whole plant of *Opuntia vulgaris* Mill (Cactaceae), four known triterpenoids friedelin, friedelan, 3α-ol, taraxerone and taraxerol, have been isolated. Friedelan 3β-ol and friedelan-3α-ol undergo a novel rearrangement with boron tribromide. Taraxeryl-acetate gives the expected β-amyrin acetate which undergoes further reactions to δ-amyrin acetate. Friedelan 3β-ol rearranges on treatment with boron trifluoride to give mainly olean 13 (18)-ene and olean 12-ene, together with an unexpected epimeric product. Mechanisms are suggested for these various reactions.

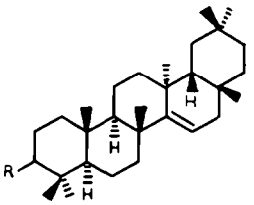
Opuntia vulgaris Mill (Family: Cactaceae) is a wild thorny tree which has been claimed as useful in the treatment of snake-bite in the indigenous system of Indian medicine.[1] A chemical investigation on this cactus was first carried out by Govindachari *et al.*[2] who reported the presence of sito-sterol. During reinvestigation of the whole plant four triterpenoids, viz. friedelin **1**, friedelan 3α-ol **2**, taraxerone **4** and taraxerol **5** have been isolated. Incidentally this is the first report of the occurrence of such triterpenoids in the genus Opuntia.

BF_3 Catalysed isomerisation, transformation and condensation reactions[3] are well known. This reagent has been employed successfully for the conversion of epoxy compounds to the corresponding ketones in steroids[4,5] and terpenoids.[6,7] Recently in our laboratory a contrathermodynamic isomerisation of double bond in isopropyl chain of osthol[8] with Lewis acid has been observed.

In the present communication we report some of the Lewis acid-catalysed rearrangements involving interconversion of various members of oleanane group of pentacyclic triterpenes and the formation of oleanane skeleton from the compounds belonging to friedelane and taraxerane series.



1 R = O
2 R = α OH
3 R = β OH



4 R = O
5 R = OH
6 R = OAc

Taraxeryl acetate **6** on treatment with BF_3-etherate in dioxane and BBr_3 in methylene chloride furnished β-amyrin acetate **8**, $C_{32}H_{52}O_2$, m.p. 225–6°, $[\alpha]_D$ + 81.6°. The mass spectrum of the reaction product in addition to the molecular ion peak at *m/e* 468 showed significant ion fragments at *m/e* 218, 203 and 189 suggesting its identity with β-amyrin acetate which was confirmed by direct comparison (mixed m.p., co-TLC and superimposable IR spectra) with an authentic sample.

The reaction of β-amyrin acetate **8** with BF_3-etherate in dioxane gave a complex mixture which was resolved by column chromatography over silica gel. The least polar component was δ-amyrin acetate **11** $C_{32}H_{52}O_2$, m.p. 200–2°, $[\alpha]_D$ − 34° identified by comparison with an authentic sample (mixed m.p., co-TLC and superimposable IR spectra).

Further elution with petrol-benzene mixture gave an alcohol $C_{30}H_{50}O$, m.p. 160–5°, $[\alpha]_D$ + 88.4°. Its IR spectrum showed a broad band at 3340 cm^{-1} and a sharp peak at 850 cm^{-1} attributable to a hydroxyl and a trisubstituted double bond. NMR spectrum showed an overlapping multiplets in the region δ 0.8 to δ 1.4 which was assigned to eight tertiary methyl groups and a clear doublet at δ 4.9 (1H) due to olefinic proton at C_{12}. The compound was shown to be β-amyrin **9** by direct comparison with an authentic specimen and the cracking pattern of the molecule in the mass spectrometer was exactly the same as that of β-amyrin.

β-Amyrin acetate **8** reacted spontaneously with BBr_3 in methylene chloride as monitored by TLC and changes in specific rotation. The reaction was completed within 45 min. On chromatography of the reaction product on silica gel, δ-amyrin acetate **11** appeared in the first fraction of the eluates.

Since δ-amyrin acetate **11** is formed from taraxeryl acetate **6** by prolonged treatment with both Lewis acids and mineral acids it is proved that the double bond at 13:18 position in β-amyrane skeleton is thermodynamically more stable than that at 12:13 position.

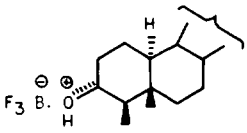
The reaction of friedelan 3β-ol **3** with BF_3-etherate in dioxane gave a complex mixture which was separated by chromatographic resolution over silica gel. The first compound eluted was a crystalline hydrocarbon $C_{30}H_{50}$, m.p. 202–4°, $[\alpha]_D$ − 12.3°, shown to be olean 13 (18)-ene **12** from spectral data and comparison with an authentic sample prepared by the method described by Corey and Ursprung.[11] It exhibited only end absorption (UV) while in the IR spectrum a sharp band appeared at 940 cm^{-1} indicative of a tetrasubstituted double bond. In the NMR spectrum of the hydrocarbon **12** two non-equivalent tertiary methyl groups at C_{14} and C_{17} exhibited two overlapping doublets (6H) centered at δ 1.38 and 1.43 respectively. Protons of other six tertiary methyl groups resonated in the region δ 0.9–1.28. The mass spectral fragmentation pattern of the hydrocarbon is in comformity with the structure **12**. Besides the molecular ion peak

at *m/e* 410, other significant fragmentations at *m/e* 205 ($M^+ - 205$, 100%) and *m/e* 189 ($M^+ - 221$) were formed by retro Diels–Alder cleavage of ring C.

On further elution another hydrocarbon $C_{30}H_{50}$, m.p. 136°, $[\alpha]_D$ +92° migrated and it was identified as olean 12-ene **10**. The compound showed in its IR spectrum a sharp band at 855 cm^{-1} characteristic of a trisubstituted double bond. The NMR spectrum displayed an unresolved multiplet centered around δ 4.89 due to the olefinic proton at C_{12}. The assignment of this double bond at 12:13 position received confirmation from mass spectral fragmentation pattern, *m/e* 218 (100%), 203, 189.

Later fractions of the eluates furnished friedelan 3α-ol **2** as the minor product identified by conventional procedure.

It is pertinent in this connection to discuss the mode of formation of olean 12-ene **10** and olean 13 (18)-ene **12** from friedelan 3β-ol **3**. The latter with BF_3-etherate forms an ion pair sheathed in a cage of solvent[10] and this carbonium ion **7** appears to be the initiator of a series of methyl and hydride shifts to give the products **10** and **12**. However, the formation of the epimer **2** in this reaction is not clear because the step at which the hydroxyl group is lost is not known. It seems probable that water molecule attacks at C_3 from unhindered equatorial site before the hydride shift occurs.



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Studies on the conformation of friedelan 3β-ol **3** and friedelan 3α-ol **2** showed that the axial C_3–OH in **3** where strong nonbonded 1,3-diaxial interaction is observed should be prone to facile epimerisation to yield the thermodynamically more stable friedelan 3α-ol **2** where this strain is found to be absent.

Supporting evidence for the above conclusion is provided by the reaction of friedelan 3α-ol **2** with BF_3-etherate. The former did not furnish any C_3-epimer rather it followed a different pathway undergoing a skeletal rearrangement to olean 13 (18)-ene **12** and olean 12-ene **10**.

Reaction of friedelan 3α-ol **2** and friedelan 3β-ol **3** with BBr_3 gave an interesting but unusual reaction product. It was shown to be a crystalline hydrocarbon $C_{30}H_{50}$, m.p. 270–2°. The UV spectrum has no characteristic absorption and the IR spectrum showed an intense peak at 940 cm^{-1}, characteristic of a tetrasubstituted double bond. No resonance signal in the olefinic region was discernible proving thereby that either the double bond in the molecule is absent or it must be tetrasubstituted. The compound was shown to be isomultiflorene **13**. Supportive evidence was provided by the mass spectral fragmentation pattern depicted below. The generation of fragment (a) at *m/e* 243 from isomultiflorene locates the double bond at C_8–C_9.The fragment (b) at *m/e* 231 is due to a retro Diels–Alder decomposition of ring C followed by the cleavage of activated C_{15}–C_{16} bond.[9]

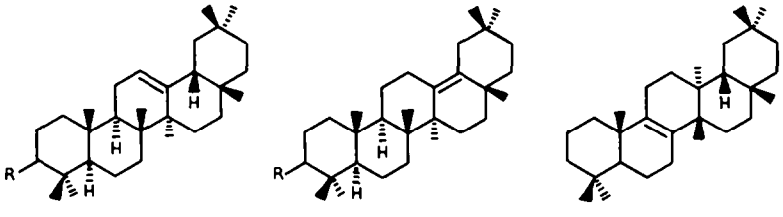
Isomultiflorene **13** arises from friedelan 3α-ol **2** or its C_3-epimer **3** on treatment with BBr_3 involving several rearrangements. The reaction is initiated with the formation of BBr_3 complex with C_3-hydroxyl followed by the hydride shift from C_4 with concomitant elimination of the C_3–OH. Simultaneous migration of C_5-methyl, hydride shift from C_{10}, methyl shift from C_9 to C_{10} and elimination of proton at C_8 complete the formation of isomultiflorene **13** from friedelan 3α-ol **2** or 3β-ol **3**.

EXPERIMENTAL

The m.ps were recorded in a Toshniwal melting point apparatus and are uncorrected. The UV absorption spectra were taken in a Carl Zeiss Universal spectrophotometer (Model VSU-1) in EtOH solution unless otherwise specified, the IR absorption spectra were recorded in a Beckman IR-20 machine in KBr and the NMR spectra were taken in a Varian A-60 spectrophotometer in $CDCl_3$ solution with $SiMe_4$ as internal standard. Petrol refers to the fraction b.p. 60–80°, silica gel (60–100 mesh, Gouri Chemical Works) was used for column chromatography.

Isolation of the neutral constituents of Opuntia vulgaris *Mill*

The dried whole plant of *O. vulgaris* Mill (2 Kg) was extracted with petrol in a Soxhlet apparatus for 72 h. The concentrate afforded a pale yellow solid (0.72 g). The solid was found to be a



8 R = OAc
9 R = OH
10 R = H

11 R = OAc
12 R = H

13

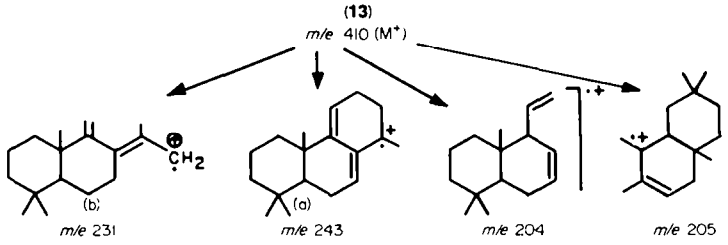


Fig. 1. Mass fragmentation pattern of isomultiflorene **13**.

mixture of four components as indicated from TLC over silica gel impregnated with 12% $AgNO_3$. The solid after chromatography on silica gel yielded, with petrol: C_6H_6 (3:2) as an eluent, friedelin **1** (0.2 g) m.p. 259–60° ($CHCl_3$–MeOH mixture), $[\alpha]_D$ −36° ($CHCl_3$) identical with an authentic sample (m.m.p. and IR) (Found: C, 84.18; H, 11.76. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81%).

Further elution with petrol: C_6H_6 (1:1) gave taraxerone **4** (0.05 g) m.p. 238–39° ($CHCl_3$–MeOH mixture), $[\alpha]_D$ −12° ($CHCl_3$) identical with an authentic specimen (m.m.p. and IR) (Found: C, 84.79; H, 11.36. Calcd. for $C_{30}H_{48}O$: C, 84.84; H, 11.39%). This was further corroborated by potassium borohydride reduction to a compound m.p. 278–280° ($CHCl_3$–MeOH mixture) which was identified as taraxerol (m.m.p., Co–TLC, IR).

On elution with the same solvent a second product, identified as taraxerol **5** (0.1 g) was obtained; m.p. 278–80°, ($CHCl_3$–MeOH mixture), $[\alpha]_D$ +2° ($CHCl_3$) identical with an authentic specimen (m.m.p. and IR) (Found: C, 84.39; H, 11.80. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81%), acetate m.p. 304–5° ($CHCl_3$–MeOH mixture), $[\alpha]_D$ +9° ($CHCl_3$).

Petrol: C_6H_6 (1:2) fraction afforded friedelan 3α-ol **2** (0.02 g), m.p. 295–96° ($CHCl_3$–MeOH mixture), $[\alpha]_D$ +16.1° ($CHCl_3$) which was identified by m.m.p., co-TLC and IR with authentic specimen (Found: C, 83.39; H, 12.21. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.22%).

BF_3-etherate treatment of taraxeryl acetate **6**

A solution of **6** (0.20 g) in dry dioxane (20 ml) was stirred at 60° in presence of BF_3-etherate (0.4 ml) for 15 h. The reaction mixture was diluted with water and extracted with ether. The ethereal layer was washed with water and dried (Na_2SO_4). Removal of solvent afforded a solid (0.15 g) which was chromatographed over silica gel. Elution with petrol furnished β-amyrin acetate **8** (0.10 g), m.p. 225–6° ($CHCl_3$–MeOH mixture), $[\alpha]_D$ +81.6° ($CHCl_3$) (Found: C, 81.84; H, 11.23. Calcd. for $C_{32}H_{52}O_2$: C, 81.89; H, 11.18%), MS: 468 (M^+), 453, 408, 218 (100%), 203, 189, 133 identical with an authentic specimen (m.m.p. and IR).

BBr_3 treatment of taraxeryl acetate **6**

To a solution of **6** (0.20 g) in dry methylene chloride (10 ml), cooled to 0°C, was added dropwise BBr_3 (0.2 ml) for 45 min. The reaction mixture was diluted with cold water and allowed to stand at room temp. for 1 h and then extracted with ether. The organic layer was washed with 2% sodium bicarbonate solution, water and dried (Na_2SO_4). The concentrated mass was chromatographed over silica gel. Elution with petrol gave β-amyrin acetate **8** (0.18 g), m.p. 225–6° ($CHCl_3$–MeOH mixture).

BF_3-etherate treatment of β-amyrin acetate **8**

To a well stirred solution of **8** (0.10 g) in dioxane (10 ml) was added BF_3-etherate (0.2 ml) and the mixture was kept at 60° for 45 h. The reaction mixture was diluted with water and extracted with ether. On usual work-up a solid (0.08 g) was obtained which was chromatographed over silica gel. Elution with petrol: C_6H_6 (4:1) furnished δ-amyrin acetate **11** (0.02 g), m.p. 200–2° ($CHCl_3$–MeOH mixture), $[\alpha]_D$ −34° ($CHCl_3$), (Found: C, 81.76; H, 11.18. Calcd. for $C_{32}H_{52}O_2$: C, 81.99; H, 11.18%).

Elution with petrol: C_6H_6 (1:1) afforded β-amyrin **10** (0.03 g), m.p. 162–65° ($CHCl_3$–MeOH mixture), $[\alpha]_D$ +88.4° ($CHCl_3$), ν_{max}^{KBr} 3340 (OH), 850 (trisubstituted double bond) cm^{-1}, NMR ($CDCl_3$): δ 0.8–1.4 (multiplet), 4.9 (1H, doublet, J = 4 Hz), (Found: C, 84.40; H, 11.79. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81%).

BBr_3 treatment of β-amyrin acetate **8**

To a solution of **8** (0.16 g) in dry methylene chloride (10 ml), cooled to 0°, was added BBr_3 (0.2 ml) dropwise for 45 min. The clear red solution was poured into cold water and the solution was left at room temp. for 1 h. Usual work up yielded a solid (0.10 g) which was chromatographed over silica gel. Elution with petrol furnished δ-amyrin acetate **11** (0.07 g), m.p. 199–200° ($CHCl_3$–MeOH mixture).

BF_3-etherate treatment of friedelan 3β-ol **3**

To a solution of **3** (0.20 g) in dry dioxane (20 ml) was added BF_3-etherate (0.4 ml). The mixture was stirred at 60° for 15 h. Following the same procedure, olean-13 (18)-ene (12) (0.06 g) was purified by chromatography over silica gel with petrol as an eluent. It was crystallised from $CHCl_3$–MeOH mixture, m.p. 202–4°, $[\alpha]_D$ −12.3° ($CHCl_3$), ν_{max}^{KBr} 940 (tetrasubstituted double bond) cm^{-1}, MS: *m/e* 410 (M^+), 395, 218, 205 (100%), 204, 191, 189, NMR ($CDCl_3$): δ 0.9–1.28 (multiplet), 1.38 (3H, singlet), 1.43 (3H, singlet) (Found: C, 87.64; H, 12.22. Calcd. for $C_{30}H_{50}$: C, 87.73; H, 12.27%).

Further elution with petrol: C_6H_6 (1:1) gave a solid (0.05 g) which was characterised as olean-12 ene **10**, m.p. 136° ($CHCl_3$–MeOH mixture), $[\alpha]_D$ +92° ($CHCl_3$), ν_{max}^{KBr} 855 (trisubstituted double bond) cm^{-1}, MS: *m/e* 410 (M^+), 395, 218 (100%), 203, 189, NMR ($CDCl_3$): δ 0.8–1.2 (multiplet), 4.89 (1H, multiplet) (Found: C, 87.58; H, 12.19. Calcd. for $C_{30}H_{50}$: C, 87.73; H, 12.27%).

A third solid (0.03 g) was obtained on elution with petrol: C_6H_6 (1:2) which was characterised as friedelan 3α-ol **2**, m.p. 295–6° ($CHCl_3$–MeOH mixture), $[\alpha]_D$ +16.1° ($CHCl_3$) by comparison with the natural product (m.m.p., co-TLC and IR) isolated from *Opuntia vulgaris* Mill.

BBr_3-treatment of friedelan 3β-ol **3**

BBr_3 (0.5 ml) was added dropwise to a cooled solution of **3** (0.5 g) in dry methylene chloride (50 ml) for 45 min. Working up in the usual manner gave a solid (0.3 g) which was chromatographed over silica gel. The product (0.15 g) obtained on elution with petrol was crystallised from $CHCl_3$–MeOH mixture and identified as iso-multiflorene **13**, m.p. 270–72°, ν_{max}^{KBr} 940 (tetrasubstituted double bond) cm^{-1}, MS: *m/e* 410 (M^+), 243, 231, 205 (100%), 204, NMR ($CDCl_3$): δ 0.8–1.4 (multiplet) (Found: C, 87.69; H, 12.38. Calcd. for $C_{30}H_{50}$: C, 87.73; H, 12.27%).

BF_3-etherate treatment of friedelan 3α-ol **2**

A solution of **2** (0.15 g) in dioxane (10 ml) was treated with BF_3-etherate (0.3 ml) and the mixture was kept at 80° for 24 h, diluted with water and extracted with ether. The crude ether residue (0.12 g) was chromatographed over silica gel. Elution with petrol afforded olean-13 (18)-ene **12** (0.04 g), m.p. 202–4° ($CHCl_3$–MeOH mixture). Further elution with petrol: C_6H_6 (1:1) furnished olean 12-ene **10** (0.04 g), m.p. 136°. Unreacted friedelan 3α-ol **2** (0.02 g), m.p. 295–96° appeared in the petrol: C_6H_6 (1:2) eluates.

BBr_3 treatment of friedelan 3α-ol **2**

To an ice cold solution of **2** (0.20 g) in dry methylene chloride (20 ml) BBr_3 (0.2 ml) was slowly added. After usual work up the crude product was chromatographed over silica gel. Elution with petrol yielded isomultiflorene **13** (0.16 g), m.p. 270–72° ($CHCl_3$–MeOH mixture) identified by conventional procedure (m.m.p., co-TLC and IR).

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REFERENCES

[1]R. N. Chopra, S. L. Nayar and I. C. Chopra, *Glossary of Indian Medicinal Plants*, p. 181. C.S.I.R., New Delhi (1956).
[2]B. Anjaneyule, V. Babu Rao, A. K. Ganguly, T. R. Govindachari, B. S. Joshi, V. W. Kamal, A. H. Manmade, P. A. Mohamed, A. D. Rohimmla, A. K. Saxsena, D. S. Verde and N. Viswanathan, *Indian J. Chem.* **3**(5), 2378 (1965).
[3]A. V. Topchiev, S. V. Zavgorodnii and Ya M. Paushkin, *International series of Mongraphs on Organic Chemistry*, Vol. II. Pergamon Press, Oxford (1959).
[4]H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4596 (1957).
[5]J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **21**, 559 (1965).
[6]D. H. R. Barton, O. C. Brockman and P. de Mayo, *J. Chem. Soc.* 2263 (1960).
[7]H. Henderson and R. Hodges, *Tetrahedron* **11**, 228 (1960).
[8]J. Banerji and R. Rej, *Chem. and Ind.* 529 (1974).
[9]H. Budzikiewicz, J. Wilson and C. Djerassi, *J. Am. Chem. Soc.* **85**, 3688 (1963).
[10]J. H. Brewster, *Ibid.* **78**, 4061 (1956).
[11]E. J. Corey and J. J. Ursprung, *Ibid.* **78**, 5041 (1956).