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Preparation of D:B-Friedoolean-5(10)-en-1-one and Related Compounds. A Comment on the Structure of "Glut-5(10)-en-1-one" from *Euphorbia Nerifolia*[1)]

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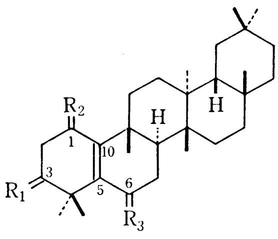
In order to examine the structure, "glut-5(10)-en-1-one", proposed for a new triterpene from *Euphorbia nerifolia*, this ketone (≡D : B-friedoolean-5(10)en-1-one) was prepared. Oxidation of D : B-friedoolean-5(10)-ene with chromium trioxide-pyridine complex gave the allylic oxidation products, D : B-friedoolean-5(10)-en-1-one, D : B-friedoolean-5(10)-en-6-one, and D : B-friedoolean-5(10)-ene-1,6-dione. The spectral data and physical constants of the synthetic ketone (D : B-friedoolean-5(10)-en-1-one) were not identical with those of the new triterpene; this requires revision of the structure of this natural triterpene. Oxidation of D : B-friedoolean-5(10)-en-3-one enol acetate under the same conditions to give D : B-friedooleane-1,5(10)-dien-3-one is also described.

From the stems and leaves of *Euphorbia nerifolia* Linn. (Euphorbiaceae), a new triterpene, $C_{30}H_{48}O$, mp 312—314 °C, $[\alpha]_D$ +50°, was isolated together with 3α- and 3β-hydroxyfriedelanes and taraxerol by Row *et al.*[2)] Based on the spectral data, this new compound was inferred to be a pentacyclic triterpene ketone conjugated with a tetrasubstituted double bond. Catalytic reduction of the ketone into glut-5(10)-ene (**1**≡D : B-friedoolean-5(10)-ene**) and investigation on the UV spectra of both the ketone and its 2,4-dinitrophenylhydrazone led to the conclusion that the new triterpene is glut-5(10)-en-1-one (**2**≡alnus-5(10)-en-1-one≡D : B-friedoolean-5(10)-en-1-one**).[2)]

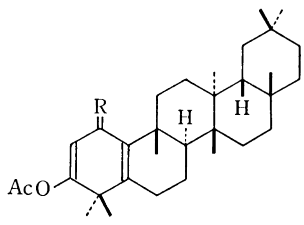
However, the proposed structure for this triterpene is very questionable, because the UV absorption at 218 nm (log ε 3.87) and three weak bands at 880, 840, and 810 cm^{-1} in the IR spectrum described for this compound,[2)] could not be compatible with the proposed structure. In this paper, we describe an unambiguous synthesis of D:B-friedoolean-5(10)-en-1-one (**2**) by oxidation of D:B-friedoolean-5(10)-ene (**1**)[3)] with chromium trioxide–pyridine complex[4)] and that the synthetic triterpene (**2**) is different from the natural one, indicating that the structure for the natural triterpene from *Euphorbia nerifolia* should be revised.

D:B-Friedoolean-5(10)-ene (**1**), prepared by the Huang-Minlon reduction of D:B-friedoolean-5(10)-en-3-one (**3**),[3,5)] was subjected to oxidation with chromium trioxide–pyridine complex[4a)] according to Ratcliffe's modified procedure[4b)] to give a complex mixture, from which two ketones (**2** and **4**) and a diketone (**5**), together with the unchanged starting material (**1**) were isolated by column chromatography on alumina and subsequent separation by preparative TLC on silica gel.

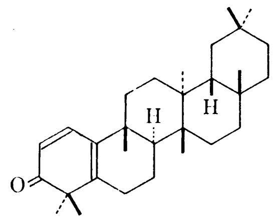
Since the carbonyl moiety in these ketones (**2** and **4**) was shown to be conjugated with a tetrasubstituted double bond from the spectral measurement (*vide infra*), these ketones were inferred to be the allylic oxidation products at C-1 and C-6, respectively. The Huang-Minlon reduction of both **2** and **4** gave the same hydrocarbon as the starting D:B-friedoolean-5(10)-ene (**1**). Thus the position of the tetrasubstituted double bond in both **2** and **4** was determined to be between C-5 and C-10.



1 $R_1=R_2=R_3=H_2$
2 $R_1=R_3=H_2$, $R_2=O$
3 $R_1=O$, $R_2=R_3=H_2$
4 $R_1=R_2=H_2$, $R_3=O$
5 $R_1=H_2$, $R_2=R_3=O$



6 $R=H_2$
7 $R=O$



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The more polar ketone (**2**), $C_{30}H_{48}O$, mp 257.5—259 °C, $[\alpha]_D$ −53°, showed the UV absorption at 249 nm (ε 19100), IR absorption band at 1660 cm^{-1}, and complex signals (4H) due to $-CO-CH_2-$ and $-\overset{|}{C}=\overset{|}{C}-CH_2-$ groupings at δ 2.0—2.7 in the PMR spectrum, while the other (**4**), $C_{30}H_{48}O$, mp 243—245 °C, $[\alpha]_D$ −11°, the UV absorption at 250 nm (ε 10800), IR absorption band at 1655 cm^{-1}, and complex signals (4H) due to $-CO-CH_2-$ and $-\overset{|}{C}=\overset{|}{C}-CH_2-$ groupings at δ 2.0—2.5 in the PMR spectrum. In the PMR measurement using $Eu(fod)_3$-d_{27} for a 7% (w/v) solution of **4** in $CDCl_3$ in a molar ratio (**4**/the shift reagent) of 1:1, two of the four protons which had given the complex signals at δ 2.0—2.5, appeared at δ_A 12.40 and δ_B 11.92 as an AB part of an ABX-type signal, respectively, and *one* proton corresponding to the X-part was also observed at δ_X 6.42. On irradiation at δ_A 12.40 and δ_B 11.92, the signals due to H_X changed into a singlet like and a doublet, respectively. Irradiation at δ_X 6.42 changed the signal due to the AB-part into an AB quartet. These observations confirmed the presence of the grouping $-CO-CH_AH_B-\overset{|}{C}H_X-$ ($J_{AB}=18$, $J_{AX}=12$, and $J_{BX}=6$ Hz) and therefore the less polar

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** In this paper, friedooleanane nomenclature was used.

Table 1. The CD spectral data for the enones (**2** and **4**)

Compound	Observed cotton effect			Predicted sign		
	R-Band	K-Band		Enone helicity	Allylic axial chirality contribution	α'-Axial chirality contribution
2	$[\theta]_{330}+2000$	$[\theta]_{242}-34500$	$[\theta]_{213}+14300$	+	4α-CH_3 (+) 6α-H (−)$^{a)}$ 9β-CH_3 (−)$^{a)}$	2α-H (+)
4	$[\theta]_{350}-3300$	$[\theta]_{268}+1900$	$[\theta]_{225}-15700$	−	1β-H (+)$^{b)}$ 4α-CH_3 (+)$^{b)}$ 9β-CH_3 (−)	7β-H (−)

a) Contribution of 9β-CH_3 and 6α-H may be greater than that of 4α-CH_3.
b) Contribution of 4α-CH_3 and 1β-H may overcome that of 9β-CH_3.

ketone (**4**) could be formulated as D : B-friedoolean-5(10)-en-6-one. Thus the structure of the polar ketone (**2**) was concluded to be D : B-friedoolean-5(10)-en-1-one.

The diketone (**5**), $C_{30}H_{46}O_2$, was identified to be D : B-friedoolean-5(10)-ene-1,6-dione based on the spectral data. This received support by the fact that each of the ketones **2** and **4** gave the same diketone (**5**) on oxidation under the same conditions as above.

The circular dichroism data (Table 1) for the enones (**2** and **4**) could be interpreted by the enone helicity rule[6] for the R-band Cotton effect, and by the allylic axial chirality contribution rule[7] and the α'-axial chirality contribution rule[7] for the K-band Cotton effect.

If an additional double bond is introduced between C-2 and C-3 in the D:B-friedoolean-5(10)-ene framework, it would be expected that the C-1 methylene group might be more susceptible to the allylic oxidation than the C-6 methylene group. D : B-Friedoolean-5-(10)-en-3-one (**3**) was converted into the corresponding enol acetate (**6**), which was subjected to the oxidation under the same conditions as above. However, the expected allylic oxidation product (**7**) could not be obtained, but only a dienone (**8**) was isolated in about 50% yield. The dienone (**8**), mp 217—219 °C, was shown to be identical with D:B-friedooleane-1,5(10)-dien-3-one.[3,8] Goldblum and Mechoulam[9] reported a novel oxidative rearrangement leading to α-benzoyloxy ketones in allylic oxidation of various enol benzoates with sodium chromate in acetic acid. The formation of the 1,5(10)-dien-3-one (**8**) could be explained by the same mechanism as described by Mechoulam.[9]

In conclusion, the spectral data and physical constants of the synthetic ketone, D:B-friedoolean-5(10)-en-1-one (**2**) are clearly shown to be different from those of the natural triterpene*** described by Row *et al.*[2] Therefore the structure proposed for the natural triterpene should be revised.

Experimental

IR spectra were measured using a Hitachi EPI-G2 spectrometer. UV spectra were determined on a Hitachi EPS-3 spectrometer. CD measurements were carried out on a JASCO Model J-20 spectrometer. Optical rotations were measured on a JASCO DIP-SL polarimeter. Mass spectra were taken on a Hitachi RMU-6 Tokugata mass spectrometer with a direct inlet system operating at 70 eV. PMR spectra were measured using a JEOL 4H-100 (100 MHz) or a Hitachi R-20 (60 MHz) spectrometer. Chemical shifts were expressed in δ downfield from TMS as an internal standard, and coupling constants in Hz. HPLC analyses were carried out at room temperature using a Liquid Chromatograph Model ALC/GPC 202/401 (Waters Assoc.) with a UV detector (column: μ-Porasil 1/8 (inch) × 1 (foot); solvent system: 25% CH_2Cl_2–hexane; flow rate: 0.4 ml/min; pressure: *ca.* 500 psi). TLC was carried out on Kieselgel G nach Stahl, Kieselgel GF_{254} nach Stahl, and Kieselgel 60 PF_{254} (E. Merck, Darmstadt). For column chromatography, Wakogel C-200 (Wako Pure Chem. Ind.) and Activated Alumina (Showa Chem.) were used. Melting points were measured on a Mel-temp capillary melting point apparatus (Laboratory Devices) and were uncorrected.

Oxidation of D:B-Friedoolean-5(10)-ene (1). Chromium trioxide (2.5 g) was added to a mixture of pyridine (4 ml) and dichloromethane (70 ml) with stirring for 15 min.[4b)] To the solution, D:B-friedoolean-5(10)-ene[3,5] [**1**; 1.04 g, prepared from D:B-friedoolean-5(10)-en-3-one (**3**)] in dichloromethane (100 ml) was added. The reaction mixture was stirred at room temperature for 21 h. Ether (*ca.* 300 ml) was added and the ethereal layer was washed with 5% aqueous sodium hydroxide solution, 5% hydrochloric acid, and then with saturated aqueous sodium hydrogencarbonate solution, and dried over sodium sulfate. Evaporation of the solvent gave a residue (1.3 g) which was dissolved in petroleum ether, passed through a column of alumina (100 g), and eluted with the following solvents (each 100 ml). Petroleum ether, frs 1—3; benzene, frs 7—15. On evaporation, fractions 1—3 gave the starting material (**1**; 64 mg), fractions 7 and 8 gave a mixture of 1,6-dione (**5**) and 6-one (**4**), and fractions 11—15 gave a mixture of 6-one (**4**) and 1-one (**2**). These mixtures were subjected to separation by preparative TLC (developed with benzene-hexane, 1 : 1) giving rise to **2** (85 mg), **4** (195 mg), and **5** (98 mg).

D : B-Friedoolean-5(10)-en-1-one (2). Mp 257.5—259 °C (recrystallized from ethyl acetate), $[\alpha]_D$ −53° (*c* 0.73, $CHCl_3$); IR (KBr) 1660 cm^{-1}; UV (EtOH) λ_{max} 249 nm (ε 19100); PMR ($CDCl_3$) δ 0.97, 1.05, 1.10, 1.14 (each s, 3H, *t*-Me), 1.00, 1.20 (each s, 6H, 2×*t*-Me), and 2.0—2.7 (4H, complex); CD (*c* 0.094, dioxane): Table 1; MS *m/e* (%) 424 (M^+; 100), 409 (37), 245 (41), 205 (62), 191 (85), 177 (78), and 163 (57); MW Found: *m/e* 424.3756. Calcd for $C_{30}H_{48}O$: 424.3703; Found: C, 85.12; H, 11.24%. Calcd for $C_{30}H_{48}O$: C, 84.84; H, 11.39%.

D : B-Friedoolean-5(10)-en-6-one (4). Mp 243—245 °C (recrystallized from ethyl acetate); $[\alpha]_D$ −11° (*c* 0.83, $CHCl_3$); IR (KBr) 1655 cm^{-1}; UV (EtOH) λ_{max} 250 nm (ε 10800); PMR ($CDCl_3$) δ 0.97, 1.06, 1.10, 1.25 (each s, 3H, *t*-Me),

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***An authentic sample was not available.

1.03, 1.20 (each s, 6H, 2 × *t*-Me), and 2.0—2.5 (4H, complex); CD (*c* 0.102, dioxane): Table 1; MS *m/e* (%) 424 (M^+; 75), 409 (9), 205 (46), and 151 (100); *MW* Found: *m/e* 424.3788. Calcd for $C_{30}H_{48}O$: 424.3703; Found: C, 84.66; H, 11.54%. Calcd for $C_{30}H_{48}O$: C, 84.84; H, 11.39%.

D : B-Friedoolean-5(10)-ene-1,6-dione (5). Mp 236—237 °C (recrystallized from chloroform-methanol); $[\alpha]_D$ −8° (*c* 1.07, $CHCl_3$); IR (KBr) 1680 cm^{-1}; UV (EtOH) λ_{max} 264 nm (ε 9800); PMR ($CDCl_3$) δ 0.98, 1.02, 1.04, 1.13, 1.20, 1.26, 1.28, 1.33 (each s, *t*-Me), and 2.1—2.65 (4H, complex); MS *m/e* (%) 438 (M^+; 100), 314 (39), 205 (50), 123 (74), and 109 (70); *MW* Found: *m/e* 438.3626. Calcd for $C_{30}H_{46}O_2$: 438.3496; Found: C, 82.15; H, 10.87%. Calcd for $C_{30}H_{46}O_2$: C, 82.14; H, 10.57%.

Conversion of D : B-Friedoolean-5(10)-en-1-one (2) and -6-one (4) into D : B-Friedoolean-5(10)-ene-1,6-dione (5). D : B-Friedoolean-5(10)-en-1-one (**2**; 14 mg) in dichloromethane (3 ml) was oxidized with chromium trioxide-pyridine complex[4b)] (chromium trioxide 100 mg, pyridine 0.2 ml, and dichloromethane 2.4 ml) at 30 °C for 5 days. The reaction mixture was worked up as before and a mixture of D : B-friedoolean-5(10)-ene-1,6-dione (**5**) and the unchanged starting material (**2**) was obtained. Although separation of the mixture was not attempetd, HPLC examination showed that the mixture consisted of **5** and **2** (their retention times 24 min and 30 min, respectively) in a ratio of 5 : 1. And the mixture gave an overlapped mass spectrum of **5** and **2** in the same ratio.

D : B-Friedoolean-5(10)-en-6-one (**4**; 18.7 mg) in dichloromethane (3 ml) was treated with the same reagent[4b)] (chromium trioxide 50 mg, pyridine 0.1 ml, and dichloromethane 1.2 ml) under the same conditions as above. After usual treatment, separation by preparative TLC gave D:B-friedoolean-5(10)-ene-1,6-dione (**5**; *ca.* 2 mg) and a minute quantity of the starting 6-one (**4**). The IR spectrum of the former product (**5**) was shown to be identical with that of D:B-friedoolean-5(10)-ene-1,6-dione (**5**).

Wolff-Kishner Reduction of D : B-Friedoolean-5(10)-en-1-one (2) and -6-one (4) under Forced Conditions. D : B-Friedoolean-5(10)-en-1-one (**2**; 15 mg) was treated with diethylene glycol (5 ml), sodium (100 mg), and anhydrous hydrazine[10)] (1 ml) under a nitrogen atmosphere according to the Barton's procedure.[11)] The reaction product was subjected to separation by column chromatography of silica gel (5 g) impregnated with silver nitrate (1.25 g) using petroleum ether as eluent. D : B-Friedoolean-5(10)-ene (**1**; 4 mg) was obtained as the major reduction product and the mp, IR, and MS were all in accord with those of an authentic specimen.

The Wolff-Kishner reduction of D : B-friedoolean-5(10)-en-6-one (**4**; 45.4 mg) was effected under the same conditions as above to give D : B-friedoolean-5(10)-ene (**1**; 10 mg), whose IR spectrum was identical with that of an antheutic sample.

D : B-Friedoolean-5(10)-en-3-one Enol Acetate (6). A mixture of D:B-friedoolean-5(10)-en-3-one (**3**; 170 mg), isopropenyl acetate (12 ml), and *p*-toluenesulfonic acid (40 mg) was heated and distilled slowly. After 2 ml of the solvent was distilled off, the reaction mixture was refluxed for 17 h. Usual treatment gave a residue, which was dissolved in benzene-ether (10 : 1), passed through a column of alumina (5 g), and eluted with the same solvents. Recrystallization from ethyl acetate afforded the enol acetate (**6**; 168 mg), mp 241—243 °C; IR (KBr) 1760, 1210, and 905 cm^{-1}; PMR ($CDCl_3$) δ 2.15 (3H, s; -OAc), 2.76 (2H, d, *J*=4 Hz; $C_{(1)}$-H_2), and 5.31 (1H, t, *J*=4 Hz; C=C-H); MS *m/e* (%) 466 (M^+; 8), 451 (35), 424 (41), 409 (11), 406 (13), 205 (91), 136 (100), 121 (91), and 109 (91); Found: C, 82.39; H, 10.61%. Calcd for $C_{32}H_{50}O_2$: C, 82.35; H, 10.80%.

Oxidation of Enol Acetate (6). D : B-Friedoolean-5(10)-en-3-one enol acetate (**6**; 100 mg) in dichloromethane (12 ml) was treated with the chromium trioxide-pyridine complex[4b)] (chromium trioxide 235 mg, pyridine 0.8 ml, and dichloromethane 12 ml) at room temperature for 1.25 h with stirring. Usual workup and recrystallization from chroloform-methanol afforded D:B-friedooleane-1,5(10)-dien-3-one (**8**; 45 mg), mp 217—219 °C (lit,[3)] 216—217 °C; lit,[8)] 212.5—215 °C); IR (KBr) 1675, 1620, and 812 cm^{-1}; UV (EtOH) λ_{max} 323 nm (ε 5470) [lit,[3)] 322 nm (ε 5500); lit,[8)] 320 (ε 5000)]; PMR ($CDCl_3$) δ 2.3 (2H, m; $C_{(6)}$-H_2), 6.0 and 7.1 (2H, ABq, *J*=10 Hz; $C\underline{H}=C\underline{H}-C=O$); MS *m/e* (%) 422 ($M^+$; 23), 407 (13), 205 (52), and 109 (100).

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