

SHORT COMMUNICATION

11-DEHYDRO (—)-HARDWICKIC ACID FROM *CROTON OBLONGIFOLIUS**

V. N. AIYAR and T. R. SESHADRI

Department of Chemistry, University of Delhi, Delhi-7, India

(Received 20 October 1971)

Abstract—Of the two closely related furanoid diterpenes isolated from the stem-bark of *Croton oblongifolius*, one is a new acid whose constitution has been established as *ent*-15,16-epoxy-3,11,13(16),14-clerodatetraen-19-oic acid and given the trivial name 11-dehydro (—)-hardwickic acid and the second has been identified as (—)-hardwickic acid by spectral and chemical methods.

INTRODUCTION

IN PART III of this series¹ we reported the isolation of the acid *C* from the acidic fraction of the stem-bark of *Croton oblongifolius*. It has now been found by TLC on silica gel G to be a mixture of two compounds having R_f 0.24 and 0.26 (solvents: ethyl acetate–cyclohexane (15:85)) and marked as *C-a* and *C-b*. Separation by preparative TLC was not successful, but by repeated column chromatography and crystallization, *C-a* could be isolated in a pure condition.

Constitution of Acid *C-a*

Acid *C-a*, $C_{20}H_{26}O_3$ (M^+ , 314) was obtained as colourless needles, m.p. 114–115° and $[\alpha]_D -186^\circ$ (in $CHCl_3$). It gave a brown colour in the Liebermann–Burchard test, a purple colour in the Ehrlich reaction (furan ring)² and a yellow colour with the tetranitromethane (unsaturation). It was therefore an unsaturated diterpene acid having a furan ring. Its IR (Nujol) had prominent absorptions at 1678 (α , β unsaturated carboxyl), 1550, 1493, 877, 763 (furan ring),³ 825 (trisubstituted double bond) and 692 (disubstituted double bond) cm^{-1} . UV spectrum (methanol) had maxima at 212 nm ($\log \epsilon$ 3.79) and 280 nm ($\log \epsilon$ 3.72). The former supported the presence of the α , β unsaturated acid and the latter that of a furan ring conjugated with a double bond as in the case of kahweol (I).⁴ NMR spectrum in (C_5D_5N) revealed the presence of two tertiary methyls (δ 0.90 and 1.25 each 3H, s.), a secondary methyl (δ 0.83, 3H, d, J 8.0 Hz), two olefinic protons (δ 6.16 and 6.23 each 1H, s.), one vinyl hydrogen β to the carboxyl (δ 7.16, 1H, t) and protons on a β -substituted furan ring (δ 6.41, 1H, s, 7.41, 1H, m., 7.53, 1H, t.). MS had base peaks at 299 and 83. Other prominent peaks appeared at 281, 219, 149, 105, and 95 besides the mass peak at 314.

With diazomethane, the acid gave a colourless oily methyl ester: reverse saponification took place smoothly at room temperature with 2 N methanolic potash. Lithium aluminium

* Part VII in the series "Chemical Constituents of *Croton oblongifolius*". For Part VI see V. N. AIYAR T. R. SESHADRI, *Indian J. Chem.* 9, 1028 (1971).

¹ V. N. AIYAR and T. R. SESHADRI, *Tetrahedron* 26, 5278 (1970).

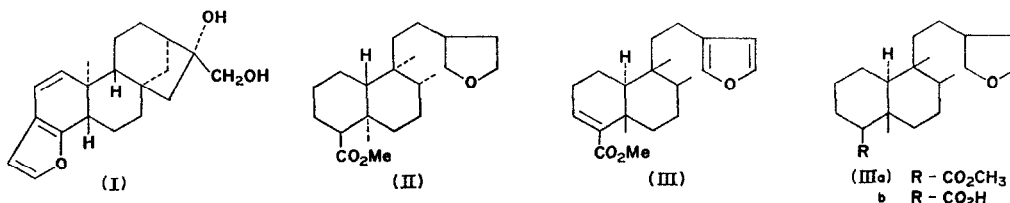
² T. REICHSTEIN, *Helv. Chim. Acta* 15, 1110 (1932).

³ T. KUBOTA, *Tetrahedron* 4, 68 (1958).

⁴ H. P. KAUFMANN and A. K. SENGUPTA, *Chem. Ber.* 96, 2489 (1963).

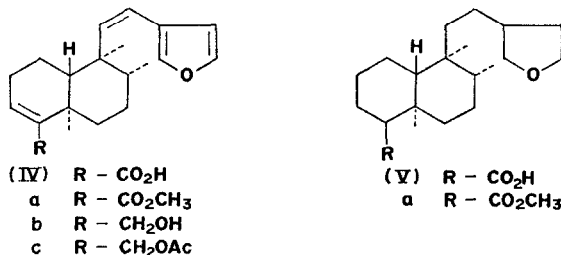
hydride reduction of the acid in dry ether at room temp. gave an oily alcohol. Catalytic hydrogenation of the acid using Pd/C yielded an oily octahydro acid which was devoid of unsaturation. It formed a liquid methyl ester with diazomethane. The cyclohexyl amine salt was prepared by treating the octahydro acid with excess of the base, m.p. 144–145°.

Physical properties of the methyl ester of the octahydro acid *C-a* agreed with those reported⁵ for hexahydro (–)-hardwickic acid methyl ester (II). Direct comparison could not be done due to the non-availability of an authentic sample. However, through the kindness of Professor Marini Bettolo we were able to get the methyl ester of (+)-hardwick acid⁶ (III). The sample on hydrogenation using Pd/C in ethyl acetate yielded the corresponding hexahydro derivative as a liquid. This product and the methyl ester of fully saturated acid *C-a* were identical on TLC and IR. The m.p. and IR spectra of the cyclohexyl amine salts prepared from hexahydro (+)hardwick acid (m.p. 143–144°) and that from fully saturated acid *C-a* were the same. But the mixture of the two in equal quantities had m.p. about 30° higher, a property typical of a racemic compound. Hence the position of the α , β unsaturated carboxyl group and the stereochemistry of the compound have been settled. The position of the second double bond is fixed by the UV absorptions at 280 nm showing that it is in conjugation with the furan ring. Therefore, acid *C-a* could be finally formulated as *ent*-15,16-epoxy-3,11,13(16),14-clerodetetraen-19-oic acid and given the trivial name 11-dehydro (–) hardwickic acid (IV).



Constitution of acid *C-b*

With diazomethane *C-b* formed an oily methyl ester whose mass spectrum showed highest mass peak at m/e 330 which was due to *C-b* methyl ester. In addition, the molecular ion peak of the impurity of *C-a* methyl ester appeared as expected at m/e 328. The base peak at m/e 81 was characteristic and indicated the presence of a furyl ethyl group and is attributed to the fragment $C_5H_5O^+$ (VI).⁷

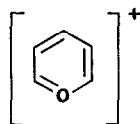


⁵ R. MISRA, R. C. PANDEY and SUKH DEV, *Tetrahedron Letters* 3751 (1964).

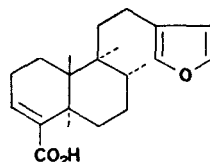
⁶ (a) W. COCKER, A. L. MOORE and A. C. PRATT, *Tetrahedron Letters*, 1983 (1965); (b) F. DELLE MONACHE, E. CORIA, I. LEONCIO, D'ALBUQUERQUE and G. B. MARINI BETTOLO, *Annali Di Chimica*, **59**, 534 (1969).

⁷ C. R. ENZELL and R. RYHAGE, *Arkiv. Kemi* **23**, 367 (1969).

Catalytic hydrogenation of acid *C-b* using Pd/C in ethyl acetate yielded a product which was found to be identical with the octahydro derivative of acid *C-a* (TLC and IR). Hence acid *C-b* (VII) consists essentially of (—)-hardwickic acid.



(VI)



(VII)

EXPERIMENTAL

M.ps are uncorrected. IR spectra were taken using Perkin-Elmer spectrophotometer. Optical rotations were measured in CHCl_3 at 20° . NMR spectra were determined on a Varian A-60 spectrometer using TMS as an internal standard. Light petroleum refers to the fraction $60-80^\circ$.

Isolation of acid C-a (11-dehydro(—)-hardwickic acid) (IV). Acid C (1.500 g) obtained from the acidic fraction of the stem-bark of *Croton oblongifolius* by chromatography was rechromatographed over silica gel (50 g). Elution with cyclohexane-EtOAc (95:5) yielded acid *C-a* (0.420 g) which crystallized from light petroleum- CHCl_3 as stout needles, m.p. $114-115^\circ$ and $[\alpha]_D -186.0^\circ$ (c, 1.139). (Found: C, 76.0; H, 8.0. $\text{C}_{20}\text{H}_{26}\text{O}_3$ requires C, 76.4; H, 8.3%.)

Methyl ester of acid (IV). An ethereal solution of the acid (IV) (0.10 g) was treated with excess CH_2N_2 . Evaporation of the solvent yielded an oily residue (0.080 g) which was dissolved in cyclohexane and passed through a column of neutral alumina (5 g). Evaporation of the eluate gave an oily residue (IVa) $[\alpha]_D -167.5^\circ$ (c, 2.126); $\nu_{\text{max}}^{\text{film}}$ 1709, 1626, 1558, 1493, 876, 826, 784, 763, and 704 cm^{-1} ; NMR ($\text{C}_5\text{D}_5\text{N}$) (δ values): 0.83 (3H, s), 1.22 (3H, s), 2 (tert. CH_3); 0.77 (3H, d., J 8 Hz) (sec. CH_3); 3.69 (3H, s, CO_2CH_3); 6.12 (1H, s), 6.16 (1H, s) ($-\text{H}-\text{C}=\text{C}-\text{H}-$); 6.80 (1H, t, $\text{HC}=\text{C}-\text{CO}_2\text{CH}_3$); 6.37 (s, 1H) (β -proton of the furan ring). 7.40 (m, 1H) and 7.53 (m, 1H) α -protons of the furan ring). (Found: C, 76.3; H, 7.3. $\text{C}_{21}\text{H}_{28}\text{O}_3$ requires C, 76.8; H, 7.9%.)

Saponification of the methyl ester (IVa). The methyl ester (IVa) (0.040 g) was treated with 2 N NaOH in MeOH (5 ml) and kept at room temp. for 12 hr. The MeOH was evaporated and the residue acidified with 2 N HCl (4 ml) and extracted with Et_2O . The Et_2O was washed (H_2O), dried (Na_2SO_4), and on evaporation of the solvent an oil was obtained (0.030 g) which crystallized from light petroleum as colourless cubes, m.p. $110-111^\circ$. It was found to be identical with 11-dehydro (—)-hardwickic acid (m.m.p. and IR).

Reduction of acid (IV). A solution of the acid (IV) (0.100 g) in Et_2O (15 ml) was added to a suspension of LiAlH_4 (0.500 g) in Et_2O (10 ml). The mixture was stirred for 2 hr at room temp. and decomposed with moist Et_2O and H_2O . The Et_2O solution was dried (Na_2SO_4) and evaporated to yield an oil (0.060 g). The oil was dissolved in cyclohexane and passed through a column of neutral alumina (5 g). Evaporation of the eluate gave the alcohol (IVb) as an oil. $\nu_{\text{max}}^{\text{film}}$ 3448, 1497, 1460, 873, 813, 778, 730 and 690 cm^{-1} . (Found: C, 79.4; H, 9.8. $\text{C}_{20}\text{H}_{28}\text{O}_2$ requires C, 80.0; H, 9.3%.) Acetylation of the alcohol (IVb) (0.020 g) by the pyridine (0.5 ml) and Ac_2O (1 ml) method gave an oily acetate (IVc): $\nu_{\text{max}}^{\text{film}}$ 1739, 1563, 1449, 873, 781 and 722 cm^{-1} .

Catalytic hydrogenation of acid (IV). A solution of the acid (IV) (0.200 g) in EtOAc (50 ml) was hydrogenated in the presence of 10% Pd-C (0.300 g) for 8 hr. The catalyst was filtered off, the solvent removed *in vacuo* and the residue (0.17 g) was dissolved in CHCl_3 and passed through a column of neutral alumina. Evaporation of the solvent yielded an oily residue (V); n_D^{25} 1.5130; $[\alpha]_D -32.8^\circ$ (c, 2.214); $\nu_{\text{max}}^{\text{film}}$ 1695, 1449 and 758 cm^{-1} ; NMR (CCl_4) (δ values): 0.70 (3H, s), 1.03 (3H, s), 2 tert. CH_3); 0.76 (3H, d., J 7.5 Hz) (sec. CH_3); 3.20-3.46 (1H, m.), 3.70-4.08 (3H, m.) (α -protons of the tetrahydro furan ring). (Found: C, 74.1; H, 10.2. $\text{C}_{20}\text{H}_{34}\text{O}_3$ requires C, 74.5, H, 10.5%.)

A solution of the octahydro acid (Va) (0.050 g) in acetone (5 ml) was added to cyclohexyl amine (2 ml). The solid separated out of the original clear solution was filtered and crystallized from light petroleum- CHCl_3 mixture as needles, m.p. $144-145^\circ$.

A solution of the acid (V) (0.050 g) in Et_2O (10 ml) was treated with excess CH_2N_2 . The solvent was evaporated and the residue passed through a column of neutral alumina. The methyl ester so obtained was a viscous liquid (Va), n_D^{25} 1.5016; $[\alpha]_D -46.5^\circ$ (c, 2.626); $\nu_{\text{max}}^{\text{film}}$ 1730, 1389 and 758 cm^{-1} ; NMR (CCl_4) (δ values): 0.70 (3H, s), 1.01 (3H, s) (2, tert. CH_3); 0.76 (3H, d., J 8 Hz); 3.65 (3H, s, $-\text{CO}_2\text{CH}_3$); 3.20-3.46 (1H, m.), 3.73-4.07 (3H, m.) (α -protons of the tetra hydrofuran ring). (Found: C, 74.6; H, 11.1. $\text{C}_{21}\text{H}_{36}\text{O}_3$ requires C, 75.0; H, 10.7%.) It was found to be identical with hexahydro (+)-hardwick acid methyl ester (TLC and IR).

Catalytic hydrogenation of (+)-hardwick acid and methyl ester (III). (+)-Hardwick acid methyl ester (0.200 g) in EtOAc (20 ml) was hydrogenated in the presence of 10% Pd-C (0.100 g) for 8 hr and worked up to yield hexahydro methyl ester (IIIa) (0.170 g) $[\alpha]_D^{25} +51.3^\circ$ (c, 1.864). Its IR spectrum was superimposable with that of Vb.

The methyl ester (IIIa) (0.150 g) was hydrolysed using NaOH in MeOH and worked up to yield an oily hexahydro acid (IIIb). The cyclohexylamine salt of IIIb was prepared using acetone and cyclohexylamine m.p. 143–144°. M.m.p. with the salt of V was 180–181°.

Esterification of acid C-b, (–)-hardwickic acid (VII). A solution of the acid (VII) in Et₂O was treated with excess CH₂N₂ the solvent was evaporated leaving an oily residue. MS: 330, 328, 313, 299, 281, 235, 219, 203, 151, 139, 121, 105, 96 and 81.

Catalytic hydrogenation of acid C-b. Acid C-b (0.200 g) in ethyl acetate (20 ml) was hydrogenated in the presence of 10% Pd-C (0.200 g) for 8 hr and worked up to yield an oily residue. It was found to be identical with the octahydro acid (V) (TLC, IR, NMR and specific rotation).

Acknowledgement—The authors are grateful to the Director, CIBA, Bombay for NMR spectra, Director, CDRI, Lucknow for mass spectrum, Professor Marini Bettolo for a sample of (+)-hardwick acid methyl ester, Dr. M. R. Parthasarathyl for helpful discussion and C.C.R.I.M.H. for financial assistance to one of us (V.N.A.).

Key Word Index—*Croton oblongifolius*; Euphorbiaceae; diterpenes; 11-dehydro-(–)-hardwickic acid; (–)-hardwickic acid.