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APACHIN, A NEW SESQUITERPENE LACTONE, AND OTHER XANTHANOLIDES FROM *IVA AMBROSIAEFOLIA**

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Abstract—The structure of *apachin* (2a), a new xanthanolide isolated from an Arizona collection of *Iva ambrosiaefolia* Gray, has been established. Xanthinin (1) and acetylparthemollin (3a) were also obtained from this collection. *Ivambrin* was the only crystalline lactone isolated from a West Texas collection of *I. ambrosiaefolia* and found to be identical with the sodium borohydride reduction product 4 of parthemollin 3b. This is the first report of 3a and 4 as natural products.

A CHLOROFORM extract of *Iva ambrosiaefolia* plant material collected in June, 1968 from Cochise county, Arizona afforded in 0·13 per cent yield the known sesquiterpene lactone xanthinin[1–4] previously isolated from *Xanthium pennsylvanicum.*[1] A second compound obtained in 0·06 per cent yield proved to be a new xanthanolide, which we have named *apachin* (2a): m.p. 80–81·5°, $C_{17}H_{24}O_5$, $[\alpha]_D^{25}$-147°. Finally, a minor constituent (0·03 per cent yield) was found to be identical with acetylparthemollin (3a) which has been described previously as a derivative of the natural xanthanolide parthemollin (3b);[5] this is the first report of 3a as a natural product.

The i.r., NMR and u.v. spectral properties of apachin suggested that it had structural features similar to acetylparthemollin (3a): an α,β-unsaturated γ-lactone ring [i.r. band: 1750 cm^{-1}, u.v. λ_{max} 210 nm (ϵ 14000) and NMR signals: two one-proton doublets at 5·52 δ and 6·23 δ ($J = 3$ c/s for each)]; an acetate group [a three-proton singlet at 2·07 δ and i.r. bands at 1730 and 1230 cm^{-1}]; and one hydroxyl group [i.r. band: 3500 cm^{-1}]. However, certain differences were noted between the NMR spectrum of apachin and the one recorded for acetylparthemollin (3a) (see Table 1). The NMR spectrum of apachin exhibited a six-proton doublet at 1·18 δ ($J = 7$ c/s) suggesting the presence of two secondary methyl groups, while the spectrum of 3a showed only a three-proton doublet in this same region (1·17 δ, $J = 7$ c/s for the C-10 methyl group but, in addition, displayed a three-proton singlet at 2·13 δ for the methyl group adjacent to the ketone function. The spectral

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* Communication XII in the series "Constituents of *Iva* Species" from Florida State University. Previous paper, W. Herz and V. Sudarsanam, *Phytochem.* **9**, 895 (1970).

[1] T. A. GEISSMAN, P. DEUEL, E. K. BONDE and F. A. ADDICOTT, *J. Am. Chem. Soc.* **76**, 685 (1954).

[2] P. G. DEUEL and T. A. GEISSMAN, *J. Am. Chem. Soc.* **79**, 3778 (1957).

[3] L. DOLEJS, V. HEROUT and F. SORM, *Collection Czech. Chem. Commun.* **23**, 504 (1958).

[4] T. E. WINTERS, T. A. GEISSMAN and D. SAFIR, *J. Org. Chem.* **34**, 153 (1969).

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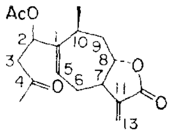
TABLE 1. NMR DATA FOR COMPOUNDS FROM *Iva ambrosiaefolia*

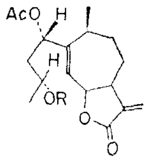
	H_2, H_5, H_6	H_4	H_3	H_7	H_{13}	C_4–Me	C_{10}–Me	Acetyl–Me
2a	5·2–5·7c	3·7c			5·52d ($J = 3$) 6·23d ($J = 3$)	1·18d ($J = 6$)	1·18d ($J = 6$)	2·07
2b	4·7–5·7c			3·04m	5·61d ($J = 3$) 6·30d ($J = 3$)	1·23d ($J = 6$)	1·23d ($J = 6$)	2·03 2·06
3a	5·2–5·9c		2·65m		5·53d ($J = 3$) 6·22d ($J = 3$)	2·13	1·17d ($J = 7$)	2·00
4	5·75m (H-5) 5·49dbr ($J = 10$, H-6) 4·51m (H-2)	4·11c		3·0m	5·59d ($J = 3$) 6·29 ($J = 2·5$)	1·25d ($J = 6$)	1·14d ($J = 7$)	

Spectra were recorded in $CDCl_3$ on a Varian A-60 spectrometer. Values are given in ppm (δ-scale) relative to TMS as an internal standard. Numbers in parenthesis denote coupling constants in c/s. Signals are singlets unless otherwise indicated.

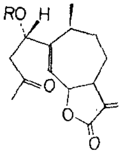
data taken together with the observation that apparently apachin does not contain a ketone function and that the hydroxyl group is acetylatable (see 2b) suggested at once that apachin might be 2a (without stereochemistry at C-4), the C-4 hydroxy analog of 3a. This postulation was confirmed by conversion of apachin to 3a by CrO_3 oxidation.



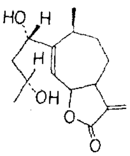
1



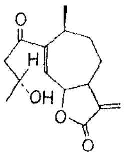
2a R=H
2b R=Ac



3a R=Ac
3b R=H



4



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The *R*-configuration of the asymmetric center at C-4 shown in 2a was determined by the Horeau method:[6] (+)-α-phenylbutyric acid was recovered in 27 per cent yield.

A chloroform extract of *Iva ambrosiaefolia* collected in December 1966 near El Paso, Texas, U.S.A., formed as the only crystalline material (0·13 per cent yield) a sesquiterpene lactone which we have named *ivambrin*. Its m.p, functional groups apparent from physical measurements (see Table 1 and Experimental Section) and its facile oxidation with manganese dioxide to a non-crystalline α,β-unsaturated ketone suggested that ivambrin might be identical with a substance 4 prepared earlier[5] by sodium borohydride reduction of parthemollin (3a). Direct comparison established the correctness of this supposition. This is the first report of 4 as a natural product.

EXPERIMENTAL[*]

Isolation of Xanthinin (1), *Apachin* (2a) *and Acetylparthemollin* (3a) *from* Iva ambrosiaefolia

Dried and ground plant material (1·33 kg) of *Iva ambrosiaefolia* Gray (collected on 6 June, 1968 about 62 miles east of Tucson, on U.S. 10 in the Dragon Mts., Cochise county, Arizona, U.S.A., voucher No. 271988)[†] was extracted with $CHCl_3$ and worked up in the usual way;[7] yield of crude syrup: 70·5 g.

The crude syrup (41 g) was chromatographed over a SiO_2 gel column (1·31 g) which was packed with benzene and was then eluted with 34 fractions (each 125 ml) of benzene–acetone (9:1), all of which were monitored by TLC (SiO_2 gel G).

Fractions 9–12 yielded 2·8 g of crude crystals which, upon recrystallization from 95% EtOH, afforded 505 mg of prisms, m.p. 120–125°, identical in all respects with an authentic sample of xanthinin (1). A second crop (450 mg) of impure xanthinin was obtained upon concentration of the mother liquor.

The residue (1·5 g) obtained from the mother liquor of the second crop was slowly recrystallized from a minimum amount of ethanol containing ether: yield, 180 mg of impure acetylparthemollin (3a),[‡] m.p. 85–90°. A fourth crop of crystals (70 mg) of slightly impure 3a was obtained upon further concentration of the mother liquor: recrystallization of this material from ether afforded analytically pure 3a, m.p. 93·5–95°, whose NMR and i.r. spectra were identical with those of acetylparthemollin.

Fractions 13–18 from the original column yielded an impure mixture of as yet unseparated compounds which appear to be new sesquiterpene lactones by NMR spectrometry.

Fractions 19–29 from the original column were concentrated to an oil which was rechromatographed over a silica gel column (120 g) packed with *n*-hexane–EtOAc (7:3) and eluted with 34 fractions, 125 ml each, of the same solvent.

Fractions 17–26 from the new column yielded 0·7 g crude crystals which, upon recrystallization from isopropyl ether, afforded 434 mg of pure apachin (2a), m.p. 80–81·5° $[\alpha]_D^{25}$ −147° ($CHCl_3$) (C, 0·15%), u.v. (EtOH) λ_{max} 210 nm (ε 14000), i.r. bands ($CHCl_3$): 3500 (hydroxyl), 1750 (carbonyl) and 1245 (acetate) cm^{-1}. [$C_{17}H_{24}O_5$ requires: C, 66·65; H, 7·25; O, 26·10. Found: C, 66·45; H, 7·08; O, 26·55%]. Under standard conditions, apachin gave an acetate (2b), m.p. 58–62° (from isopropyl ether) which had two acetate groups whereas apachin had only one (see Table 1).

Acetylparthemollin (3a) *from Apachin* (2a)

A solution of 50 mg of 2a in 1 ml of acetone was treated with 3 drops of the CrO_3–H_2SO_4 reagent[8] at room temperature. After 30 sec the reaction mixture was diluted with 5 ml H_2O and extracted with 3 × (2 ml each) CH_2Cl_2. The combined extract was washed, H_2O and aq. $NaHCO_3$, and then dried (Na_2SO_4). Evaporation of the solvent and recrystallization of resultant crude crystals from Et_2O yielded 35 mg of 3a, m.p. 93–95°. The specimen was identical in all respects with a sample of natural acetylparthemollin.

Asymmetric Esterification of Apachin (2a) *by the Horeau Method*

Apachin (2a) (44·5 mg) was esterified with 201 mg of (±)-α-phenylbutryic acid anhydride in 1·5 ml of anhydrous pyridine. The resultant mixture was worked up by the standard procedure.[9] Recovered α-phenyl-

[*] All m.ps are uncorrected. Analyses were determined by Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium, Elbach über Engelskirchen, Germany.

[†] Voucher deposited in The University of Texas at Austin Herbarium.

[‡] The crude crystals consisted of a 3:1 ratio of 3a and 1 (by NMR).

[6] A. Horeau, *Tetrahedron Letters* 506 (1961).

[7] T. J. Mabry, H. E. Miller, H. B. Kagan and W. Renold, *Tetrahedron* **22**, 1142 (1966).

[8] C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.* **21**, 1548 (1956).

[9] W. Herz and H. B. Kagan, *J. Org. Chem.* **32**, 216 (1967).

butyric acid (yield 154·1 mg) showed $[\alpha]_D^{25}$ + 3·44° (benzene). A fully stereospecific esterification should give $[\alpha]_D^{25}$ + 12·9°. Therefore, the optical yield was 27 per cent.*

Isolation of Ivambrin (4) *from* Iva aobrosiaefolia

Above ground parts of *Iva ambrosiaefolia* sp. *ambrosiaefolia* Jackson,[10] wt. 5·9 kg, collected near El Paso, Texas, U.S.A. by Drs. W. D. Lloyd and R. Johnson (voucher in herbarium of University of Texas at El Paso), was extracted with $CHCl_3$ and worked up in the usual manner[11] to give 93·3 g of crude gum. The gum was taken up in benzene and chromatographed over 1200 g of SiO_2 (Mallinckrodt 100 mesh), 2 l. fractions of eluate being collected. Fractions 1–25 (benzene), 26–40 (benzene-chloroform (1:1)) and 41–50 (chloroform) gave gums giving several spots on TLC. Fractions 51–59 gave 7·8 g (0·13 per cent) of ivambrin (4) after recrystallization from ethyl acetate. The more polar eluates gave gums.

Ivambrin exhibited the following NMR signals (90 mHz, $CDCl_3$): 6·28 d (J = 2·9 Hz, H-13a) 5·76 m (H-5), 5·57 d (2·9, H-13b), 5·47 dbr (10·6, H-6), 4·59 m (Hz), 4·15 c (H-4), 2·95 c (H-7), 1·22 d (6·5) and 1·12 d (7, two CH–CH_3); mol. wt. (high resolution mass spectrometry) 266·158 calc. for $C_{15}H_{22}O_4$ 266·152; other significant peaks were at 248 ($C_{15}H_{20}O_3$), 233 ($C_{14}H_{17}O_3$), 207 ($C_{12}H_{15}O_3$), 204 ($C_{13}H_{16}O_2$), 203 ($C_{13}H_{15}O_2$), 190 ($C_{12}H_{14}O_2$) and 177 ($C_{11}H_{13}O_2$). The substance melted at 156–157°; the mmp with the $NaBH_4$ reduction product 4 of parthemollin (3b) was undepressed and the NMR and i.r. spectra were superimposable. The diacetate of 4 could not be induced to crystallize.

Dehydroivambrin (5)

A solution of 100 mg of ivambrin in 50 ml of benzene was refluxed for 3 days with lg of activated MnO_2.[12] The progress of the reaction was monitored by TLC. The MnO_2 was filtered and washed with ethyl acetate and then with MeOH. The combined filtrate and washings were evaporated at reduced pressure. The residue was taken up in benzene and chromatographed over 10 g of Florisil. Elution with $CHCl_3$ furnished 63 mg of gummy dehydroivambrin which could not be induced to crystallize. It had i.r. bands at 3500 1760 and 1665 cm^{-1}, NMR signals (60 mHz, $CDCl_3$) at 6·33 d (3, H-13a) superimposed on 6·3 m (H-5), 5·62 (2·5, H-13b), 5·58 dd (10, 3, H-6), 4·25 qbr (6, H-4) 3·0 m (H-7, partially superimposed on three proton signal -H-3 and H-10 at 2·9), 1·17 d (6) and 1·16 d (6, two CH–CH_3); λ_{max} 228 nm.

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* The NMR spectrum of the acylated sesquiterpene lactone recovered from the Horeau esterification showed the presence of two acetates in a 2:1 ratio (acetyl signals at 2·00 for the major and 2·06 for the minor acetate) indicating that trans esterification had occurred. However, a (−) acid was recovered in 25–30 per cent optical yield (measured at 546·1 nm)[4] from parthemollin (3b) (the C-4 keto analog of apachin) and on this basis was assigned an S-configuration at C_2. Thus, the recovery of a (+) acid from apachin supports an R-configuration at C_4 as shown in 2a.

[10] R. C. JACKSON, *Univ. Kansas Sci. Bull.* **41,** 793 (1960).

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