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NEW CLERODANE DITERPENOIDS FROM AJUGA IVA (LABIATAE)[1]

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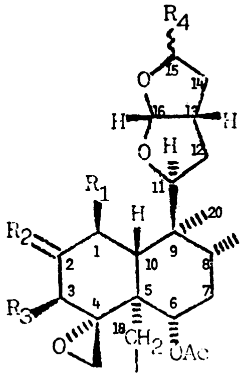
Four new clerodane diterpenoids, Ivains I - IV (1-4), have been isolated from Ajuga iva, and their structures have been elucidated by spectral methods and confirmed by the X-ray diffraction analysis of 2-oxo-Ivain I (7).

In the context of our search for potential insect antifeedants in Ajuga plants[2,3], we report herein the isolation and structure determination of four new clerodane diterpenoids, ivains I-IV (1-4) from Ajuga iva (Labiatae). The structural elucidation of these compounds was carried out by comparison of their spectral data with those of ajugareptansin (5), previously isolated by us from Ajuga reptans[2].

The residue from a diethyl ether extract of air dried whole plant, collected in Beer-Sheva (Israel), was dissolved in acetone, and this solution was evaporated under reduced pressure to give a residue, which was chromatographed on silica gel, eluting with a 5:1 to 0:1 hexane: ethyl acetate gradient solvent system and a 95:5 ethyl acetate:methanol mixture, to afford crude diterpenoid fractions. Further rechromatography of these fractions on silica gel eluting with 1:1 or 1:2 hexane:ethyl acetate mixture yielded pure ivains I-IV (1-4)[4] (Table 1).



		R_1	R_2	R_3	R_4
Ivain I	1	H	HO H	$OCOCH(CH_3)_2$	H
II	2	H	H_2	$OCOCH(CH_3)_2$	H
III	3	H	HO H	$OCOCH(CH_3)_2$	OEt
IV	4	H	HO H	$OCOCH(CH_3)C_2H_5$	H
Ajugareptansin	5	$OCOCH(CH_3)C_2H_5$	H_2	OH	H
2-Oxo-ivain I	7	H	O	$OCOCH(CH_3)_2$	H

MS data of 1,2, and 4 (m/z 113,85,83,81, and 69) suggested the presence of the hexahydrofurofuran moiety in these compounds[5], which was further confirmed by comparison of the ^1H-NMR spectra of 1,2, and 4, and ^{13}C-NMR spectra of 1, and 4 with those of 5 (Tables 2 and 3). On the other hand, the spectral data of 3, MS peaks at m/z 157 and 111, and ABX_3 signals at δ 3.80 and

3.44 (J=9 and 6 Hz) and the observed shift for H-15 signal at δ 5.12 (d, J=6 Hz), in the ^{1}H-NMR spectrum, were consistent with the occurrence of a 15-ethoxyhexahydrofurofuran moiety in this compound.

As summarized in Table 2, the ^{1}H-NMR spectra of all four ivains 1-4 showed peaks at δ 2.6-3.0 (AB system, J=4 Hz), 4.4-4.8 (AB system, J=12 Hz), and 4.75-4.82 (dd, J=5 and 11 Hz) in agreement with the presence of C_4-C_{17} epoxide, C_{18} primary acetate, and C_6 secondary acetate groups respectively. Likewise, in compounds 1, 2, and 3, the occurrence of a 2-methylpropanoyloxy group was ascertained from the H-C-O-C=O signals at δ 5.30-5.48 as well as from the methyl doublets at δ 1.10-1.16 (J=6.5 Hz) and the methine heptuplets at δ 2.46-2.57 (J=6.5 Hz) in the corresponding ^{1}H-NMR spectra and was further confirmed by signals at δ 174.8, 35.7, 18.6, and 18.5 in the ^{13}C-NMR spectrum of 1. Similarly, the appearance of methyl signals at δ 0.90 (t, J=6 Hz) and δ 1.14 (d, J=6 Hz) in the ^{1}H-NMR of 4, in conjunction with signal at δ 175.3, 40.9, 26.6, 16.0, and 11.1 in the corresponding ^{14}C-NMR spectrum, pointed to the presence of a 2-methylbutanoyloxy substituent in this compound.

The IR spectra of 1,3, and 4 showed hydroxyl absorptions at 3450 cm^{-1}, in agreement with the broad one proton signal at δ 4.18-4.20 attributable to a >CHOH moiety, in the ^{1}H-NMR spectra. Both features were absent in the corresponding spectra of 2.

The relative positions of the ester and hydroxyl substituents in ring A could be inferred from the multiplicities of the above signals at δ 5.30-5.48, which appeared as a doublet with axial-equatorial coupling (J=2 Hz) in the ^{1}H-NMR spectra of 1, 3, and 4 and as a double doublet with axial-axial and axial-equatorial couplings (J=12 and 5 Hz) in the corresponding spectrum of 2. These data were consistent with the assignments of position 3 for the ester moiety and 2 for the hydroxyl group.

In accordance with these stereochemical assignments, compound 6, amorphous solid with a molecular formula of $C_{28}H_{42}O_{10}$ {M^{+}, 538. $[\alpha]_D$ -19.7° (c 3.64, $CHCl_3$)} was formed when p-bromobenzoylation of 1 was attempted under conventional conditions (p-bromobenzoyl chloride-pyridine)[6]. The structure of 6 was ascertained from the disappearance of the above epoxide AB signals and the concurrent appearance of an AB system at δ 4.12 and 3.70 (J=10 Hz) in the ^{1}H-NMR spectrum and of a sharp absorption at 3600 cm^{-1} in the IR spectrum (KBr), assigned to a tertiary hydroxyl. As deduced from the H-2,H-3 relative coupling constants, the formation of the furan ring promotes a distortion of ring A in 6, H-2 appearing as a doublet at δ 4.22 (J=6 Hz) and H-3 as a singlet at δ 5.10, in agreement with the new relative angle between both protons of ca. 90°. Likewise, oxidation of 1 with CrO_3-pyridine afforded 2-oxo-ivain I(7), mp 195-203°C (d)(MeOH) {Calcd: C, 62.7; H, 7.5%. Found: C, 62.6; H, 7.6%. $[\alpha]_D$ +1.3° (c 4.32, $CHCl_3$)} which exhibited the AB epoxide signals at δ 2.80 and 2.98 (J=4 Hz) and shift of the H-3 singlet to δ 5.97 and H-1 signals to δ 2.98 and 3.10. The structure of 7 has been confirmed by an X-ray diffraction analysis: Crystals are orthorhombic $P2_12_12_1$, a=16.16 (7), b=21.81 (9), c=7.95 (2) Å, Z=4. The structure was determined with the computer program MULTAN-80 system[7] and refined to R=0.059 for 617 observed reflections. Rings of the trans decalin system adopt respectively chair and deformed chair conformations[8].

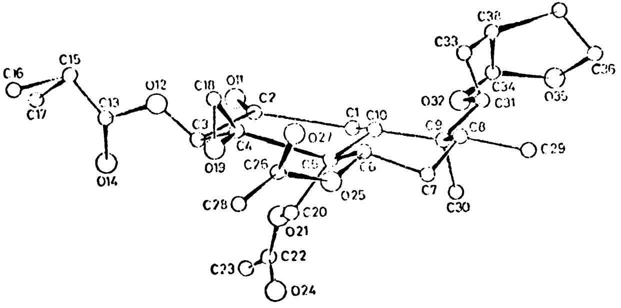
Table 1. Physical data of Ivains $\underline{1}$-$\underline{4}$

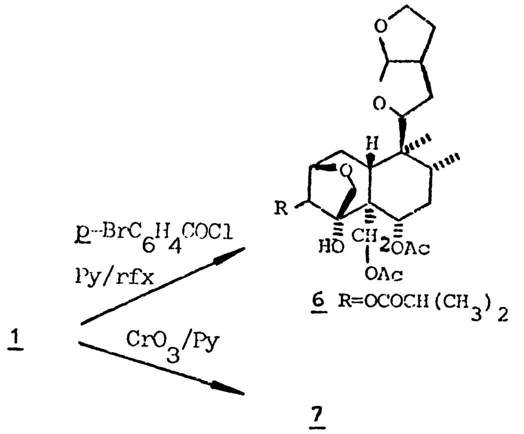
Compd.	Yield %	Mol.form.	M^+	Calcd. C%	Calcd. H%	Found C%	Found H%	$[\alpha]_D$ ($CHCl_3$)	$\underline{c}$
$\underline{1}$ (amorph. sol.)	0.031	$C_{28}M_{42}O_{10}$	538	62.4	7.9	62.3	8.2	-8.0	8.0
$\underline{2}$ (mp 158-161 C)	0.001	$C_{28}H_{42}O_9$	522	64.3	8.2	64.4	8.0	-26.8	6.2
$\underline{3}$ (amorph. sol.)	0.004	$C_{30}H_{46}O_{11}$	582	61.9	7.9	61.9	8.1	+31.7	4.6
$\underline{4}$ (amorph. sol.)	0.008	$C_{29}H_{44}O_{10}$	552	63.0	8.0	62.9	7.9	+4.1	4.2

Table 2. ^{1}H-NMR data of compounds $\underline{1}$-$\underline{5}$ (δ multiplicity/J in Hz)

H	$\underline{1}$	$\underline{2}$	$\underline{3}$	$\underline{4}$	$\underline{5}$
1					5.62 ddd/10;6;4.5
2	4.18 br		4.18 br	4.20 br	
3	5.48 d/2.5	5.30 dd/12;5	5.44 d/2	5.44 d/2	4.55 dd/11;6
6	4.82 dd/11;5	4.75 dd/12;5	4.80 dd/11;5	4.82 dd/11;5	4.80 dd/10;5.5
11	4.14 dd/11;5	4.11 dd/11;6	4.48 dd/11;6	4.18 dd/11;6	4.21 dd/11;6
15	3.90 m	3.88 m	5.12 d/6	3.92 m	3.84 m
16	5.68 d/4	5.64 d/5.5	5.86 d/5	5.72 d/5	5.62 d/6
17	2.74 and 2.98 AB/4	2.60 and 2.83 AB/3.5	2.70 and 3.00 AB/3.5	2.70 and 2.98 AB/3.5	2.92 s
18	4.48 and 4.76 AB/12	4.40 and 4.80 AB/12	4.48 and 4.78 AB/12	4.48 and 4.78 AB/12	4.15 and 5.00 AB/13
19	0.88 d/6.5	0.85 d/7	0.92 d/6.5	0.90 d/6.5	0.90 d/6
20	0.98 s	0.95 s	0.98 s	0.98 s	0.84 s
$(\underline{CH_3})_2CHCO$	1.14 d/7	1.10 d/6.5	1.16 d/6.5		
$(CH_3)_2\underline{CH}CO$	2.54 h/7	2.46 h/6.5	2.57 h/6.5		
$\underline{CH_3}CH_2CH(CH_3)CO$				0.90 t/6	0.90 t/6
$CH_3CH_2CH(\underline{CH_3})CO$				1.14 d/6	1.12 d/6
$\underline{CH_3}CH_2O$			1.20 t/6		
$CH_3\underline{CH_2}O$			3.44 and 3.80 ABX_3/9;6		

Perspective drawing of **7**





$\underline{6}$ R=OCOCH$(CH_3)_2$

Table 3. ^{13}C-NMR data of compounds 1,4 and 5 (δ multiplicity). a: assignment could be exchanged.

C	1	4	5	C	1	4	5	C	1	4	5
1	28.4 t	28.4	69.5 d	8	33.6 d	36.0	32.7 d	15	68.0 t	68.3	67.7 t
2	68.0 d	68.6	37.9 t	9	39.7 s	39.9	41.5 s	16	107.4 d	107.6	108.2 d
3	68.7 d	68.8	63.7 d	10	41.8 d	42.0	51.7 d	17	43.8 t	43.9	43.5 t
4	61.2 s	61.3	66.5 s	11	85.0 d	85.2	83.6 d	18	61.4 t	61.6	61.5 t
5	45.8 s	46.1	44.7 s	12	32.2 t[a]	32.4[a]	33.9 t[a]	19	13.5 q	13.7	14.2 q
6	71.4 d	71.7	71.3 d	13	40.0 d	40.1	41.0 d	20	15.9 q	16.0	18.6 q
7	32.8 t[a]	32.9[a]	32.6 t[a]	14	31.5 t[a]	31.7[a]	34.1 t[a]				
$\underline{C}H_3COO$	20.9 q	21.0	21.2 q	$CH\underline{C}OO$	174.8 s	175.3	174.8 s	$CH_3\underline{C}H_2$		26.6	26.9 t
$\underline{C}H_3COO$	20.6 q	20.9	21.2 q	$\underline{C}HCOO$	35.7 d	40.9	42.0 d	$\underline{C}H_3CH_2$		11.1	11.4 q
$CH_3\underline{C}OO$	170.7 s	169.7	170.0 s	$\underline{C}H_3CH$	18.6 q	16.0	15.8 q				
$CH_3\underline{C}OO$	169.8 s	170.8	169.4 s	$\underline{C}H_3CH$	18.5 q						

Preliminary insect antifeedant bioassays with crude diterpenoid fractions exhibited high activity against *Spodoptera littoralis*. The biological tests with pure compounds are in progress and the corresponding results will be published elsewhere.

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