Professor W. Saenger for giving him the opportunity to carry out this study in his laboratory and the Deutsche Forschungsgemeinschaft for support (Sa 196/25-1).

Lists of structure factors, anisotropic displacement parameters, atomic coordinates and complete geometry have been deposited with the IUCr (Reference: JZ1143). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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3-Ethoxycarbonyl-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)pyridinium Nitrate, Dineopentyl 2,6-Dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate and Dihexyl 2,6-Dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate

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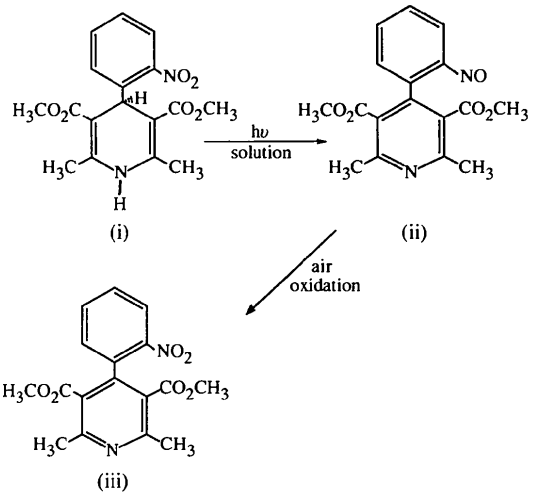
Abstract

The single-crystal X-ray structures of three oxidation products of 4-(3-nitrophenyl)-1,4-dihydropyridine, namely, 3-ethoxycarbonyl-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)pyridinium nitrate, $C_{18}H_{19}N_2O_6^+.NO_3^-$, dineopentyl 2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate, $C_{25}H_{32}N_2O_6$, and dihexyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate, $C_{27}H_{36}N_2O_6$, suggest that their decreased calcium-blocking activity arises from incompatibility of the phenyl ring and ester conformation with the receptor site.

Comment

Derivatives of 1,4-dihydropyridine (DHP) are often prescribed as calcium-channel blockers, effective in the treatment of angina and hypertension (Triggle, Langs & Janis, 1989; Hurwitz, Partridge & Leach, 1991). Nifedipine [(i); dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] has been shown to undergo a photodecomposition sequence (see below) forming nitrosopyridine and finally a nitropyridine product (Rowan & Holt, 1995).



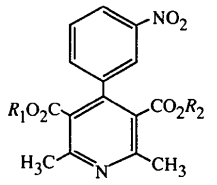
This decomposition has been reported to be wavelength sensitive, with UV radiation believed to cause aromatization of the 1,4-dihydropyridine ring and reduction of the nitro group to a nitroso moiety. Daylight, followed by air oxidation, leads to re-oxidation of the nitroso group to a nitro function. The observation of this decomposition sequence has led to concern about its shelf life, packaging and potency (Núnez-Vergara, Sunkel & Squella, 1994; Sadana & Ghogare, 1991; Hayase, Itagaki, Ogawa, Akutsu, Inagaki & Abiko, 1994).

Oxidation of the 1,4-dihydropyridine ring to pyridine is reported to significantly diminish activity in some cases (Loev, Goodman, Snader, Tedeschi & Macko, 1974). The nitropyridine decomposition product has been identified as one of the major metabolites of the parent 1,4-dihydropyridine compound (Shibanuma, Iwanami, Fujimoto, Takenaka & Murakami, 1980) and has been reported to be as much as 1000 times less active (Squella, Zanocco, Perna & Núnez-Vergara, 1990). Some of the oxidized derivatives, however, do display some activity.

Structure–activity relationships (SARs) for 1,4-dihydropyridine compounds suggest that planarity of the hetero-ring correlates with increased activity, as does a perpendicular orientation of the phenyl ring with respect to the hetero-ring (Triggle, Langs & Janis, 1989). These structural features are present in the decomposition products.

While there is abundant information about the effects of identity and position of substituents on the phenyl ring and at the 2 and 6 positions of the DHP ring upon activity, there is somewhat conflicting evidence about the influence of changes in the alkyl moiety of the ester group substituted at C(3) and C(5) (Loev, Goodman, Snader, Tedeschi & Macko, 1974; Rodenkirchen, Bayer, Steiner, Bossert, Meyer & Moeller, 1979; Bossert, Horstmann, Meyer & Vater, 1979). We have made a systematic study of the conformational changes associated with changes in the ester alkyl groups of DHP compounds (Rowan & Holt, 1996*b*). In an extension of this work, we have chemically oxidized a number of these compounds in order to observe the patterns of structural change with the aromatization of the hetero-ring and thus to assess possible reasons for the loss of activity of the decomposition products with respect to their unoxidized parent compounds.

3-Ethoxycarbonyl-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)pyridinium nitrate, (1), dineopentyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate, (2), and dihexyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate, (3), crystallize, as anticipated, with planar pyridine rings. Aromatization of the DHP ring mandates that the C(7) and C(10) atoms of the phenyl ring are collinear with the C(4) and N(1) atoms of the pyridine ring and thus the 4-phenyl ring is fully extended from the hetero-ring and not in a pseudo-axial position.

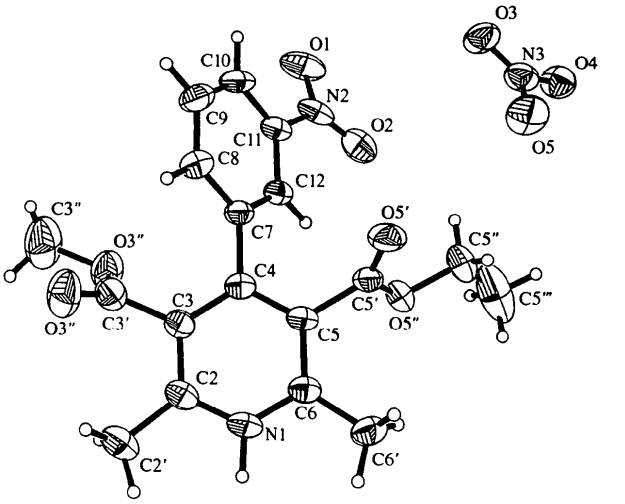


(1) R_1=methyl, R_2=ethyl (as .HNO_3)
(2) R_1=R_2=neopentyl
(3) R_1=R_2=hexyl

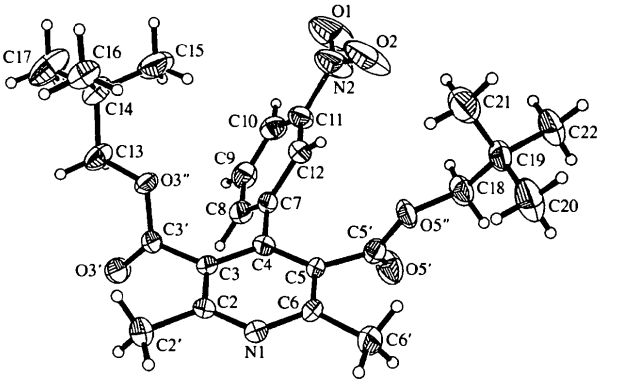
Aromatization of the 1,4-dihydropyridine ring results in the loss of the H atom at N(1), removing possible hydrogen-donor activity with the receptor site.

The angles between the planes of the phenyl and pyridine rings are 39.1, 35.2 and 21.2° in (1), (2) and (3), respectively, compared with the angle of 13° observed for the active nifedipine molecule. Decomposition thus results in significant non-orthogonality of the two-ring system.

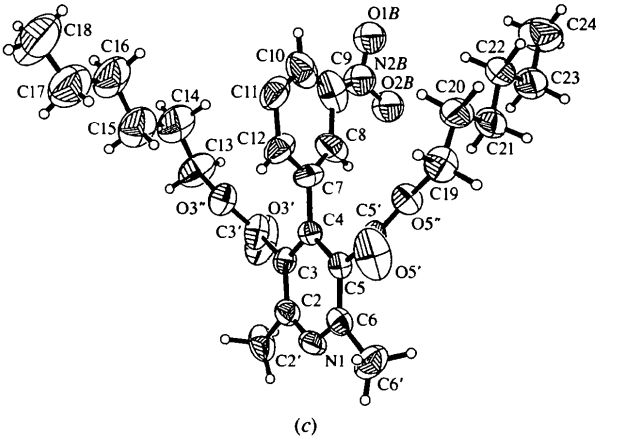
The conformation of the ester groups changes significantly with decomposition. In the majority of the more than 30 reported crystal structures of members of the nifedipine family, the ester carbonyl groups are found to be nearly coplanar with the nearest double bond in the DHP ring, with the carbonyl group oriented either *cis* (*sp*, synperiplanar) or *trans* (*ap*, antiperiplanar) with respect to that bond (Triggle, Langs & Janis, 1989). In the decomposition products, the carbonyl groups of the esters are no longer coplanar with any double bond in the pyridine ring (Fig. 1). This moves the O atoms of the ester groups out of the possible optimum position for hydrogen bonding with the receptor site.



(*a*)



(*b*)



(*c*)

Fig. 1. Projection views of (*a*) 3-ethoxycarbonyl-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)pyridinium nitrate, (*b*) dineopentyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate and (*c*) dihexyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate, with ellipsoids shown at 50% probability levels.

3-Ethoxycarbonyl-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)pyridinium nitrate, (1), the decomposition product of nitrendipine, was found to exhibit no activity.

It could therefore be concluded that the conformational changes arising upon decomposition abolish the calcium antagonistic properties of the 1,4-DHPs, due to changes in ester position, the positioning of the phenyl rings and possibly loss of hydrogen-bonding potential to the 1,4-dihydropyridine ring.

Experimental

For the preparation of 3-ethoxycarbonyl-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)pyridinium nitrate, (1), a solution of 2 g (5.55 mmol) of ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (nitrendipine) and 2 *N* HNO_3 (100 ml) was refluxed for 4 h. The resulting solution was extracted with methylene chloride (CH_2Cl_2). The organic layer was washed twice with water, dried with Na_2SO_4 and the CH_2Cl_2 removed under reduced pressure. The resulting oil was dissolved in ethyl acetate and upon slow evaporation, yielded clear crystals of (1) suitable for X-ray diffraction analysis. For the preparation of dineopentyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate, (2), a mixture of 4 g of neopentyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and 5 *N* HNO_3 (100 ml) was warmed to 353 K. The mixture was stirred for 30 min and extracted with $CHCl_3$. The organic layer was washed twice with water and then concentrated to yield clear crystals of (2). For the preparation of dihexyl 2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate, (3), a solution of hexyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (0.01 mol, 5.0 g), potassium permanganate (0.01 mol, 1.58 g), montmorillonite KSF (3.42 g) and benzene (60 ml) was refluxed for 24 h. After the benzene was removed, the resulting oil was dissolved in hexane which yielded clear transparent crystals of (3) upon slow evaporation.

Compound (1)

Crystal data

$C_{18}H_{19}N_2O_6^+.NO_3^-$
M_r = 421.36
Triclinic
$P\bar{1}$
a = 9.034 (1) Å
b = 10.228 (1) Å
c = 12.392 (2) Å
α = 78.71 (1)°
β = 71.05 (1)°
γ = 69.40 (1)°
V = 1009.4 (2) Å^3
Z = 2
D_x = 1.386 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 66 reflections
θ = 3.69–12.43°
μ = 0.1057 mm^{-1}
T = 298 K
Rhombohedral
0.2 × 0.1 × 0.1 mm
Colorless

Data collection

Syntex $P4$ four-circle diffractometer
$\theta/2\theta$ scans
Absorption correction: none
4289 measured reflections
3552 independent reflections
3501 reflections with $F > 2\sigma(F)$
R_{int} = 0.0256

θ_{max} = 25°
$h = -1 \rightarrow 10$
$k = -11 \rightarrow 12$
$l = -14 \rightarrow 14$
3 standard reflections
frequency: 97 min
intensity decay: insignificant

Refinement

Refinement on F^2
$R(F)$ = 0.0579
$wR(F^2)$ = 0.1494
S = 0.898
3552 reflections
316 parameters
H atoms not refined
$w = 1/[\sigma^2(F_o^2) + (0.1127P)^2 + 0.3691P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.032

$\Delta\rho_{max}$ = 0.227 e Å^{-3}
$\Delta\rho_{min}$ = −0.253 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.029 (5)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected bond lengths (Å) for (1)*

N(1)—C(6)	1.332 (4)	C(3'')—C(99'')	1.30 (3)
N(1)—C(2)	1.351 (4)	C(3'')—O(3'')	1.471 (5)
N(2)—O(1)	1.210 (4)	C(4)—C(5)	1.386 (4)
N(2)—O(2)	1.224 (4)	C(4)—C(7)	1.500 (4)
N(2)—C(11)	1.463 (5)	C(5)—C(6)	1.395 (4)
N(3)—O(8)	1.13 (2)	C(5)—C(5')	1.499 (4)
N(3)—O(7)	1.19 (2)	C(5')—O(5')	1.201 (4)
N(3)—O(3)	1.195 (7)	C(5')—O(5'')	1.321 (4)
N(3)—O(5)	1.199 (11)	C(5'')—C(5''')	1.269 (8)
N(3)—O(6)	1.271 (12)	C(5'')—O(5'')	1.430 (4)
N(3)—O(4)	1.290 (6)	C(6)—C(6')	1.478 (4)
C(2)—C(3)	1.389 (4)	C(7)—C(12)	1.373 (4)
C(2)—C(2')	1.491 (5)	C(7)—C(8)	1.394 (4)
C(3)—C(4)	1.399 (4)	C(8)—C(9)	1.372 (5)
C(3)—C(3')	1.492 (5)	C(9)—C(10)	1.373 (5)
C(3')—O(3')	1.197 (4)	C(10)—C(11)	1.365 (5)
C(3')—O(3'')	1.298 (4)	C(11)—C(12)	1.384 (4)
C(3'')—C(99')	1.23 (5)		

Compound (2)

Crystal data

$C_{25}H_{32}N_2O_6$
M_r = 456.5
Monoclinic
$P2_1/c$
a = 17.736 (3) Å
b = 6.139 (1) Å
c = 24.756 (4) Å
β = 108.46 (1)°
V = 2556.8 (9) Å^3
Z = 4
D_x = 1.186 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 48 reflections
θ = 3.65–12.83°
μ = 0.085 mm^{-1}
T = 298 K
Rhombohedral
0.2 × 0.2 × 0.2 mm
Colorless

Data collection

Syntex $P4$ four-circle diffractometer
$\theta/2\theta$ scans
Absorption correction: none
5973 measured reflections
4511 independent reflections
1486 reflections with $F > 5\sigma(F)$
R_{int} = 0.0288

θ_{max} = 22.5°
$h = -1 \rightarrow 21$
$k = -1 \rightarrow 7$
$l = -29 \rightarrow 28$
3 standard reflections
frequency: 97 min
intensity decay: insignificant

Refinement

Refinement on F
$R = 0.0578$
$wR = 0.0654$
$S = 1.26$
5973 reflections
299 parameters
H atoms not refined
$w = 1/[\sigma^2(F) + 0.0008F^2]$
$(\Delta/\sigma)_{max} = 0.011$
$\Delta\rho_{max} = 0.28$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}
Extinction correction: insignificant
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 2. *Selected bond lengths (Å) for (2)*

N(1)—C(2)	1.341 (7)	C(7)—C(8)	1.374 (11)
N(1)—C(6)	1.344 (9)	C(7)—C(12)	1.403 (10)
C(2)—C(2′)	1.512 (9)	C(8)—C(9)	1.382 (11)
C(2)—C(3)	1.384 (10)	C(9)—C(10)	1.378 (11)
C(3)—C(3′)	1.493 (8)	C(10)—C(11)	1.373 (12)
C(3)—C(4)	1.424 (9)	C(11)—C(12)	1.367 (11)
C(3′)—O(3′)	1.187 (9)	C(11)—N(2)	1.487 (13)
C(3′)—O(3″)	1.326 (7)	C(13)—C(14)	1.517 (10)
O(3″)—C(13)	1.452 (7)	C(14)—C(15)	1.525 (12)
C(4)—C(5)	1.399 (8)	C(14)—C(16)	1.472 (14)
C(4)—C(7)	1.470 (9)	C(14)—C(17)	1.519 (10)
C(5)—C(5′)	1.508 (10)	C(18)—C(19)	1.505 (12)
C(5)—C(6)	1.377 (10)	C(19)—C(20)	1.497 (12)
C(5′)—O(5′)	1.182 (11)	C(19)—C(21)	1.488 (10)
C(5′)—O(5″)	1.328 (10)	C(19)—C(22)	1.548 (12)
O(5″)—C(18)	1.469 (8)	N(2)—O(1)	1.178 (12)
C(6)—C(6′)	1.507 (8)	N(2)—O(2)	1.191 (14)

Compound (3)

Crystal data

$C_{27}H_{36}N_2O_6$
$M_r = 484.58$
Triclinic
$P\bar{1}$
$a = 8.089$ (2) Å
$b = 11.495$ (2) Å
$c = 15.707$ (5) Å
$\alpha = 69.29$ (2)°
$\beta = 88.12$ (2)°
$\gamma = 87.03$ (2)°
$V = 1364.2$ (6) Å^3
$Z = 2$
$D_x = 1.180$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 49 reflections
$\theta = 4.69$–$11.80°$
$\mu = 0.083$ mm^{-1}
$T = 298$ K
Rhombohedral
0.3 × 0.2 × 0.2 mm
Colorless

Data collection

Syntex $P4$ four-circle diffractometer
$\theta/2\theta$ scans
Absorption correction: none
9318 measured reflections
7803 independent reflections
7748 reflections with $F > 2\sigma(F)$
$R_{int} = 0.0802$
$\theta_{max} = 30°$
$h = -1 \rightarrow 11$
$k = -15 \rightarrow 15$
$l = -20 \rightarrow 22$
3 standard reflections
frequency: 97 min
intensity decay: insignificant

Refinement

Refinement on F^2
$R(F) = 0.0583$
$wR(F^2) = 0.1267$
$S = 0.853$
7803 reflections
314 parameters
H atoms not refined
$\Delta\rho_{max} = 0.15$ e Å^{-3}
$\Delta\rho_{min} = -0.10$ e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.004 (3)
$w = 1/[\sigma^2(F_o^2) + (0.1127P)^2 + 0.3691P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.015$
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 3. *Selected bond lengths (Å) for (3)*

N(1)—C(6)	1.340 (12)	C(9)—C(10)	1.41 (2)
N(1)—C(2)	1.349 (12)	C(9)—N(2B)	1.49 (3)
C(2)—C(3)	1.341 (11)	C(10)—C(11)	1.38 (2)
C(2)—C(2′)	1.492 (13)	C(11)—C(12)	1.36 (2)
C(3)—C(4)	1.396 (11)	C(11)—N(2A)	1.49 (2)
C(3)—C(3′)	1.506 (14)	C(13)—C(14)	1.50 (2)
C(3′)—O(3′)	1.191 (11)	C(14)—C(15)	1.46 (2)
C(3′)—O(3″)	1.326 (11)	C(15)—C(16)	1.48 (2)
O(3″)—C(13)	1.453 (11)	C(16)—C(17)	1.47 (2)
C(4)—C(5)	1.439 (11)	C(17)—C(18)	1.38 (2)
C(4)—C(7)	1.458 (12)	C(19)—C(20)	1.484 (13)
C(5)—C(6)	1.376 (12)	C(20)—C(21)	1.49 (2)
C(5)—C(5′)	1.488 (13)	C(21)—C(22)	1.533 (14)
C(5′)—O(5′)	1.193 (11)	C(22)—C(23)	1.49 (2)
C(5′)—O(5″)	1.330 (12)	C(23)—C(24)	1.519 (14)
O(5″)—C(19)	1.458 (10)	O(2A)—N(2A)	1.24 (2)
C(6)—C(6′)	1.495 (13)	O(1A)—N(2A)	1.22 (2)
C(7)—C(8)	1.338 (14)	O(1B)—N(2B)	1.26 (3)
C(7)—C(12)	1.401 (14)	N(2B)—O(2B)	1.48 (4)
C(8)—C(9)	1.47 (2)		

A variable scan rate and a scan width of 0.6° below $K\alpha_1$ and 0.6° above $K\alpha_2$ to a maximum 2θ value of 50° were used. Refinement was completed using full-matrix least-squares methods. 3-Ethoxycarbonyl-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)pyridinium nitrate, (1), crystallizes with disorder in the methyl and ethyl ester positions and also in the position of the nitrate group. The terminal ethyl C(5″′) atom refines to an occupancy of 80.4%. There are two partially occupied positions [C(99′) (7.7%) and C(99″) (11.9%)] attached to the methyl C(3″) atom, indicating that the ethyl group exists as 80.4% [as shown in Fig. 1(*a*)] and 19.6% in two other positions involving the C(3″) atom on the opposite side of the molecule. There are two sets of nitrate O-atom positions about the N(3) atom. Those shown refine to 65.4% occupancy, whereas a second set [O(6), O(7) and O(8); occupancy 34.6%] lie on a plane 85° from that shown. Dineopentyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate, (2), shows disordered H-atom positions at the methyl C(2′) and C(6′) atoms. Only one group is shown in Fig. 1(*b*). Dihexyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate, (3), has disordered nitro groups [70% attached to C(9) and 30% bonded to C(11)]. The H atoms on the C(9) and C(11) atoms were not included in the refinement. The positions of major occupancy are shown in Fig. 1(*c*). The two N atoms and four O atoms were refined with isotropic displacement parameters.

For all compounds, data collection: *XSCANS* (Siemens, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structures: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structures: *SHELXL*93 (Sheldrick, 1993) for (1) and (3); *SHELXS*86 (Sheldrick, 1990) for (2). For all compounds, molecular graphics: *XP* (Siemens, 1990)

Lists of structure factors, anisotropic displacement parameters, atomic coordinates and complete geometry have been deposited with the IUCr (Reference: PA1238). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Triterpenoide. X.† Über neue isomere Triterpenlactone

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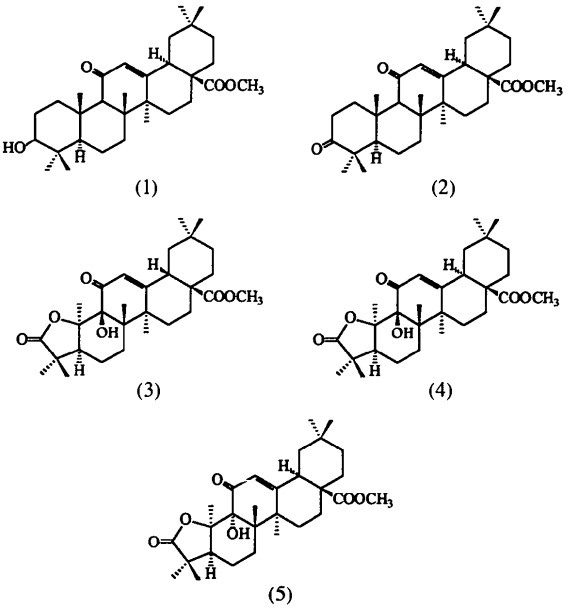
Abstract

The X-ray crystal structure analyses of three new triterpene lactones ($C_{29}H_{42}O_6$), namely 9β-hydroxy-28-methoxy-11,28-dioxo-1,2-dinor-10α,18β-olean-12-en-3,-10β-olide, (3), and its 18α- and 9α,18α-isomers, (4) and (5) [9β-hydroxy-28-methoxy-11,28-dioxo-1,2-dinor-10α,18α-olean-12-en-3,10β-olide and 9α-hydroxy-28-methoxy-11,28-dioxo-1,2-dinor-10α,18α-olean-12-en-3,10β-olide, respectively], are described. Compounds (3)–(5) were obtained by treatment of 3β-hydroxy-11-oxo-18α-olean-12-en-28-oic acid methyl ester, (1), with sodium dichromate in acetic acid. In compounds (3)–(5), the six-membered ring *A* of (1) is replaced by a γ-lactone ring. In contrast to compound (1), the C25 methyl group at C10 has an α configuration. The newly introduced hydroxyl group at C9 is β oriented in compounds (3) and (4), and α oriented in (5). Ring *B* in (3) has a boat form, but in (4) and (5) it has different equivalent chair conformations. Ring *C* in (3) has a sofa form, in (4), it has a slightly distorted half-chair form and in (5), it has a conformation intermediate between the half-chair and sofa forms. Rings *D* and *E* have chair conformations in all three compounds and are *trans*-fused in compounds (4), (5) and (1), and *cis*-fused in (3). In contrast to compound (1), rings *A*/*B* in compounds (3)–(5) and rings *B*/*C* in compounds (3) and (4) are *cis*-fused. In compounds (3)–(5), formation of hydrogen bonds has been observed. Inversion of the α configuration to a β configuration at C18 in oleanolic acid derivatives [transformation of (1) to (3)] has been observed for the first time. The triterpene lactones (3)–(5) are the first known oleanane derivatives with *cis*-fused *A*/*B* [(3)–(5)] and *B*/*C* rings [(3) and (4)].

Kommentar

Die Einwirkung von Natriumdichromat in Eisessig auf 3β-Hydroxy-11-oxo-18α-olean-12-en-28-säuremethylester, (1), führt neben dem bekannten 3-Oxo-derivat, (2) (Wrzeciono, Zaprutko, Budzianowski, Wójtowicz & Dubowska, 1987) zu drei weiteren isomeren Verbindungen (3)–(5) mit der Summenformel $C_{29}H_{42}O_6$ (MS: $M^{+\cdot}$ = 486). Aufgrund spektroskopischer Untersuchungen (IR, MS, ^{13}C sowie ^2D NMR) konnten die Strukturen dieser Verbindungen nicht eindeutig aufgeklärt werden. In dieser Mitteilung soll über



† Teil IX. Zaprutko (1995).