were determined as the negative slope of plots of ln $(1 - A_p/A_t)$ vs. time, where A_p and A_t are areas of the product and total area, respectively. Good first-order rate plots were obtained to 75% reaction using the methyl groups and are comparable in quality to those of earlier studies. The data taken from the benzylic region of the NMR was subject to greater experimental error because of the signal-to-noise ratio. However, the data are representative of the gross overall changes which occurred during the reaction. Products were identified by comparison of their NMR spectra and GLC retention times with those of authentic materials previously prepared.[5]

Acknowledgment. We thank Professor Paul E. Peterson for his interest and valuable suggestions regarding this problem.

Registry No. 1c (isomer 1), 81671-52-5; 1c (isomer 2), 81671-53-6; 3, 6323-18-8; 4, 81671-54-7; 1-(*o*-chlorophenyl)-2-chloro-1-propanone, 81671-55-8; 1-(*o*-chlorophenyl)-2-bromo-2-chloro-1-propanone, 81671-56-9.

Structure of Goyazensolide and Its Congeners[1]

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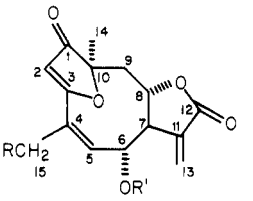
Received February 2, 1982

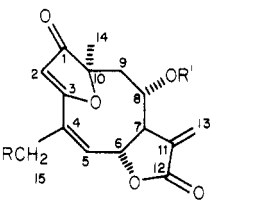
At the time of their discovery[2] the heliangolides goyazensolide and 15-deoxygoyazensolide were assigned formulas **1a** and **1b** (Chart I) rather than **2a** and **2b** for two reasons. (1) Chemical shifts and coupling constants involving H-6, H-7, H-8, and H-9 differed significantly from those exhibited by calaxin,[3] ciliarin,[3] and budlein A[4] which were then believed to possess structures **2b**, **2g**, and **2c**, respectively. (2) H-8 near 4.5 ppm was identified with the hydrogen on carbon carrying the lactone oxygen and H-6 near 5.3 ppm with the hydrogen on carbon carrying the ester group since lactone hydrogens at C-6 or C-8 of sesquiterpene lactones generally resonate at higher fields than C-6 or C-8 hydrogens under ester moieties.

In the interval the first of these arguments has been rendered invalid by the demonstration[5,6] that calaxin, ciliarin, and budlein A actually possess structures **3a–c**.[7] Moreover, goyazensolide, 15-deoxygoyazensolide, and several similar compounds to which structures **1c–f** were assigned by analogy have since been isolated from other plant sources where they are generally accompanied by substances whose lactone ring is invariably closed toward C-6.[8] In particular, goyazensolide and its analogues are

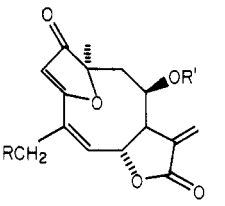
Chart I



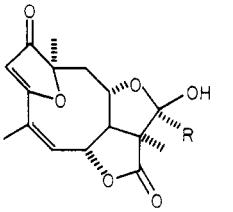
1a, R = OH; R′ = MeAcr
b, R = H; R′ = MeAcr
c, R = OH; R′ = Ang
d, R = H; R′ = Ang
e, R = H; R′ = Epoxyang
f, R = H; R′ = Tigl
g, R = H; R′ = *i*-Bu



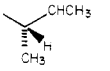
2a, R = OH; R′ = MeAcr
b, R = H; R′ = MeAcr
c, R = OH; R′ = Ang
d, R = H; R′ = Ang
e, R = H; R′ = Epoxyang
f, R = H; R′ = Tigl
g, R = H; R′ = *i*-Bu



3a, R = H; R′ = MeAcr
b, R = H; R′ = *i*-Bu
c, R = OH; R′ = Ang

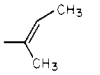


4a, R = *i*-Pr



b, R =

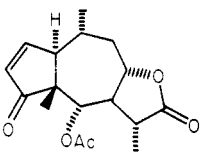
c, R =



d, R =

e, R =

f, R =



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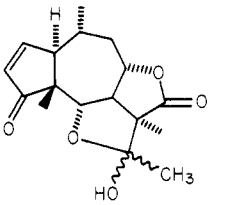

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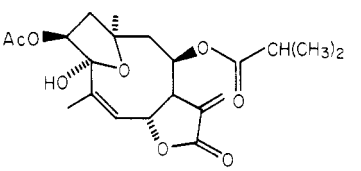

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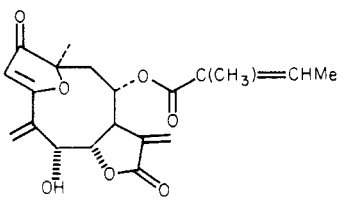

8

(1) Supported in part by a grant (CA-13121) from the U.S. Public Health Service through the National Cancer Institute.

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0022-3263/82/1947-2798$01.25/0

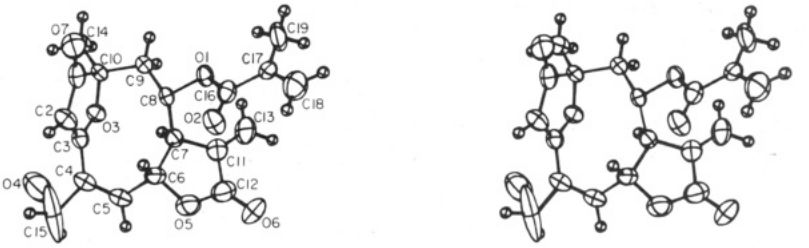

Figure 1. Stereoscopic view of the goyazensolide molecule (**2a**) with 35% ellipsoids of thermal motion.

Table IV. Selected Torsion Angles (deg) in 2a[a]

C(10)-C(1)-C(2)-C(3)	0.1
C(1)-C(2)-C(3)-C(4)	166.3
C(1)-C(2)-C(3)-O(3)	-6.6
C(2)-C(3)-C(4)-C(5)	-92.9
C(2)-C(3)-O(3)-C(10)	10.4
C(3)-O(3)-C(10)-C(1)	-9.2
O(3)-C(10)-C(1)-C(2)	5.7
C(3)-C(4)-C(5)-C(6)	6.5
C(4)-C(5)-C(6)-C(7)	-66.0
C(5)-C(6)-C(7)-C(8)	113.8
C(6)-C(7)-C(8)-C(9)	-123.2
C(6)-C(7)-C(11)-C(12)	0.4
C(6)-C(7)-C(11)-C(13)	179.5
C(7)-C(11)-C(12)-O(6)	-179.8
C(7)-C(11)-C(12)-O(5)	1.0
C(11)-C(12)-O(5)-C(6)	-2.1
C(12)-O(5)-C(6)-C(7)	2.4
O(5)-C(6)-C(7)-C(11)	-1.6
C(13)-C(11)-C(12)-O(6)	1.1
C(7)-C(8)-C(9)-C(10)	76.9
C(8)-C(9)-C(10)-C(1)	55.4
C(8)-C(9)-C(10)-C(14)	-176.5
C(8)-C(9)-C(10)-O(3)	-57.2
C(9)-C(10)-O(3)-C(3)	109.3
O(3)-C(3)-C(4)-C(5)	80.0

[a] Estimated standard deviation of 1°.

often associated with the eremantholides (compounds of type **4**).[9] This has led us to suspect that goyazensolide might be related to eremantholide C (**4c**) in the same way as isotenulin (**5**) is to tenulin (**6**).[10] This would require that the compounds in question be reformulated as **2a–f**.

To clear up this doubt an X-ray analysis of goyazensolide was undertaken. Crystal data are given in the Experimental Section. Figure 1 is a view of the molecule which shows that, as suspected, formula **2a** rather than **1a** is correct. It probably represents the absolute configuration as well for reasons given earlier.[2] It follows that centratherin[8a] is **2c**, isocentratherin[8b] is **8**, lychnopholide[8c,e,f] and its epoxide are **2d** and **2e**, respectively, and the tiglate analogue[8d] is **2f**. Tables I–III listing final aromatic and final anisotropic thermal parameters, bond lengths, and bond angles are available as supplementary material. Table IV presents selected torsion angles.

As shown by the endocyclic torsion angles, the conformation of the oxacyclononene ring of **2a** is quite different from the conformation adopted by this ring in woodhousin (**7**)[11b] but surprisingly similar to the conformation found for eremantholide A and B (**4a,b**).[9b] The dominant factor in shaping these molecules appears to be the 3(2*H*)-furanone ring of **2a**, **4a**, and **4b** rather than the 2,5-dioxabicyclo[3.3.0] system involving C-6, C-7, and C-8 found in the eremantholides. The 3(2*H*)-furanone ring is relatively planar, the sum of the internal torsion angles being 34° and the largest displacement from the least-square plane encompassing C(1), C(2), C(3), O(3) and C(10) being 0.05 Å. As in the eremantholides,[9b] the C(2)–C(3) and the C(4)–C(5) double bonds are essentially orthogonal in the solid state [C(2)–C(3)–C(4)–C(5) torsion angle -92.9°]; the situation in solution cannot be very different as the UV maxima of **2a–f** near 268 nm (and those of the related compounds of type **3**) are not those of dienones, but of β-alkoxy-substituted enones.

The α-methylene γ-lactone ring of **2a** is planar [sum of internal torsion angles is 8°; largest displacement from least-squares plane encompassing C(6), C(7), C(11), C(12), and O(5) is 0.1 Å]. Because of this, a comparison of the very small C(13)–C(11)–C(12)–O(6) and O(5)–C(6)–C(7)–C(11) torsion angles (ω_2 = 1.1°, ω_3 = 1.6°) whose signs are not paired[12] is probably not very meaningful. However, with ω_4 [the C(5)–C(6)–C(7)–C(8) torsion angle] = 113.6°, the rule[13] that for $\omega_4 < 120°$, ω_3 is negative is obeyed. The sign of ω_3 and the magnitude of ω_4 have been related to the sign of the lactone Cotton effect in the 250–260 nm region; if the latter were known, the asbolute configuration of **2a** could be deduced. Unfortunately the observed negative maximum near 267 nm[2] is a composite of the enone and α,β-unsaturated lactone chromophores.[14]

Experimental Section

Single crystals of goyazensolide were prepared by Dr. J. Siva Prasad by slow crystallization from benzene–ethyl acetate. The crystals were orthorhombic, space group $P2_12_12_1$, with a = 8.67 (1) Å, b = 10.879 (2) Å, c = 18.997 (2) Å, and d_{calcd} = 1.302 g cm^{-3} for Z = 4 ($C_{19}H_{24}O_6$, M_r = 348.4). The intensity data were measured on a CAD4 diffractometer (Mo radiation, mono-

(8) (a) Ohno, N.; McCormick, S.; Mabry, T. J. *Phytochemistry* **1979**, *18*, 681. (b) Bevelle, C. A.; Handy, G. A.; Segal, R. A.; Cordell, G. A.; Farnsworth, N. R. *Ibid.* **1981**, *20*, 1605. The assignments given by these authors for the ^{1}H NMR spectrum of isocentratherin are incorrect, possibly due to a series of misprints, and should be 1.55 (H-14), 1.80 (H-5′), 1.85 (d, H-4′), 2.09 (Ac), 2.34 (dd) and 2.55 (dd, H-9), 4.18 (m, H-7), 4.31 (ddd, H-8), 4.90 (br d, H-6), 5.51 (d) and 6.25 (d) (H-13), 5.87 (H-2), 5.93 (br, H-5), 6.08 (br) and 6.18 (br) (H-15). (c) Bohlmann, F.; Zdero, C.; Robinson, H.; King, R. M. *Ibid.* **1980**, *19*, 2381. (d) Bohlmann, F.; Zdero, C.; King, R. M.; Robinson, H. *Ibid.* **1980**, *19*, 2663. (e) Bohlmann, F.; Zdero, C.; Robinson, H.; King, R. M. *Ibid.* **1981**, *20*, 739. (f) Bohlmann, F.; Gupta, R. K.; Jakupovic, J.; Robinson, H.; King, R. M. *Ibid.* **1981**, *20*, 1609. (g) Bohlmann, F.; Muller, L.; King, R. M.; Robinson, H. *Ibid.* **1981**, *20*, 1149.

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(12) McPhail, A. T.; Sim, G. A. *Tetrahedron* **1973**, *29*, 1751.

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(14) **Note Added in Proof**: In a recent article[15] formula **2a** was established by X-ray analysis for lynchnophorolide A, mp 165.5–166.5 °C, a cytotoxic sesquiterpene lactone from *Lychnophora affinis*. In spite of the difference in melting points, lynchnophorolide A must therefore be identical with centratherin[8a] and the noncrystalline lychnophorolide B, for which formula **2f** was proposed[15] by analogy, is identical with tiglate **2f** previously[8d] isolated from *Eremanthus bicolor* and assigned formula **1f**.

(15) Le Quesne, P. W.; Menachery, M. D.; Pastore, M. P.; Kelley, C. J.; Brennan, T. F.; Onan, K. D.; Raffauf, R. F.; Weeks, C. M. *J. Org. Chem.* **1982**, *47*, 1519.

chromated, θ-2θ scans). The size of the crystal used for data collection was approximately 0.3 × 0.3 × 0.3 mm. No absorption correction was necessary (μ = 0.902). A total of 1830 independent reflections were measured for θ < 27.8°, of which 1317 were considered to be observed [$I > 2\sigma(I)$]. The structure was solved by direct methods using MULTAN 78[16] and refined by full-matrix least-squares methods. In the final refinement anisotropic thermal parameters were used for the nonhydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices were R = 0.075 and R_w = 0.077 for the 1317 observed reflections. The final difference map had no peaks greater than ±0.6 e Å^{-3}.

Registry No. 2a, 60066-35-5; **2b**, 81767-50-2; **2c**, 71939-83-8; **2d**, 77448-64-7; **2e**, 81724-60-9; **2f**, 80795-28-4; **8**, 80377-52-2.

Supplementary Material Available: Tables I–III listing final atomic and final anisotropic thermal parameters, bond lengths, and bond angles for compound **2a** (4 pages). Ordering information is given on any current masthead page.

(16) Main, Peter "MULTAN 78. A System of Computer Programs for Automatic Solution of Crystal Structures from X-Ray Diffraction Data", Department of Physics, University of York: York, England.

Nicotinic Acid Crown Ethers.[1] An Unexpected Facile Etherification Process

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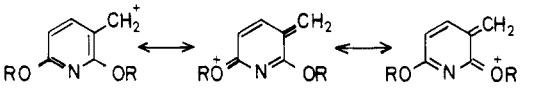
Received November 17, 1981

During our studies to functionalize macrocycles containing subheterocyclic rings, the 3-carbinol moiety on a pyridine subunit was of interest. The availability of 2,6-dichloronicotinic acid[2] provided an excellent starting material for (a) generation of the crown ether portion via nucleophilic heteroaromatic substitution and (b) appendage construction via the carboxyl group.

Esterification of the substituted nicotinic acid was accomplished (100%) by Fischer esterification conditions.[3] Although 2-carbethoxypyridine was readily reduced to the carbinol with sodium borohydride,[4] **1** was recovered unchanged under these conditions. However, **2a** was obtained (93%) when **1** was subjected to lithium aluminum hydride–aluminum chloride in ether (Scheme I). Attempted conversion of **2a** directly to **5a** was plagued with competitive side reactions such as the abstraction of the acidic proton by sodium hydride and subsequent intermolecular cyclization(s).

In order to circumvent these rival reactions, **2a** was transformed into the base-stable tetrahydropyranyl ether **3a**. Treatment of **3a** with sodium pentaethylene glycolate or ethoxide under standard conditions[5] gave macrocycle **4a** or **4b**, respectively. The multiplet at δ 4.73 confirmed the presence of the protective group, and, in the case of **4a**, the characteristic α-ϵ-methylenic region supported the presence of the crown ether bridge.

Hydrolysis of **4a** in aqueous ethanol with traces of hydrochloric acid gave the ethyl ether **5b** and *no traces* of the anticipated alcohol **5a**. Use of other aqueous alcoholic solvents resulted in similar results. Only with the exclusion of alcoholic solvents (THF–aqueous HCl) can the desired carbinol **5a** be prepared. For evaluation of the ring substituents, carbinols **2** were quantitatively regenerated by aqueous–alcohol hydrolysis of ethers **3** (X = H or Cl); other acidic conditions[6,7] gave similar results. For elimination of any unusual effects caused by the "crown ether" unit, **4b** was readily transformed to the corresponding ether **6b,c**, and again no traces of the carbinol **6a** were detected. The rationale for this facile etherification process can be envisioned as cleavage of **4** under the acidic conditions to generate a stabilized cation **7**, which is trapped by solvent. Further, treatment of carbinols **5a** or **6a** with acidic alcohol quantitatively gave the corresponding ether.



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An alternate protective procedure was the conversion of **2a** to aldehyde **8** via mild oxidation with acetic anhydride and Me_2SO.[8] Subsequent protection of the formyl group, bridge-formation, and deprotection offered no advantage to generate functionalized subunits.

Experimental Section[9]

2,6-Dichloro-3-(hydroxymethyl)pyridine (2a). To a stirred suspension of $LiAlH_4$ (860 mg) and $AlCl_3$ (3.03 g) in anhydrous ether (100 mL) at 0 °C under nitrogen was added ethyl 2,6-dichloronicotinate (**1**; 5 g, 22.7 mmol). The mixture was refluxed for 3 h, cooled, and quenched with water. The ether layer was separated, washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give the crude alcohol, which was chromatographed on a short neutral alumina column eluted with dichloromethane to afford **2a**, as colorless crystals: 3.70 g (93%); mp 62–64 °C; ^{1}H NMR δ 3.30 (s, OH, 1 H), 4.68 (s, py CH_2, 2 H), 7.21 (d, 5-py H, J = 8.2 Hz, 1 H), 7.83 (d, 4-py H, J = 8.2 Hz, 1 H); IR (KBr) 3245, 2910, 1570, 1534, 1420, 1142, 826 cm^{-1}; MS (70 eV) m/e (relative intensity) 178 (M$^+$, 14.8), 142 (100). Anal. Calcd for $C_6H_5Cl_2NO$: C, 40.48; H, 2.83; N, 7.83. Found: C, 40.58; H, 2.67; N, 7.76.

3-[[(Tetrahydropyran-2-yl)oxy]methyl]-2,6-dichloropyridine (3a). To a stirred solution of 3,4-dihydropyran (1 mL) in ether (20 mL) was added **2** (1.6 g, 9.0 mmol) and concentrate HCl (1 drop). After 24 h at 25 °C, potassium hydroxide (3 pellets) was added, and the mixture was stirred and decanted. Concentration, followed by Kugelrohr distillation gave the desired ether **3a**, as a colorless oil: bp 240 °C (1.3 mm); 2 g (85%); ^{1}H NMR δ 1.72 [m, $(CH_2)_3$, 6 H], 3.75 (m, CH_2, 2 H), 4.67 (s, CH, 1 H), 4.79 (s, py CH_2, 2 H), 7.33 (d, 5-py H, J = 8.0 Hz, 1 H), 7.80 (d, 4-py H, J = 8.0 Hz, 1 H); IR (neat) 2940, 1583, 1550, 1440, 1130, 837 cm^{-1}; MS m/e (relative intensity) 261 (M$^+$, 1.3), 160 (100). Anal. Calcd for $C_{11}H_{13}Cl_2NO_2$: C, 50.40; H, 5.34; N, 5.00. Found: C, 50.18; H, 5.30; N, 5.06.

Preparation of Macrocycle 4a. To a suspension of NaH (230 mg) in anhydrous toluene (200 mL) under nitrogen was added slowly pentaethylene glycol (910 mg). The mixture was stirred at 25 °C for 30 min, and then ether **3a** (1 g, 3.8 mmol) in toluene (50 mL) was added. The mixture was heated at 80 °C for 24 h, cooled and quenched with water. The organic layer was separated,

(1) Part 72 of the series: "Chemistry of Heterocyclic Compounds". For previous papers in the "Nicotonic Acid Crown Ethers" series see: (a) Newkome, G. R.; Kawato, T.; Benton, W. H. *J. Org. Chem.* **1980**, *45*, 5423. (b) *Ibid.* **1980**, *45*, 626. (c) Newkome, G. R.; Kohli, D. K.; Kawato, T. *Ibid.* **1980**, *45*, 4508. (d) Newkome, G. R.; Kawato, T. *Ibid.* **1980**, *45*, 629. (e) *Ibid.* **1979**, *44*, 2697. (f) *Ibid.* **1979**, *44*, 2693.

(2) We thank Dr. C. D. Weis of CIBA-GEIGY, Basel, Switzerland, for supplying the sample of 2,6-dichloronicotinic acid.

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(4) Newkome, G. R.; Roper, J. M.; Robinson, J. M. *J. Org. Chem.* **1980**, *45*, 4380.

(5) Loewenthal, H. J. E. *Tetrahedron* **1959**, *6*, 269. Review: Reese, C. B. In "Protective Groups in Organic Chemistry"; McOmie, J. F. W., Ed.; Plenum Press: New York, 1973; Chapter 3, especially pp 104–106.

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