J. Org. Chem. 1981, *46*, 761-765

Structures of the Rolandrolides and Isorolandrolides, Unusual Germacradienolides from *Rolandra fruticosa*[1]

Werner Herz* and Serengolam V. Govindan

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

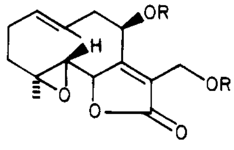
John F. Blount

Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received September 26, 1980

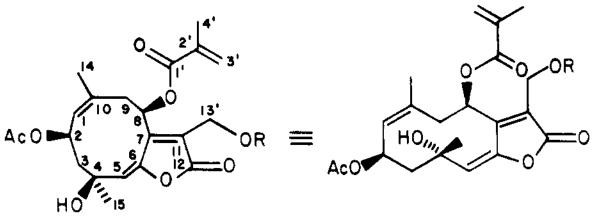
Four new sesquiterpene lactones, rolandrolide (**2b**), 13-acetoxyrolandrolide (**2a**), isorolandrolide (**3b**), and 13-ethoxyisorolandrolide (**3a**), were isolated from the medicinal plant *Rolandra fruticosa* (L.) Kuntze. Structures **2a,b** were determined by spectroscopy and X-ray analysis of **2a** which as the first member of the class of 1(10)-*cis*-5,6-*cis*-7,11-germacratrien-6,12-olides possesses an unusual tublike conformation. Structures and stereochemistries of **3a,b** which are 3,4-*trans*-5,6-*cis*-7,11-germacratrien-6,12-olides were deduced by spectroscopic techniques. Acetoxyrolandrolide showed borderline activity in the P-388 lymphoid sarcoma system.

Germacranolides of the glaucolide type (1) and variants thereof are characteristic constituents of certain sections of the large genus *Vernonia*[2-4] and have been found in some species of allied genera.[5] We now report isolation from *Rolandra fruticosa* (L.) Kuntze of several new members of this group which possess the unprecedented stereochemistry shown in formulas **2a,b** and **3a,b**. In the case of **2a,b** this results in a highly unusual conformation of the ten-membered ring.

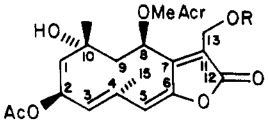


1

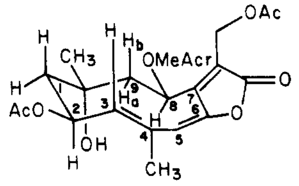
Decoctions and poultices from the leaves of *Rolandra fruticosa* (Compositae, Vernonieae), a tropical species of the Western hemisphere, are used medicinally through much of its range.[6a] Prompted by this we undertook a chemical study; chloroform extraction of a collection from Panama furnished four sesquiterpene lactones which we have named rolandrolide (**2b**), acetoxyrolandrolide (**2a**), isorolandrolide (**3b**), and ethoxyisorolandrolide (**3a**). Acetoxyrolandrolide exhibited dosage dependent toxicity and borderline activity in preliminary tests against P-388 lymphoid leukemia (T/C 122 at 22 mg/kg).[6b]



2a, R = Ac
b, R = H

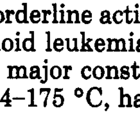


3a, R = Et
b, R = H

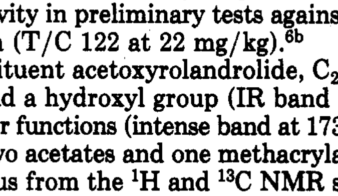


3A

The major constituent acetoxyrolandrolide, $C_{23}H_{28}O_9$, mp 174–175 °C, had a hydroxyl group (IR band at 3475 cm^{-1}) and three ester functions (intense band at 1730 cm^{-1}) whose character, two acetates and one methacrylate, was immediately obvious from the ^1H and ^{13}C NMR spectra. The remaining two oxygen atoms of the molecular formula were accounted for by assuming that the substance was an α,β-unsaturated γ-lactone (IR band at 1760 cm^{-1}, carbon singlet at 167.15 ppm); however, the ^1H and ^{13}C NMR spectra clearly ruled out the usual α-methylene-α,β-unsaturated lactone of type A.



A



$$-\underset{H}{\overset{H}{C_3}}-\underset{\underset{O}{\|}{OCR}}{\overset{H}{C_2}}-\overset{H}{C_1}=\overset{CH_3}{C_{10}}-\underset{H}{\overset{H}{C_9}}-\underset{\underset{O}{\|}{OC-R}}{\overset{H}{C_8}}-$$

B

The presence of partial structure B (numbering as in final formula) was demonstrated as follows. H-1 at 5.17 ppm, vinylic because attached to a carbon near 128 ppm as shown by single-frequency resonance decoupling (SFRD), was coupled to H-2 at 5.56 ppm and allylically coupled to the protons of a vinyl methyl at 1.71 ppm

---

[1] Work at the Florida State University was supported in part by a grant from the U.S. Public Health Service (CA-13121) through the National Cancer Institute.

[2] (a) Abdel-Baset, Z. A.; Southwick, L.; Padolina, W. G.; Yoshioka, H.; Mabry, T. J. *Phytochemistry* **1971**, *10*, 2201. (b) Padolina, W. G.; Yoshioka, H.; Nakatani, N.; Mabry, T. J.; Monti, S. A.; Davis, R. E.; Cox, P. J.; Sim, G. A.; Watson, W. H.; Wu, I. B. *Tetrahedron* **1974**, *30*, 1161. (c) Padolina, W. G.; Nakatani, N.; Yoshioka, H.; Mabry, T. J.; Monti, S. A. *Phytochemistry* **1974**, 13, 2225. (d) Mabry, T. J.; Abdel-Baset, Z. A.; Padolina, W. G.; Jones, S. B. *Biochem. Syst. Ecol.* **1975**, *7*, 185. (e) Cox, P. J.; Sim, G. A. *J. Chem. Soc., Perkin Trans. 2* **1975**, 455. (f) Betkowski, M.; Mabry, T. J.,; Taylor, I. F.; Watson, W. H. *Rev. Latinoam. Quim.* **1975**, *6*, 191. (g) Taylor, I. F.; Watson, W. H.; Betkowski, M.; Padolina, W. G.; Mabry, T. J. *Acta Crystallogr., Sect. B* **1976**, *32*, 107. (h) Betkowski, M.; Mabry, T. J.; Adams, T. W.; Watson, W. H.; Jones, S. B. *Rev. Latinoam. Quim.* **1976**, *7*, 111. (i) Gopalakrishna, E. M.; Adams, T. W.; Watson, W. H.; Betkowski, M.; Mabry, T. J. *Cryst. Struct. Commun.* **1977**, *6*, 201.

[3] Toubiana, R.; Toubiana, M. J., Das, B. C. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1970**, *270*, 1033; *Tetrahedron Lett.* **1972**, 207. Toubiana, R.; Toubiana, M. J.; Torii, K.; Kuriyama, K. *Ibid.* **1974**, 1753.

[4] Bohlmann, F.; Brindöpke, G.; Rastogi, R. C. *Phytochemistry* **1978**, *17*, 475. (b) Bohlmann, F.; Mahanta, P. K.; Dutta, L. N. *Ibid.*, **1979**, *18*, 289.

[5] (a) Bohlmann, F.; Czerson, H. *Phytochemistry* **1978**, *17*, 1190. (b) Bohlmann, F.; Zdero, C.; King, R. M.; Robinson, H. *Ibid.* **1979**, *18*, 987.

[6] (a) E.g.: Busey, P. *Ann. MO Bot. Garden*, **1975**, *62*, 873. Wong, W. *Econ. Bot.* **1976**, *30*, 103. The monotypic tropical genus ranges from Honduras southward and from Puerto Rico and the Lesser Antilles through Northern South America. (b) Tests were carried out under the auspices of the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute.

[7] Irradiation of the proton at 5.56 ppm simplified the multiplet at 2.23 ppm to an AB pattern whose appearance indicated the absence of adjacent protons.

[8] Attachment of a hydroxyl or alkoxy group to C-2 or C-8 was eliminated by the 5.56- and 6.20-ppm frequencies of H-2 and H-8.

0022-3263/81/1946-0761$01.00/0

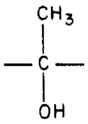
Table I. ^{1}H NMR Spectral Data of *Rolandra fruticosa* Constituents[a]

	2a	2b	3a	3b
H-1	5.17 br d (10)	5.11 br d (10)	2.22 dd (10, 12.5), 2.05 m[b]	2.21 dd (10, 12.5), 2.07 m[b]
H-2	5.56 dt (3.5, 10)	5.54 dt (3.5, 10)	5.82 dt (3, 10)	5.83 dt (3, 10)
H-3	2.23 m[c]	2.16 m[c]	4.74 br d (10)	4.77 br d (10)
H-5	6.23	6.14	5.66	5.66
H-8	6.20 dd (8.5, 12)	6.14 dd (9, 10)	6.42 dd (1.5, 5.5)	6.41 br d (5.5)
H-9a	3.57 br[d] dd (8.5, 12.5)	3.49 br[d] dd (8, 12.3)	2.79 dd (5.5, 14)	2.84 dd (5.5, 14)
H-9b	2.35 br[d] dd (12, 12.5)	2.29 br[d] dd (10, 12.5)	2.37 dd (1.5, 14)	2.33 br d (14)
H-13	5.04[e]	4.66[f]	4.37[e]	4.57[e]
H-14[g]	1.71 br[d]	1.64 br[d]	1.71	1.71
H-15[g]	2.06	1.96	2.04 br[h]	2.04 br[h]
H-3′	6.20 br, 5.74 br	6.21 br, 5.71 br	6.14 br, 5.68 br	6.15 br, 5.69 br
H-4′[g]	2.07 br	1.99 br	1.98 br	1.98 br
Misc.	2.16,[g] 2.14[g] (Ac)	2.05[g] (Ac)	2.00[g] (Ac), 3.57 m,[c] 1.27 t (7)[g] (EtO-)	2.00 (Ac),[g] 2.00 (Ac)[g]

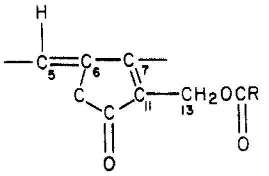
[a] Run at 270 MHz in $CDCl_3$. Shifts in parts per million downfield from Me_4Si. Unmarked signals are singlets. Figures in parentheses are coupling constants in hertz. [b] Partially obscured. [c] Two-proton intensity. [d] Broadened by coupling to H-1. [e] Center of AB system, $J_{AB} = 12$ Hz. [f] Center of AB system, $J_{AB} = 13.5$ Hz. [g] Three-proton intensity. [h] Coupled to H-3.

(corresponding carbon signal at 27.08 ppm by SFRD) and a methylene (H-9) at 3.57 and 2.35 ppm (carbon triplet at 37.11 ppm by SFRD). H-9a and H-9b were in turn coupled to H-8 at 6.20 ppm, while H-2 was further coupled to the protons of a second methylene group near 2.2 ppm (H-3) which like H-8 exhibited no additional coupling.[7] Hence C-3 and C-8 were assumed to adjoin quaternary carbons.[8]

Although the oxygen-containing functional groups of acetoxyrolandrolide required five carbon–oxygen single bonds, the ^{13}C NMR spectrum displayed only two signals in the 55–90-ppm region in addition to the two C–O doublets of B found at 68.28 and 68.63 ppm (SFRD). One, a singlet at 70.80 ppm, was attributed to partial structure



C



D

C as the ^{1}H NMR spectrum displayed a methyl singlet at 2.06 ppm associated with a carbon quartet at 29.46 ppm (SFRD). The second, a triplet at 55.21 ppm, was associated with a two-proton AB system at 5.04 ppm (H-13). It and the remaining signals of the ^{1}H and ^{13}C NMR spectra were accommodated most easily by the $\alpha,\beta,\gamma,\delta$-unsaturated lactone system D. This structural feature incorporated the sharp singlet of H-5 at 6.23 ppm and four vinylic carbon atoms, one of which was the carbon of an enol lactone appearing at 150.59 ppm. It was also in accord with the UV spectrum which indicated the presence of extended conjugation (λ_{max} 299 nm).

Combination of B, C, and D was possible in two ways. Only one of these, **2a** (devoid of stereochemistry), is in accord with the biogenetic isoprene rule. The question of how the three ester groups were distributed over C-2, C-8, and C-13 of this formula was partially solved by means of a minor somewhat more polar and noncrystalline constituent $C_{21}H_{26}O_8$. The ^{1}H NMR spectrum of this substance (Table I) clearly showed that it was a deacetyl derivative of **2a**, with C-13 carrying a hydroxyl instead of an acyloxy function. Acetylation of **2b** afforded **2a**, hence the methacryl ester of **2a** was attached to C-2 or C-8, but attempts at partial hydrolysis of **2a** to decide between the two possibilities were unsuccessful.

An X-ray analysis was undertaken to resolve this ambiguity and to ascertain the stereochemistry of the molecule which did not yield easily to NMR techniques. Crystal data are given in the experimental section. Tables III–VI listing final atomic and final anisotropic thermal parameters, bond lengths, and bond angles are available as

Table II. ^{13}C NMR Spectral Data of *Rolandra fruticosa* Constituents[a]

carbon	2a	3a	3b
1	128.76 d[b]	51.15 t[b]	51.15 t[b]
2	68.28 d[e]	68.86 d[e]	68.77 d
3	46.36 t	132.99 d[e]	133.11 d
4	70.80	135.49[c]	135.31[c]
5	128.65 d[b]	129.40 d	129.28 d
6	150.59	151.96	150.48
7	147.50	143.87	143.66
8	68.63 d[e]	70.08 d[e]	69.87 d
9	37.11 t[e]	44.19 t[b]	44.27 t[b]
10	133.90	72.55	72.62
11	127.43	123.61	125.57
12	167.15	168.84	169.07
13	55.21 t	61.82 t	54.39 t
14	27.08 q[e]	28.68 q	28.68 q
15	29.46 q	20.18 q[d]	20.14 q[d]
1′	165.70	166.06	166.31
2′	134.97	135.34[c]	135.31[c]
3′	127.20 t	126.97 t	127.35 t
4′	18.12 q	18.38 q	18.38 q
Ac	170.17, 169.94, 21.14 q, 20.67 q	170.21 21.17 q[d] 66.72 t[f] 15.10 q[f]	170.43 21.22 q[d]

[a] Run in $CDCl_3$ at 67.9 MHz. Unmarked signals are singlets. [b-d] Assignments may be interchanged. [e] Assignment confirmed by single proton frequency resonance decoupling. [f] Signals of ethoxy group.

Table VII. Torsion Angles (deg) in 2a with Standard Deviations in Parentheses

C(10)-C(1)-C(2)-C(3)	125.3 (5)
C(1)-C(2)-C(3)-C(4)	−85.0 (6)
C(2)-C(3)-C(4)-C(5)	67.6 (6)
C(3)-C(4)-C(5)-C(6)	−81.9 (8)
C(4)-C(5)-C(6)-C(7)	4.9 (13)
C(5)-C(6)-C(7)-C(8)	6.3 (11)
C(6)-C(7)-C(8)-C(9)	97.8 (5)
C(7)-C(8)-C(9)-C(10)	−45.1 (4)
C(8)-C(9)-C(10)-C(1)	−65.5 (5)
C(9)-C(10)-C(1)-C(2)	0.5 (7)
O(4)-C(6)-C(7)-C(11)	2.8 (6)
C(6)-C(7)-C(11)-C(12)	−3.2 (6)
C(7)-C(11)-C(12)-O(4)	2.5 (6)
C(11)-C(12)-O(4)-C(6)	−0.8 (6)
C(12)-O(4)-C(6)-C(7)	−1.2 (6)

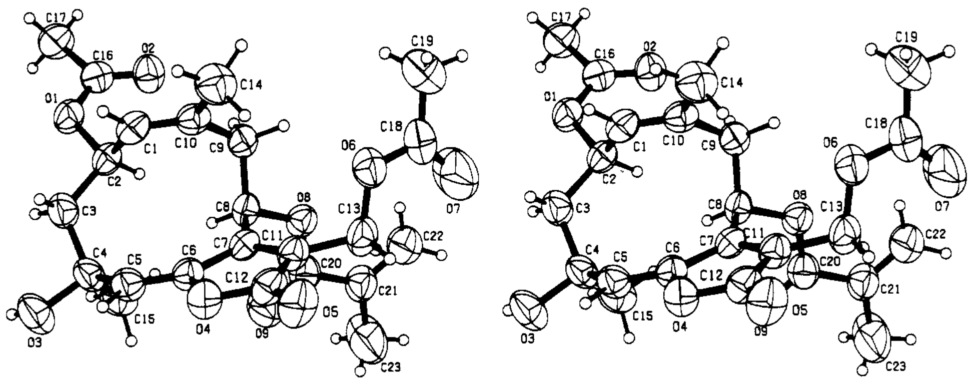


Figure 1. Stereoscopic view of **2a**.

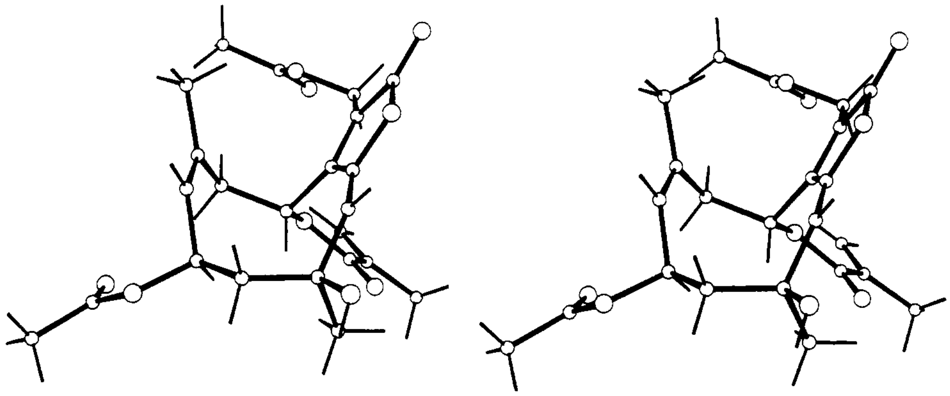
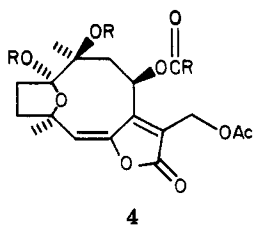


Figure 2. Atom framework of **2a**.

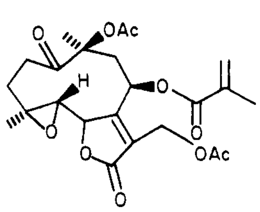
supplementary material; Table VII contains selected torsion angles.

Figure 1 is a stereoscopic drawing of the molecule showing its relative configuration in an orientation selected to conform to planar formula **2a**. The methacrylate is on C-8, both ring ester functions are quasi-equatorial and β as is the hydroxyl group on C-4. The 1,10 and 5,6 double bonds are cis; a curious feature of the molecule is the close alignment of these bonds. They are nearly parallel and three of the four nonbonded distances are quite short (Table VIII). The dihedral angle between the planes of the two double bond systems [C(9), C(10), C(1), C(2), C(14) vs. C(4), C(5), C(6), C(7), O(4)] is 50°.

As a result the molecule adopts an unusual conformation which may be likened to the seam on a tennis ball. This is seen more clearly in Figure 2, which shows the atom framework of the molecule. The five-membered lactone ring is essentially planar, the sum of the internal torsion angles being only 10.5°. Figure 2 also illustrates the essential coplanarity of the double bonds of the dienol lactone system (see Table VIII for relevant torsion angles); this may account for the bathochromic shift of 15–20 nm of **2a** compared with the UV absorption of the hirsutenolides for which structures of type **4** have been proposed.[4,5b]



4



5a

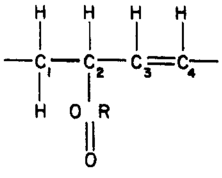
That the conformation in the crystalline state remains essentially the same in solution is indicated by the observed coupling constants which conform to those calculated from the dihedral angles and by the chemical shift of the C-10 methyl group which appears to be somewhat shielded by projecting over the C-7, C-11 double bond.

Table VIII. Nonbonded Distances, A

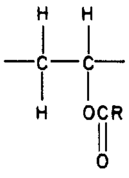
C(1)-C(5)	3.40
C(1)-C(6)	3.46
C(10)-C(5)	3.80
C(10)-C(6)	3.36

In addition to **2a** and **2b** the *R. fruticosa* extract also contained two unstable noncrystalline lactones **3a** and **3b** whose ultraviolet absorption maxima occurred at somewhat longer wavelengths, 318 and 312 nm, than those of **2a** and **2b**. IR and ^{1}H and ^{13}C NMR spectra (Tables I and II) of **3a**, $C_{23}H_{30}O_8$, indicated the presence of two esters (acetate and methacrylate), a tertiary hydroxyl under a methyl group (partial structure C), and again the enol lactone system D where H-5 occurred at somewhat higher field (5.66 ppm) than in **2a,b**. The substance also contained an ethoxy group which as revealed by the upfield shifts of H-13 and C-13 was attached to C-13 of D. SFRD experiments showed that the multiplets at 6.42 and 5.82 ppm, somewhat displaced to lower field in comparison with similar multiplets in the spectra of **2a,b**, represented hydrogens under the two ester functions, irradiation at these frequencies collapsing carbon doublets at 70.08 and 68.82 ppm, respectively, and that the broad doublet at 4.74 ppm was that of a second vinylic proton associated with a carbon doublet at 132.99 ppm. This vinyl proton was allylically coupled to the protons of a vinyl methyl group and vicinally coupled to the ester multiplet at 5.82 ppm. The latter was in turn coupled to the protons of a methylene group, thus permitting deduction of partial structure E. The remaining protons of the molecular formula were represented by the ABX system of partial structure F, the components of which exhibited no additional coupling. Hence E and F were not joined to give B as in the case of

2a.



E



F

Combination of C, D, E, and F to satisfy the NMR evidence and the biogenetic isoprene rule then yielded the carbon skeleton of formula **3a** in which the tertiary hydroxyl and the unconjugated double bond of **2a** have been interchanged. An analogous procedure based on the spectroscopic evidence of Tables I and II showed that the fourth lactone constituent of *R. fruticosa* was the 13-deethyl derivative **3b**. By comparison with **2b**, we named this substance which decomposed too rapidly for chemical studies isorolandrolide. 13-Ethoxyisorolandrolide (**3a**) which is somewhat more stable may or may not be an artifact formed during the isolation procedure.

An attempt to hydrolyze selectively one of the ester groups of **3a** in order to allocate the acetyl and methacrylate groups between C-2 and C-8 failed; however, we assume that, in analogy to **2a,b**, the methacryl esters of **3a,b** are attached to C-8 and the acetates to C-2. As regards stereochemistry, the absence of an NOE involving H-3 and H-15 of **3a** indicates that the 3,4 double bond is *E* (or trans). This requires (model) that the 5,6 double bond of **3a,b** be cis (or *E*).

The stereochemistry at C-2, C-8, and C-10 and the conformation in solution could then be inferred from the following. Irradiation at the frequency of H-15 caused a 25% enhancement in the strength of the H-2 signal. The H-3 signal was enhanced (10%) by irradiation at the frequency of H-9b at 2.37 ppm, but not by irradiation at the frequency of H-9a at 2.79 ppm, nor was it affected significantly by irradiation at the frequency of H-14. These data are best accommodated by the stereochemistry shown in planar formula **3a** and spatial representation **3A**. In this conformation, with the esters at C-2 and C-8 quasi-equatorial and β, H-15 is close to axial H-2 and that H-9 proton (H-9b) exhibiting the smaller coupling to α-oriented H-8 (J = 1.5 Hz) is close to H-3, thus accounting for the observed NOE's. The 3,4 double bond is at right angles or nearly so to the plane of the dienol lactone system which probably accounts for the unduly small bathochromic shifts in the UV spectra of **3a** and **3b** (19 and 13 nm, respectively) relative to **2a,b**.

The lack of an NOE involving H-14 and H-2 suggests the relative stereochemistry depicted for C-10; this was supported by the observation that H-2 was the only proton exhibiting a significant Eu(fod)$_3$-induced shift.[9] It should be noted that this proposal differs from the C-10 stereochemistry of glaucolide A (**15**).[2b,e,10]

The shapes of the two types of lactones from *R. fruticosa* are thus radically different. It is possible that this is responsible for the essentially antipodal nature of the CD curves (see Experimental Section). The absolute configurations, like those of all other "glaucolide" type lactones from Vernonieae, remain to be determined.

Experimental Section

Above ground parts of *Rolandra fruticosa* (L.) Kuntze, 13 kg, collected by Dr. E.L. Tyson on Feb 7, 1971, in El Nazito, Chiriqui, Panama (Tyson 6392 on deposit in Florida State University herbarium), were extracted with CHCl$_3$ and worked up as usual. The crude gum, 11.5 g, was preadsorbed on 18 g of silicic acid (Mallinckrodt 100 mesh) and chromatographed over a column of 200 g of the same adsorbent packed with CHCl$_3$–toluene (3:1), 200-mL fractions being collected as follows: fractions 1–18 (CHCl$_3$–toluenes 3:1), 19–21 (CHCl$_3$–MeOH, 49:1), and 22 (MeOH). Fractions 8 and 9 were combined and subjected to preparative TLC (CHCl$_3$–MeOH, 47:3) which resulted in two bands. The less polar component was further purified by TLC to yield 80 mg of noncrystalline **3a** which decomposed on standing even in the freezing compartment of a refrigerator: IR (CHCl$_3$) 3480, 1768, 1730, 1250 cm^{-1}; UV (MeOH) λ_{max} 318, 250 (sh), 212 nm (ϵ_{max} 4300, 4500, 9800); CD (MeOH) $[\theta]_{315}$ −12 400 (min), $[\theta]_{275}$ 0, $[\theta]_{240}$ +27 700 (last reading). The molecular ion was very weak but was detected by negative CI, the exact molecular weight then being determined by peak matching.

Anal. Calcd for $C_{23}H_{30}O_8$: mol wt 434.1941. Found: mol wt (mass spectrum) 434.1940.

Other significant peaks in the high-resolution mass spectrum were at *m/e* (composition, %) 288 ($C_{17}H_{20}O_4$, 38.0), 270 ($C_{17}H_{18}O_3$, 21.4), 260 ($C_{15}H_{16}O_4$, 24.1), 259 ($C_{15}H_{15}O_4$, 23.8), 244 ($C_{15}H_{16}O_3$, 95.9), 243 ($C_{15}H_{15}O_3$, 100), 242 ($C_{15}H_{14}O_3$, 91.1), 228 ($C_{14}H_{12}O_3$, 38.2), 226 ($C_{15}H_{16}O_2$, 36.2), 218 ($C_{13}H_{14}O_3$, 26.0), 217 ($C_{13}H_{13}O$, 63.2).

The more polar constituent **2a** of fractions 8 and 9 was also obtained from fractions 10 and 11 by preparative TLC and was recrystallized from ethyl acetate: total yield 0.55 g; mp 174–175 °C; $[\alpha]_D$ +60.6° (*c* 0.0495, CHCl$_3$); IR (CHCl$_3$) 3475, 1760, 1730 (very strong), 1640, 1250 cm^{-1}; UV (MeOH) λ_{max} 299, 257, 207 nm (ϵ_{max} 8600, 7400, 12 900); CD (MeOH) $[\theta]_{313}$ +2110 (max), $[\theta]_{248}$ −34 200 (min), $[\theta]_{210}$ +28 300 (last reading). The molecular ion was very weak, but detected by CI, the exact molecular weight then being detected by peak matching.

Anal. Calcd for $C_{23}H_{28}O_9$: mol wt 448.1733. Found: mol wt (mass spectrum) 448.1743.

Other significant peaks in the high-resolution mass spectrum occurred at *m/e* (composition, %) 302 ($C_{17}H_{18}O_5$, 4.3), 284 ($C_{17}H_{16}O_4$, 0.7), 262 ($C_{15}H_{18}O_4$, 0.4), 260 ($C_{15}H_{16}O_4$, 11.4), 259 ($C_{15}H_{15}O_4$, 18.9), 243 ($C_{15}H_{15}O_3$, 26.4), 242 ($C_{15}H_{16}O_3$, 43.6), 199 ($C_{13}H_{11}O_2$, 58.9), 173 ($C_{11}H_9O_2$, 100), 85 ($C_4H_5O_2$, 5.4).

Fractions 15–17 were combined and subjected to preparative TLC which gave 10 mg of **2b** and 40 mg of **3b**. The former was noncrystalline and exhibited IR bands (CHCl$_3$) at 3450, 1750, 1730, 1635, and 1250 cm^{-1}. The molecular ion was extremely weak; significant peaks in the mass spectrum which appeared to arise by fragmentation of the M + 1 ion were at *m/e* 261, 243, 218, and 200.

Anal. Calcd for $C_{21}H_{26}O_0$: mol wt 406.1628. Found: mol wt (mass spectrum) 406.1631.

Acetylation of 3 mg of **2b** (acetic anhydride–pyridine) followed by the usual workup and TLC (CHCl$_3$–MeOH, 47:3) gave material identical in all respects with **2a**.

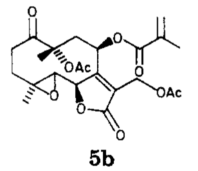
The more polar fraction **3b** from fractions 15–17 was a gum which decomposed rapidly. The low-resolution mass spectrum showed significant peaks at *m/e* 406 (M$^+$, extremely weak), 260, 242, 217, 199, 99, 83, 70, 55, and 43.

Anal. Calcd for $C_{21}H_{26}O_8$: mol wt 406.1628. Found: mol wt (mass spectrum) 406.1635.

---

(9) The experiment was marred by line broadening and rapid decomposition of the sample. In 0.2 M Eu(fod)$_3$, $\Delta\delta_{H2}$ was 0.2 ppm, in more concentrated solution $\Delta\delta_{H2}$ was ca. 0.4 ppm; other signals were not affected significantly.

(10) Much confusion has been caused by a mistake which occurred when the ring of formula **5a** was drawn in another way.[2b] In going from **5a** to the equivalent **5b**, an apical carbon is converted to a reentrant one, hence wedges and dashes must be interchanged and the substituents drawn inside the ring.[11]



5b

(11) Rogers, D.; Moss, G. P.; Neidle, S. *J. Chem. Soc., Chem. Commun.* **1972**, 142.

(12) Herz, W.; Högenauer, G. *J. Org. Chem.* **1962**, *27*, 905.

J. Org. Chem. **1981,** *46,* 765–770 **765**

X-ray Analysis of 2a. Single crystals of **2a** were tetrahedral, space group $P4_3$ (for the configuration shown in Figure 1) or $P4_1$, with a = 12.896 (1) Å, c = 13.773 (3) Å, and $d_{\text{cald}} = 1.300$ g cm^{-3} for $Z = 4$ ($C_{23}H_{28}O_9$, mol wt 448.47). The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse-height discrimination). A crystal measuring approximately 0.30 × 0.6 × 0.6 mm was used for data collection. A total of 1616 reflections was measured for $\theta < 57°$, of which 1570 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[13] and was refined by full-matrix least-squares. In the final refinement anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are $R = 0.043$ and $wR = 0.051$ for the 1570 observed reflections. The final difference map has no peaks greater than ±0.2 e Å^{-3}.

Registry No. 2a, 76010-16-7; **2b**, 76010-17-8; **3a**, 76010-18-9; **3b**, 76010-19-0.

Supplementary Material Available: Tables III–VI listing final atomic and final anisotropic thermal parameters, bond lengths, and bond angles (5 pages). Ordering information is given on any current masthead page.

---

[13] Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 368.

α-Nitro Sulfones. 2. Convenient New Synthesis and Selected Functional Group Transformations

Peter A. Wade,* Harry R. Hinney, Nayan V. Amin, Peter D. Vail, Scott D. Morrow,
Steven A. Hardinger, and Mallory S. Saft

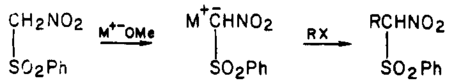
Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

Received September 25, 1980

(Phenylsulfonyl)nitromethane (1) is preferentially C-alkylated by benzylic halides and primary alkyl iodides, affording secondary α-nitro sulfone products. α-Nitro sulfones are also obtained from the corresponding C-alkylation of allylic acetates in the presence of catalytic tetrakis(triphenylphosphine)palladium. The palladium(0)-catalyzed reaction is stereospecific for geranyl and neryl acetates and is also regioselective. Desulfonation of α-nitro sulfones is readily accomplished by light-induced reduction with 1-benzyl-1,4-dihydronicotinamide (BNAH). Reduction of secondary α-nitro sulfones with 20% aqueous titanium(III) chloride affords nitriles. Oxidation with alkaline permanganate affords carboxylic acids.

α-Nitro sulfones have been known since the early 1900's[1] but have only recently received much attention.[2] Our interest in these compounds stems from their potential as useful synthetic intermediates. In particular, a variety of chemospecific reactions at the carbon bearing both nitro and sulfone functionalities is envisioned. For example, secondary α-nitro sulfones bear one highly acidic (p$K_a \approx$ 6)[2a] proton and are therefore known to undergo a limited number of carbanion processes such as Michael addition to 3-buten-2-one.[2b] Also of interest is the ease with which the sulfonyl group of tertiary α-nitro sulfones can be replaced in radical anion alkylations.[2c,d]

α-Nitro sulfones have previously been synthesized by three principal routes: sulfonylation of α-halo nitro compounds,[1,3] oxidation of α-nitro sulfides,[4] and alkaline nitration of sulfones.[2e] An alternate general route, useful for the preparation of secondary α-nitro sulfones, is presented here.[5] This new route involves alkylation of (phenylsulfonyl)nitromethane (1) (eq 1 and 2).



$$\underset{\textstyle SO_2Ph}{CH_2NO_2} \xrightarrow{M^{+}\,{}^{-}OMe} \underset{\textstyle SO_2Ph}{M^{+}\bar{C}HNO_2} \xrightarrow{RX} \underset{\textstyle SO_2Ph}{RCHNO_2} \tag{1}$$

1 **2a**, M = Na **b**, M = Li **3-10**

(Phenylsulfonyl)nitromethane was converted to its sodium (**2a**) or lithium salt (**2b**) by reaction with the appropriate alkali metal methoxide. The salts thus obtained are air insensitive and nonhygroscopic, so that they are easily handled without decomposition. The sodium salt **2a** gave predominant C-alkylation when treated with methyl iodide, primary alkyl iodides, and benzylic bromides or iodides, giving the alkylation products listed in Table I (eq 1). This is in sharp contrast to typical nitronates which give predominant O-alkylation under these conditions.[6] Yields of the C-alkylates were typically 50–75%, at least when polar aprotic solvent was employed. Conditions not permitting unencumbered nucleophile were deleterious to smooth reaction. For example, the lithium salt **2b** reacted only very slowly with benzyl iodide in re-

---

[1] Tröger, J.; Nolte, E. *J. Prakt. Chem.* **1920**, *101*, 136.

[2] (a) Zeilstra, J. J.; Engberts, J. B. F. N. *Synthesis* **1974**, 49. (b) Zeilstra, J. J.; Engberts, J. B. F. N. *J. Org. Chem.* **1974**, *39*, 3215. (c) Kornblum, N.; Boyd, S. D.; Ono, N. *J. Am. Chem. Soc.* **1974**, *96*, 2580. (d) Zeilstra, J. J.; Engberts, J. B. F. N. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 954. (e) Truce, W. E.; Klingler, T. C.; Paar, J. E.; Feuer, H.; Wu, D. K. *J. Org. Chem.* **1969**, *34*, 3104. (f) Zeilstra, J. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1975**, *97*, 7091.

[3] (a) Kornblum, N.; Kestner, M. M.; Boyd, S. D.; Cattran, L. C. *J. Am. Chem. Soc.* **1973**, *95*, 3356. (b) Arndt, F.; Rose, J. D. *J. Chem. Soc.* **1935**, 1. (c) Farrer, W. V. *Ibid.* **1964**, 904. (d) The reaction of arenesulfonyl bromides and iodides with nitronates apparently proceeds in a similar fashion: Zeilstra, J. J.; Engberts, J. B. F. N. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 11.

[4] (a) Kharasch, N.; Cameron, J. L. *J. Am. Chem. Soc.* **1953**, *75*, 1077. (b) Kharasch, N.; Cameron, J. L. *Ibid.* **1951**, *73*, 3864. (c) Hünig, S.; Boes, O. *Justus Liebigs Ann. Chem.* **1953**, *579*, 23.

[5] For a preliminary account, see: Wade, P. A.; Morrow, S. D.; Hardinger, S. A.; Saft, M. S.; Hinney, H. R. *J. Chem. Soc., Chem. Commun.* **1980**, 287.

[6] The difference is attributed to the electronic effect of the phenylsulfonyl substituent. For reviews concerning the chemistry of nitro compounds, particularly alkylation reactions, see: (a) Coombes, R. G. In "Comprehensive Organic Chemistry"; Sutherland, I. O., Ed.; Pergamon: New York, 1979; Vol. 2, p 305; (b) von Schickh, O.; Apel, G.; Padeken, H. G.; Schwartz, H. H.; Segnitz, A. In "Methoden der Organische Chemie (Houben-Weyl-Müller)"; Georg Thieme Verlag: Stuttgart, 1971; Vol. 10, p 1; (c) Ioffe, S. I.; Leont'eva, L. M.; Tartakovskii, V. A. *Russ. Chem. Rev. (Engl. Transl.)* **1977**, *46*, 872.

0022-3263/81/1946-0765$01.00/0