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STUDIES ON STRUCTURALLY SIMPLE BUTENOLIDES. VI. THE POLYCYCLIC 3:1 ADDUCTS OF PROTOANEMONIN WITH *C*-NUCLEOPHILES

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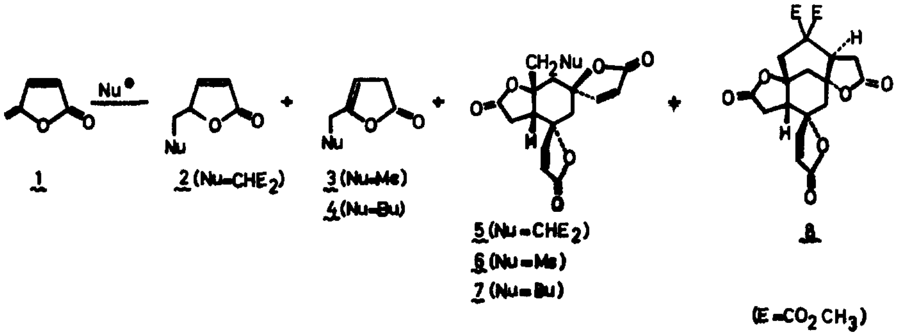
Abstract.- X-Ray diffraction analysis yielded the constitution, configuration and conformation of a tetracyclic 3:1 adduct formed by reaction of protoanemonin 1 with lithium dimethylcuprate. The same configuration was assigned by analogy to other tetracyclic 3:1 adducts formed by reaction of 1 with lithium di-*n*-butylcuprate or dimethyl sodiomalonate. A pentacyclic 3:1 adduct also formed in the last reaction was fully assigned (constitution, configuration, conformation) by analysis of its 300 MHz 2-D COSY NMR spectrum.

INTRODUCTION

The reaction of protoanemonin 1 with several types of nucleophiles has been thoroughly investigated in recent years[1]. Thus *O*- and *S*-heteronucleophiles are known to give initially 1:1 adducts by 1,6-addition, the nucleophile becoming linked to the exocyclic methylene carbon of 1[2]. *C*-Nucleophiles, such as dimethyl sodiomalonate or lithium dialkylcuprates, also behave in the same way, and thus the 1:1 adducts 2, 3 and 4 have been isolated[3] (Scheme 1). However, considerable yields of tetracyclic 3:1 adducts 5, 6 and 7 were also obtained from these reactions, and in addition the pentacyclic 3:1 adduct 8 has also been isolated along with 5 (Scheme 1). Although mechanistically reasonable[3], the structures assigned to adducts 5-8 could not be confirmed from routine spectral and physical data. The present paper reports the full characterization of tetracyclic 3:1 adduct 6 by X-ray diffraction analysis, the structural assignment of the related 3:1 adducts 5 and 7 by analogy with 6, and the full constitutional and stereochemical assignment of pentacyclic 3:1 adduct 8 by analysis of its 300 MHz 2-D COSY NMR spectrum.



Scheme 1

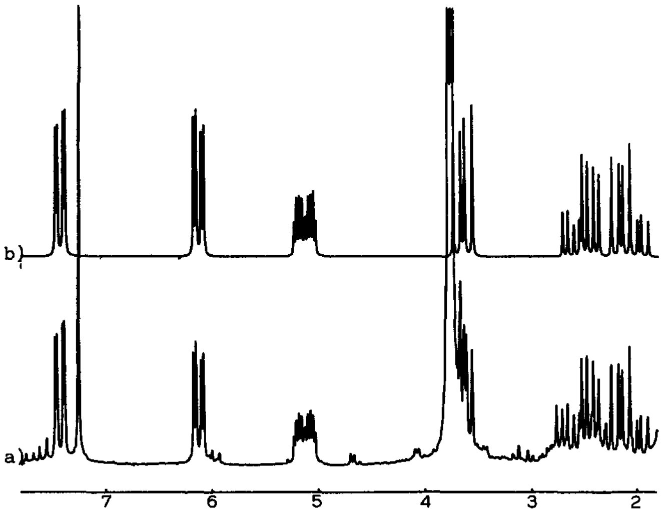


Fig. 1.- 80 MHz ^1H NMR spectra of 2 in $CDCl_3$: a) Experimental; b) simulated (refined data given in Table I).

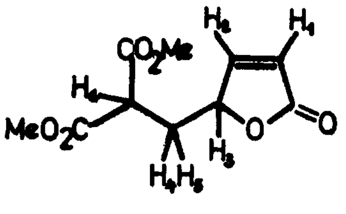


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Table 1. Analysis of the 80 MHz ^1H NMR spectrum of 2 in $CDCl_3$[a]

Proton	δ	mult.	J's
H_1	6.13	dd	$J_{1,2} = 5.7$; $J_{1,3} = -2.0$
H_2	7.42	dd	$J_{2,3} = 1.7$
H_3	5.13	m	$J_{3,4} = 8.8$; $J_{3,5} = 3.8$
H_4	2.10	ddd	$J_{4,5} = -14.6$; $J_{4,6} = 5.5$
H_5	2.53	ddd	$J_{5,6} = 8.8$
H_6	3.65	dd	

a) The two methoxycarbonyl groups appeared as singlets at δ 3.75 and 3.78 ppm.

RESULTS AND DISCUSSION

A comment on the ^1H NMR spectrum of 1:1 adduct 2 (Fig. 1) is pertinent here. Iterative simulation analysis of this spectrum yielded the shifts and couplings given in Table 1. This spectrum shows two important features of γ-substituted-α,β-butenolides[4], namely the rather deshielded position of the absorption due to the olefinic H_β proton H_2 (at $\delta \simeq 7.5$ ppm; c.f. $\delta \simeq 6.9$ ppm for related α,β-unsaturated-δ-lactones[5]), and the similar magnitude ($\simeq 2$ Hz) of the scalar couplings between the allylic proton H_3 and both olefinic protons, H_1 and H_2 (opposed signs, however). Both properties were important in the structural assignment of 3:1 adducts[3].

Comparison of the spectral properties of tetracyclic 3:1 adducts 5-7, reported in the preceding paper[3], showed a common structure for the three adducts. Thus, a peak at m/e 275 ($M - CH_2Nu$) was present in their MS. Furthermore, the NMR spectra showed two pairs of doublets at the normal[4] α,β-butenolide H_β ($\delta \simeq 7.5$ ppm) and H_α ($\delta \simeq 6.0$-6.2 ppm) positions. The absence of further couplings for these signals indicated γ-disubstitution of both butenolide rings. However, complete structural assignment could not be achieved from routine spectral data alone. All three compounds were crystalline solids, but only 6 gave crystals suitable for X-ray analysis. Therefore a sample of 6 was subjected to X-ray diffraction analysis (see experimental). This settled the constitution and configuration of 6 (and, by analogy, of 5 and 7) as depicted in Scheme 1. The X-ray structure of 6 is reproduced in Fig. 2. As seen, the six-membered ring showed a distorted-flattened chair conformation, and the cis-fused butyrolactone displayed a half chair conformation, while both spiranic butenolide rings were practically planar.

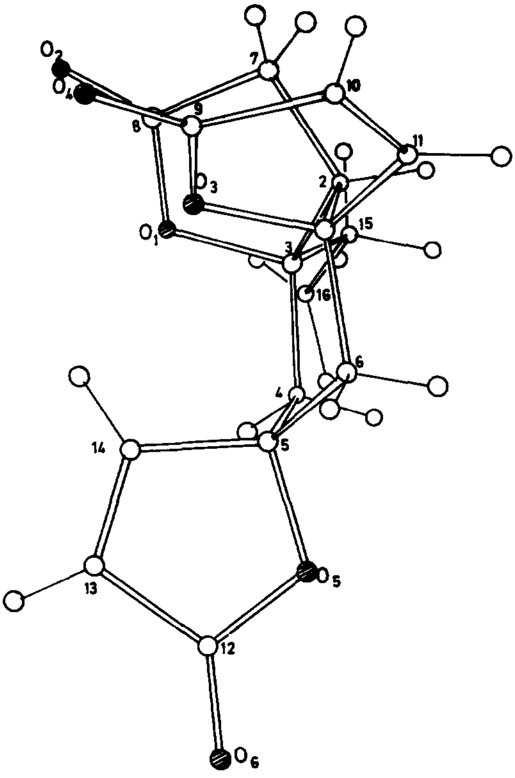

Fig. 2.- X-ray structure of 6.

Assuming for 5 a structure similar to that of 6, comparison of the routine spectra of tetracyclic adduct 5 with those of 8[3] suggested clearly a related pentacyclic structure for the latter, with only one spiranic α,β-butenolide ring. The 80 MHz ^1H NMR spectrum of 8 was not very informative[3], except for the unusual position of the spirobutenolide H_β olefinic proton at δ 7.03 ppm. As mentioned above, the normal range for H_β in α,β-unsaturated-γ-lactones is δ 7.4-7.8 ppm[4]. Examination of models revealed that, for some configurations of constitution 8, H_β could be quite close to one of the methoxycarbonyl groups. Since shielding has been demostrated above and below the plane of ester carbonyl groups[6], we concluded that this effect could explain the upfield shift featured by H_β. Furthermore, a NOE difference experiment performed by coherent irradiation at the methoxy groups (too close to irradiate selectively one of them) resulted in a clear, although small (1%), enhancement of the H_β signal at δ 7.03 ppm, thus confirming the proximity of H_β and a methoxycarbonyl group. Finally, a 300 MHz ^1H NMR 2-D COSY spectrum allowed the complete stereochemical assignment of 8 as depicted in Fig. 3. This particular type of 2-D experiemnt yields the normal 1-D spectrum on the main diagonal, while off diagonal crossed peaks correlate scalarly coupled protons. The bigger cross peaks are due to strongly coupled protons (geminal or vicinal couplings), while smaller cross peaks correlate long-range coupled protons. The 300 MHz 1-D ^1H NMR spectrum of 8, plotted in Fig. 3 on top of the 2-D COSY spectrum, confirmed the presence of twelve protons at 1.9-3.4 ppm, appearing as two ABX plus three AB overlapping systems, with several additional long-range couplings. Spectrum analysis was readily effected on the 2-D COSY contour plot, and

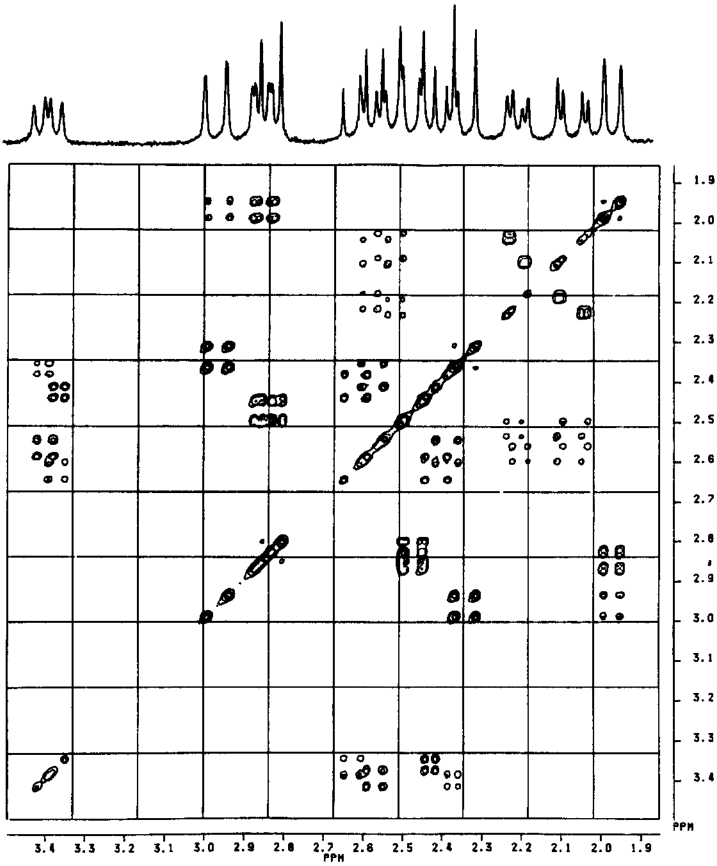

Fig. 3.- 300 MHz 2-D COSY spectrum of 8.

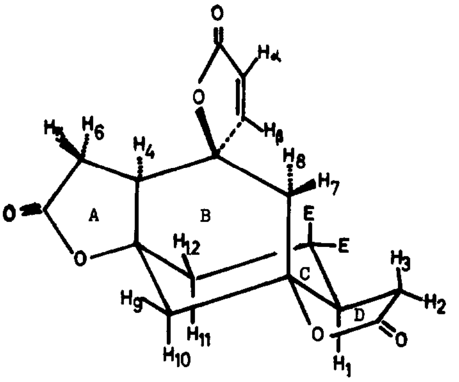

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Table 2. Analysis of the upfield region of the 300 MHz ^1H NMR spectrum of 8 in $CDCl_3$

Proton	δ	J's
H_1	3.38	$J_{1,2}$ = 8.5
H_2	2.40	$J_{1,3}$ = 12.7
H_3	2.59	$J_{2,3}$ = -17.2
H_4	2.21	$J_{4,5}$ = 4.4
H_5	2.07	$J_{4,6}$ = 11.5
H_6	2.55	$J_{5,6}$ = -19.1
H_7	2.96	$J_{7,8}$ = -15.9
H_8	2.34	$J_{9,10}$ = -12.9
H_9	2.85	$J_{11,12}$ = -14.8
H_{10}	1.98	$J_{7,10}$ = 0.5
H_{11}	2.83	$J_{9,12}$ = 2,6
H_{12}	2.47	$J_{1,10}$ = 1Hz
		$J_{7,9}$ = 1Hz

yielded the chemical shifts and coupling constants listed in Table 2.

The key for the proton assignment was the presence of an isolated (non overlapping) proton appearing as a double doublet (J = 12.7 Hz, J' = 8.5 Hz) at δ 3.38 ppm, an empty region in tetracyclic 3:1 adducts 5-7. COSY connectivities identified this proton as part of an ABX system, and its methine nature was clearly demonstrated by the presence of a geminal coupling (J = -17.2 Hz) between the two protons coupled to it. The absence of any signal in the δ 3.4 ppm region for tetracyclic adduct 5 ruled out the assignment of this signal to H_4 in 8, since the corresponding proton in 5 should appear in the same chemical shift region. Therefore, this absorption at δ 3.38 ppm was assigned to H_1, the only remaining methine proton in 8. Moreover, in spite of the presence of four methylene protons in ring C in 1,3 relationship with H_1, the latter did not show any long-range coupling, thus revealing the axial position of H_1 with respect to ring C. This defined the C/D ring fusion as trans, ring C as a chair and ring B as a boat, with a cis A/B ring fusion as in 5-7.

A second isolated (not long range coupled) ABX spin system was easily recognized in the 2.0-2.3 and 2.6 ppm region, and assigned to H_4-H_6. From the data shown in Table 2, it will be noted that for ring A $^{cis}J_{4,6} > {}^{trans}J_{4,5}$, while for ring D $^{trans}J_{1,3} > {}^{cis}J_{1,2}$. A study of vicinal coupling constants in butyrolactones, recently carried out in these laboratories[7] using Molecular Mechanics[8] and program 3JHH[9] demonstrates that both situations are equally common in γ-lactones, depending on their conformations.

The three remaining AB spin systems were easily recognized in the 2-D COSY spectrum. However, their assignment to individual protons H_7-H_{12} was not straightforward. Examination of models revealed that only in one case (H_9 and H_{10}) were the two protons of a single methylene group involved in long-range coupling through "W" pathways ($J_{9,12}$ and $J_{10,7}$). Therefore, the signals centered at 2.85 and 1.98 ppm should be assigned to the H_9/H_{10} pair. The great value (2.6 Hz) of the long-range coupling of the proton appearing at δ 2.85 ppm suggested the presence of a 1,3-diequatorial relationship within a chair cyclohexane ring, and therefore this signal was assigned to H_9. Then, following COSY connectivity patterns, including long range couplings, all other protons were assigned. Thus, the full assignment of the 300 MHz spectrum of 8 was completed, and the constitution and conformation proposed for this compound rested on a secure basis.

EXPERIMENTAL SECTION

80 MHz ^1H and 20 MHz ^{13}C NMR spectra were recorded in $CDCl_3$ solutions under FT mode using a Bruker WP 80 SY spectrometer. MS data were obtained under electron impact (70 eV) on a Hewlett-Packard 5985B spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument. ^1H NMR spectral simulations were carried out under ASPECT 2000 computer control, using the iterative program PANIC (a Bruker version of LAOCOON[10]). Compounds 2 and 5-8 were obtained as described in the preceding paper[3].

X-Ray Structure Determination and Refinement. A crystal of compound 6 (0.30 x 0.30 x 0.25 mm) was used to determine the cell parameters on a Philips 1100 four circle diffractometer. Lattice parameters were refined by a least-squares fit of 91 reflections. Crystal data are: $C_{16}H_{16}O_6$, Mr = 304.299, monoclinic, space group $P2_1/n$, a = 10.740(4) Å, b = 13.293(3) Å, c = 10.094(3) Å, β = 91.518(3)°, V = 1440.6(8) $Å^3$, Z = 4, Dx = 1.403(2), Do = 1.41 g/cm^3, F(000) = 640, μ = 8.650(1) cm^{-1}, λ ($CuK_α$) = 1.5418 Å.

Intensity data were collected from the same crystal on the same diffractometer with graphite monochromated, $CuK_α$ radiation for $2 < θ < 65°$ at a rate of 1 reflection/min. The w - 2θ scan technique was used. Two reflections were used as standard and remeasured after every 90 min, showed no variation. A total of 2449 independent reflections were measured of which 1966 were considered as observed with $I < 2σ(I)$, σ being determined from counting statistics. Lorentz and polarization correction were applied, but no correlation was made for absorption.

The structure was solved by direct methods (MULTAN 80)[11]. An E map generated from the phase set (288 reflections) with the highest combined figure of merit located all atoms of the molecule. After isotropic and anisotropic full-matrix least-square refinement (R = 0.085) a difference Fourier map revealed the positions of all H atoms that were included with isotropic temperature factor in the final refinement that converged at $R = Σ(|Fo| - |Fc|)/ |Fo| = 0.045$ and $R_w = (ΣwΔ^2/w|Fo|^2)^{½} = 0.057$. The minimized function was $Σ w(|Fo| - |Fc|)^2$ with $w = k/σ^2$, $σ^w = a + b(Fo)$ and k = 0.605 (a = 0.439, b = 0.003 when $0.22 < |Fo| < 11.42$; a = 0.057, b = 0.033 when $|Fo| > 11.42$). A difference Fourier final map had residual peaks less than 0.15 $eÅ^{-3}$.

The scattering factors were taken from International Tables for X-ray Crystallography[12]. The computations were made with programs of the X-ray 80 system[13], PARST[14] and PESOS[15] on a Vax 11/750 computer.

300 MHz 1-D and 2-D NMR spectra. These were obtained under FT mode using a Bruker AM 300 instrument, with Aspect 2000 computer control. The 1-D spectrum was recorded using quadrature detection, on 16 K data points for a spectral width of 2500 Hz, with a pulse width of 3.0 μs (30°) with no relaxation delay; 1169 scans were accumulated. The 2-D COSY spectrum was obtained using the pulse sequence π/2 - T - π/4 - FID, the COSY sequence[16]. A total of 256 FID's were obtained, with T (the continously variable mixing period) initially set at 3.0 μs, incrementing in 1.012 ms steps. The spectral widths were 840 Hz (from δ 1.2 to 4.0 ppm) in both dimensions. Double Fourier transformation in the magnitude spectrum mode, with sinebell windows in both dimensions, followed by symmetrization of the matrix about its diagonal, yielded the 2-D spectrum (Fig. 3).

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REFERENCES AND NOTES

1. P. Camps, J. Cardellach, J. Corbera, J. Font, R.M. Ortuño and O. Ponsatí, Tetrahedron, **39**, 395 (1983)
2. A. Calderón, J. Font and R.M. Ortuño, Ibid., **40**, 3787 (1984).

3. J. Bigorra, J. Font, C. Jaime, R.M. Ortuño and F. Sánchez-Ferrando, *Ibid.*, preceding paper in this issue.
4. a) J. Cardellach, C. Estopà, J. Font, M. Moreno-Mañas, R.M. Ortuño, F. Sánchez-Ferrando, S. Valle and L. Vilamajó, *Ibid.*, **38**, 2377 (1982); b) P. Camps, J. Cardellach, J. Font, R.M. Ortuño and O. Ponsatí, *Ibid.*, p. 2395.
5. J.A. Elvidge and P.D. Ralph, *J. Chem. Soc. (B)*, **1966**, 243.
6. a) L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd. Edition, Pergamon Press, Oxford, 1969, p. 88-92; b) J.W. ApSimon, P.V. Demarco, D.W. Mathieson, W.G. Craig, A. Karim, L. Saunders and W.B. Whalley, *Tetrahedron*, **26**, 119 (1970).
7. a) C. Jaime, unpublished results; b) J. Font, C. Jaime, F. Sánchez-Ferrando, L. Vilamajó, J.L. Briansó, J.F. Piniella and X. Solans, *Tetrahedron*, submitted.
8. a) A. Burkert and N.L. Allinger, "Molecular Mechanics", American Chemical Society, Washington, D.C. (1982); b) O. Erner, "Aspekte von Krafteldrechnungen", Wolfgang Baur Verlag, Münich (1981); c) E. Osawa and H. Musso, *Angew. Chem. Int. Ed. Engl.*, 22, 1 (1983); d) E. Osawa and H. Musso, *Topics Stereochem.*, 13, 117 (1982).
9. E. Osawa and C. Jaime, *Quantum Chemistry Program Exchange*, III (3), program no. 461 (1983).
10. S.M. Castellano, "LAOCN3", in "Computer Programs for Chemistry", D.F. De Tar (ed.), Benjamin, New York, 1968, Vol. 1, p. 10.
11. P. Main, S.E. Hull, L. Lessinger, G. Germain, J.P. Declercq and M.M. Woolfson, "MULTAN 80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data", Universities of York, England, and Louvain, Belgium (1980).
12. "*International Tables for X-Ray Crystallography*", vol. IV, p. 99, Kynoch Press, Birmingham (1974).
13. J.M. Stewart, F.A. Kundell and J.C. Balwin, "The XRAY 80 System", University of Maryland, College Park, Maryland (1980).
14. M. Nardelli, "PARST", University of Parma, Italy (1980)
15. M. Martínez-Ripoll and F.H. Cano, "PESOS", Instituto Rocasolano, C.S.I.C., Madrid, Spain (1975).
16. a) W.P. Aue, E. Bartholdi and R.R. Ernst, *J. Chem. Phys.*, **64**, 2229 (1976); b) K. Nagayama, *et al.*, *J. Magn. Reson.*, **40**, 321 (1980).
17. The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this paper.
18. Supplementary data available: Atomic coordinates and thermal parameters for all atoms in compound 6, bond distances and bond angles, all with standard deviations. See Notice to Authors, *Tetrahedron*, 40(2), ii (1984).