AN UNUSUAL ACID-CATALYZED REARRANGEMENT OF 1,2,4-TRIOXANES

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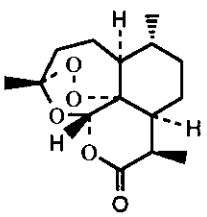
Abstract - A new Lewis acid-catalyzed rearrangement of the peroxide group in two 1,2,4-trioxanes, deoxoartemisinin and 12β-allyldeoxoartemisinin, yielding ring enlarged oxide, is described.

The discovery in 1979 that artemisinin (**1**), the active principle of the medicinal herb *Artemisia annua*, was an effective antimalarial drug against chloroquine-resistant strains of *Plasmodium faciparum* [1] prompted several groups to synthesize artemisinin, its derivatives,[2] and other 1,2,4-trioxanes.[3] A variety of esters, ethers, carbonates and other derivatives of dihydroartemisinin (**2**) were prepared. A study of the metabolites of the ethyl ether of dihydroartemisinin, arteether, with rat liver microsomes revealed that the ethyl group was rapidly lost to form dihydroartemisinin.[4] Hydrolysis of esters of dihydroartemisinin probably also occurred to yield dihydroartemisinin. Several groups[5] prepared 12α- and 12β-alkyldeoxoartemisinin derivatives from artemisinic acid in an effort to obtain compounds that would not be degraded enzymatically to dihydroartemisinin (**2**). We prepared 12β-allyldeoxoartemisinin (**3**) from dihydroartemisinin[6] and found it was accompanied by small quantities of an isomeric product (**4**), which was found to have arisen from the action of boron trifluoride etherate on **3**. The ^{1}H-nmr spectrum of **4** was similar to that of **3** except for a new resonance at δ = 4.10 (1H). The presence of overlapping resonances between the allyl group and another proton in its ^{1}H nmr spectrum made a structural assignment difficult. To circumvent this difficulty we treated a sample of deoxoartemisinin (**5**),[7] with boron trifluoride etherate. A less polar isomeric product (**6**) was formed in satisfactory yield (57%), with a new

resonance at $\delta = 4.03$ (1H) similar to that present in **4**. The DEPT spectrum of **6** showed it had the same number of CH, CH_2, and CH_3 resonances as that of the starting material. Comparison of the ^{13}C nmr spectra of **5** and **6** showed that the C-6 resonance, at the terminus of the peroxide group, had undergone a large downfield shift (80.1 to 110.2 ppm) in **6**, while the shift of C-4 was much smaller (104 to 108 ppm). The similarity in the chemical shifts of both quaternary carbons (108 and 110 ppm) suggested that C-6 had become attached to two oxygen atoms in **6**. The fact that **5** and **6** were isomeric and the need to attach a second oxygen to C-6 indicated that the peroxide group had been destroyed in forming **6**. A tentative structural assignment of the rearranged product as **6** was made based on the above nmr data in addition to its ^1H, homonuclear COSY and HMQC (Figure 1) spectra. Structure-activity studies of artemisinin derivatives demonstrated that their antimalarial properties required the presence of the peroxide group.[8] An *in vitro* test of **6** as an antimalarial drug demonstrated that this compound no longer possessed antimalarial activity, a finding that is consistent with the above mentioned structure-activity results.



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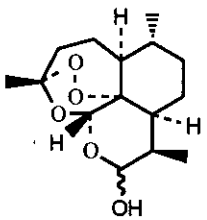

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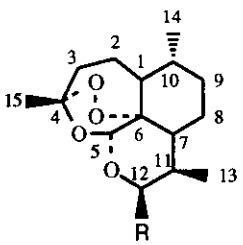
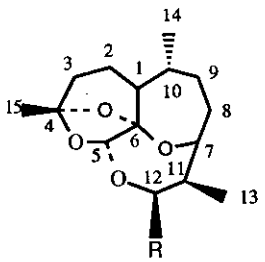


3. R = $CH_2CH{=}CH_2$



4. R = $CH_2CH{=}CH_2$

5. R = H

6. R = H

In order to obtain additional data to confirm the structure of **6**, a series of nmr measurements, long range heteronuclear correlation experiments (HMBC)[9] were performed to identify protons and carbons separated by two or three bonds. The results from the above experiments enabled us to identify protons on carbons separated by an oxygen atom. The observed correlations between protons and carbons separated by two or three bonds are showed

Figure 1. HMQC Spectrum of **6**

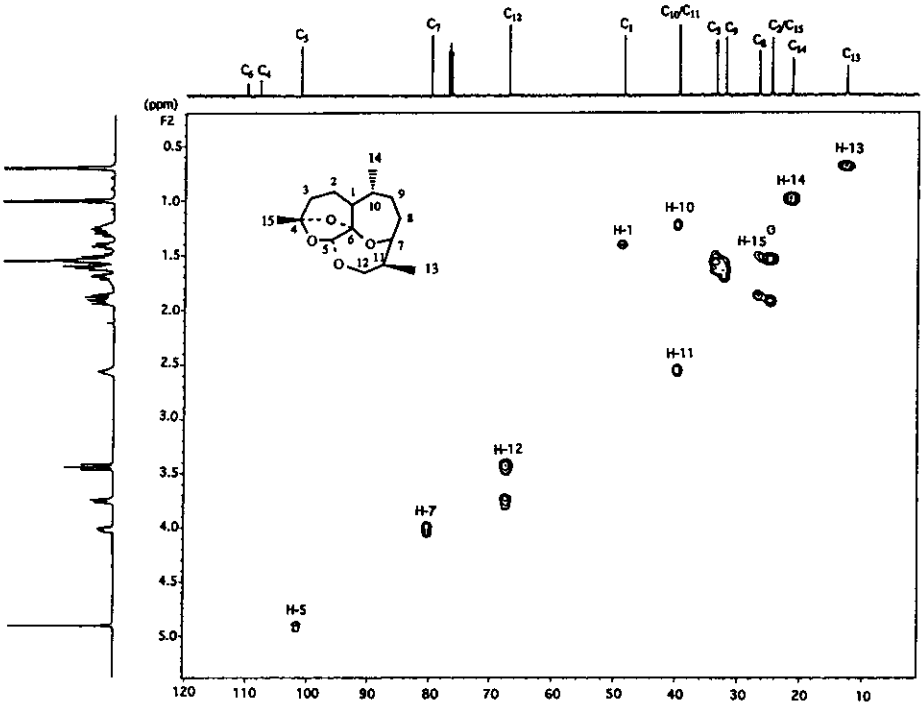
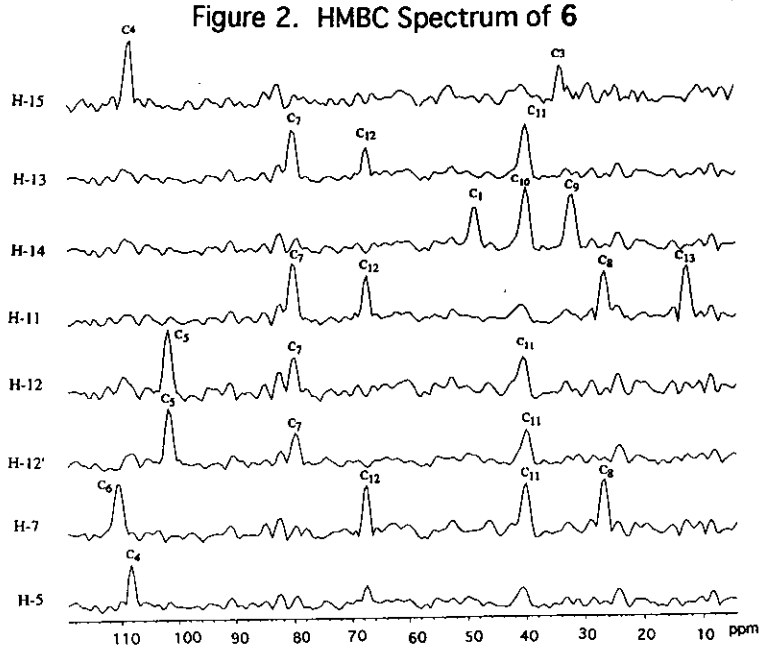


Figure 2. HMBC Spectrum of **6**



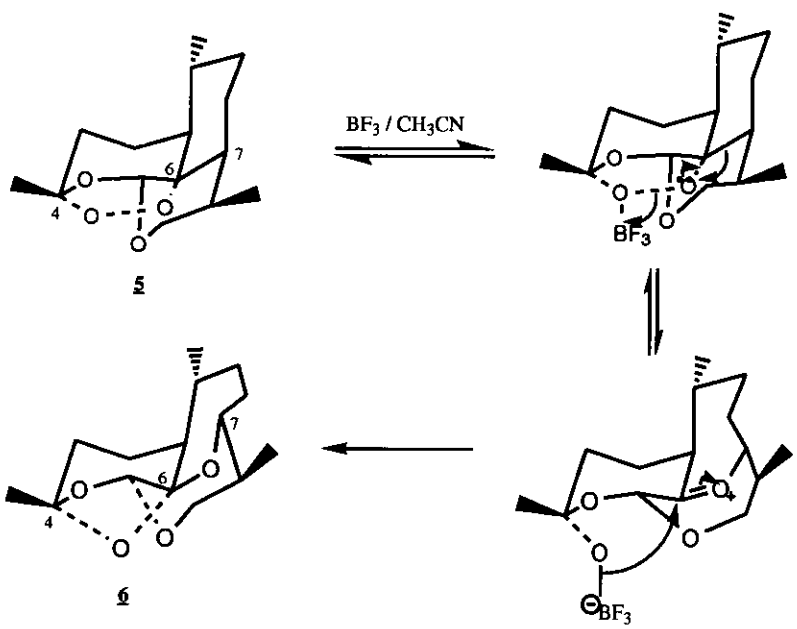
in Figure 2. The spectra show that H-7 ($\delta = 4.03$) is two or three bonds removed from C-6, C-12, C-11, and C-8. The downfield shift (35 ppm) of C-7 in **6** is accounted for by the new oxygen-bridge between C-6 and C-7. The presence of an oxygen atom on C-7 accounts for its chemical shift and suggested that one of the peroxide's oxygen atoms was inserted into the C_6-C_7 bond. The structure deduced for **6** accounts for all the long range couplings as well as for the coupling between the H-13 and C-7. No other structural changes in the starting material are required to account for the coupling between H-15, C-3 and C-4. The couplings between C-14, C-1, C-10, and C-9 are those present in the starting material and appear unchanged in **6**. An comparison between the ^{13}C chemical shifts of each carbon in **5** and **6** shows that the major chemical shift differences between the starting material and product involves C-6 and C-7 and are readily accounted for structure (**6**). Smaller differences in ^{13}C resonance between the starting material and product, i.e., C-5, C-8 and C-11, occur on carbons two bonds removed from the new oxygen atom bridge between C-6 and C-7.

Table 1: ^{13}C-Nmr Spectral Data and Assignment of the Rearrangement Products and the Corresponding Starting Materials in $CDCl_3$ (ppm).

Carbon	**5**	**6**	**3**	**4**
1	52.18(d)	48.58(d)	52.40(d)	47.95(d)
2	24.74(t)	24.78(t)	24.81(t)	25.06(t)
3	36.28(t)	33.69(t)	36.69(t)	33.04(t)
4	104.1(s)	108.1(s)	103.1(s)	108.0(s)
5	92.12(d)	101.4(d)	89.10(d)	98.14(d)
6	80.13(s)	110.19(s)	81.07(s)	105.6(s)
7	44.91(d)	80.13(d)	44.39(d)	77.98(d)
8	20.73(t)	26.78(t)	25.00(t)	29.29(t)
9	34.06(t)	32.20(t)	34.58(t)	33.31(t)
10	37.32(d)	39.87(d)	37.56(d)	39.21(d)
11	27.95(d)	39.93(d)	30.30(d)	40.67(d)
12	66.21(t)	67.36(t)	74.67(d)	72.35(d)
13	13.08(q)	12.86(q)	13.08(q)	8.46(q)
14	20.28(q)	21.53(q)	20.29(q)	20.46(q)
15	26.08(q)	24.85(q)	26.19(q)	23.92(q)
16	-----	---	34.33(t)	36.60(t)
17	---	---	136.4(d)	136.0(d)
18	--	---	116.0(t)	116.2(t)

Is it necessary to invoke a complex mechanism to rationalize cleavage of the peroxide group in **5** followed by reattaching the oxygen on C-4 to C-6 and inserting the other in the carbon bond between C-6 and C-7? Examination of a molecular model of **5** suggested a possible facile rearrangement as outline in Figure 3. The first step, formation of a complex between a peroxide oxygen and a Lewis acid, has precedence in an electrophile-induced rearrangement of 1,2,4-trioxanes catalyzed by trifluoromethanesulphonate described by Jefford *et al.*[10] Although there are differences between Jefford's mechanism and that in Figure 3, there are also analogies between the subsequent shift of a carbon-carbon bond to form an oxonium cation followed by addition of an oxygen to the carbon on the oxonium ion. Thus, the postulated rearrangement of **5** to **6** can be proceed via a facile, new rearrangement.

Figure 3. Mechanism of the Acid-Catalyzed Rearrangement of **5** to **6**



One consequence of our suggested mechanism is that other Lewis acids should be able to catalyze the same rearrangement. We have examined this point and data summarized in Table 2 show that a variety of Lewis acids catalyze the rearrangement. Although the yield of **6** with aluminum chloride is low, there were few differences

among the Lewis acids in their ability to catalyze the rearrangement in acetonitrile with the exception of zinc chloride, which neither catalyzed the reaction nor destroyed the starting material. The catalytic properties of Lewis acids depend both upon their strength and relative hardness.[11] Since they bind to one of the peroxide oxygens (a hard base), Pearson's law predicts hard acids should be the most effective catalysts. That appears to be the case; the behavior of zinc chloride is probably related to its position as a borderline acid.[11] Solvents such as acetonitrile or other molecules (e.g. ether) complex with the Lewis acid and increase the yield of the product, presumably by reducing the rate for the destruction of the starting material.

Table 2: Lewis Acid-Catalyzed Rearrangement of Deoxoartemisinin.

Lewis Acid	Solvent	**5** (Recovered, %)	**6** (%)
$BF_3{\cdot}O(C_2H_5)_2$	CH_2Cl_2	<<1%	60%
	CH_3CN	8%	65%
$SnCl_4$	CH_2Cl_2	11% (15%, 2 h)	9% (19%, 2 h)
	CH_3CN	13%	75%
$TiCl_4$	CH_2Cl_2	8%(10%, 2h)	<<1%
	CH_3CN	<<1%	65%
TMSOTF [a]	CH_2Cl_2	<<1%	40%
	CH_3CN	14%	70%
$ZnCl_2$ [b]	CH_2Cl_2	70%	<<1%
	CH_3CN	60%	<<1%
$AlCl_3$ [b]	CH_2Cl_2	<<1%	<<1%
	CH_3CN	30%	30%

a: Ratio of Deoxoartemisinin to Lewis Acid 1:1.5

b: Ratio of Deoxoartemisinin to Lewis Acid 1:10

In addition to providing a route for converting **5** to **6** the above mechanism enables us to assign stereochemistry at different carbons which were not possible from the earlier nmr experiments. Since the rearrangement initially

only involves a shift of C_6-C_7 bond to form an oxonium ion, the stereochemistry at the other centers should not differ in **5** and **6**. Support for that conclusion comes from data in Table 1 where the ^{13}C chemical shifts at most centers are unchanged in the product compared to that in the starting material. The chemical shifts of C-6 and C-7 differ greatly as would be expected as the termini of the new oxygen bridge. Other smaller chemical shift differences between **5** and **6** involve carbons two bonds removed from the new bridge. The stereochemistry at C-6 is dictated by geometric constrains, i.e., an examination of models indicates that it is difficult for the α-oxygen at C-4 to attack C-6 from the β-face because of the presence of the other rings which make it difficult of the intermediate to undergo a change in conformation. Reaction at the carbon of the oxonium ion also determines the stereochemistry of the new bond between C-6 and the oxygen atom of the oxonium ion. The suggested mechanism for the rearrangement and the nmr measurement have enabled us to assign the structure and stereochemistry of **6** and thus of **4** by analogy to **6**.

EXPERIMENTAL

Deoxoartemisinin (**5**) A solution of dihydroartemisinin (456 mg, 1.6 mmol) in dry CH_2Cl_2 (16 ml) in a 50 ml RB flask under argon was cooled to -20 °C. To this solution were added triethylsilane (0.40 ml, 2.4 mmol) and boron trifluoride etherate (0.24 ml, 1.92 mmol). The solution was then allowed to warm to 5°C over 2 h, and 15 ml of water added. The organic layer was separated, washed several times with water and dried over Na_2SO_4. The solution was concentrated and the crude product was purified by flash chromatography, hexane/CH_2Cl_2/ether=5/5/1 to afford 380 mg of pure product (88%); mp 103-105 °C (lit.,[7] 103-104 °C), $[\alpha]_D$= +86 ° (*c* 0.20, $CHCl_3$), +93 ° (*c* 0.20, EtOH).

Preparation of **6** A solution of deoxoartemisinin (56.0 mg, 0.21 mmol) in dried acetonitrile (10.0 ml) under argon was cooled to 0 °C. To this solution was injected boron trifluoride etherate (0.78 ml, 6.3 mmol). The solution was stirred at 0-5°C for 7 h, and 15.0 ml of dichloromethane was added. The organic layer was washed several times with water, dried over Na_2SO_4. The solution was concentrated, and the crude product chromatographed with hexane:CH_2Cl_2:ether=5:5:1 to yield 32.0 mg (57%); mp 158-160 °C ; $[\alpha]_D$= -52° (*c* 0.25, $CHCl_3$), -46 °(*c* 0.25, EtOH); ^1H-nmr ($CDCl_3$) δ 4.92 (1H, s), 4.03 (1H, m), 3.77 (1H, dd, J=12.9, 4.3 Hz), 3.45 (1H, t, J=12.0 Hz), 1.52 (3H, s), 1.00 (3H, d, J=6.4 Hz), 0.70 (3H, d, J=7.3 Hz); ^{13}C-nmr (Table 1); FT-ir (KBr)

2931, 1470, 1379, 1065, 876, 842, 821 cm^{-1}; ms (EI) m/z 268, 250, 207, 164, 124; Anal. Calcd for $C_{15}H_{24}O_4$; C, 67.14; H, 9.01. Found C, 67.26; H, 9.03.

12β-Allyldeoxoartemisinin (**3**) The preparation from the reaction of dihydroartemisinin (**2**) with allytrimethylsilane in the presence of boron trifluoride etherate will be described elsewhere (50%).[6] It had mp 76-78 °C (uncorrected), $[\alpha]_D$ = +66 °(*c* 0.47, $CHCl_3$), +71 °(*c* 0.47, EtOH); ^{1}H-nmr ($CDCl_3$) δ 5.89 (1H, m, *CH*=), 5.28 (1H, s, 5-*CH*), 5.05 (2H, m, =CH_2), 4.26 (1H, ddd, J=9.8, 6.0, 4.0 Hz, 12-*CH*), 1.40 (3H, s, 15-CH_3), 0.96 (3H, d, J=5.9 Hz, 14-CH_3), 0.84 (3H, d, J=7.6 Hz, 13-CH_3), ^{13}C-nmr (Table 1); FT-ir (KBr) 3075, 2958, 1378, 1050, 880, 823 cm^{-1}; ms (CI-NH_3) m/z 326 (M+NH_4^+, 100%), 309 (M+NH_4^+ - NH_3, 84%), 291 (M+NH_4^+ - NH_3 - H_2O, 17%); Anal. Calcd for $C_{18}H_{28}O_4$; C, 70.10; H, 9.15. Found C, 69.78; H, 9.13.

Preparation of **4** Compound (**4**) was prepared in 64% yield as described for **6**. mp 106-108 °C; $[\alpha]_D$= -48° (*c* 0.70, $CHCl_3$), -38° (*c* 0.70, EtOH); ^{1}H-nmr ($CDCl_3$) δ 5.85 (1H, dddd, J=16.8, 10.8, 8.1, 6.0 Hz), 5.17 (1H, s), 5.09 (1H, m), 5.04 (1H, m), 4.60 (1H, ddd, J= 9.6, 6.0, 3.9 Hz), 4.10 (1H, m), 2.28 (1H, m), 2.23(1H, m), 1.50 (3H, s), 0.97 (3H, d, J=6.4 Hz), 0.83 (3H, d, J=7.4 Hz); ^{13}C-nmr (Table 1); FT-ir (KBr) 3070, 2950, 1380, 1060, 875, 840, 820 cm^{-1} ; ms (CI-NH_3) m/z 326(M+ NH_4^+, 49%), 309(M+NH_4^+ - NH_3, 100%), 291(M+NH_4^+ - NH_3 - H_2O, 4%); Anal. Calcd for $C_{18}H_{28}O_4$; C, 70.10; H, 9.15. Found C, 70.17; H, 9.14.

General Procedure for the quantitative analysis of **6** by GC A solution of **5** (6.7 mg, 0.025 mmol) in 1.25 ml of dry acetonitrile or dichloromethane under argon was cooled in an ice-water bath for 10 min.; various Lewis acids (0.75 mmol) were added and the solution was stirred at 0 °C for 7 h. The solution was quenched with 1.0 ml of water and extracted into CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in ethanol (1.0 ml) and diluted as necessary for analysis by gc.

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