

## On the Relationship between Intramolecular Hydrogen Abstraction by Alkoxy Radicals and Deshielding by the Corresponding Hydroxy-groups as indicated by Nuclear Magnetic Resonance

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The  $^1\text{H}$  n.m.r. spectra of various steroids and triterpenoids and their hydroxy-derivatives have been studied. It is shown that a consideration of deshielding by hydroxy-groups can provide valuable information on the likely course of intramolecular hydrogen abstraction reactions of alkoxy radicals.

EFFICIENT intramolecular hydrogen abstraction by an alkoxy radical (Barton reaction<sup>1</sup>) normally requires a six-membered transition state in which the alkoxy radical and the carbon atom bearing the hydrogen to be abstracted can approach to within 2.5—2.7 Å of each other.<sup>2</sup> In systems where two or more transition states could fulfil these requirements it has not previously been possible to make any *a priori* predictions regarding the likely outcome of the reaction.<sup>1,2</sup> Thus, with steroids, structural changes in remote parts of the molecule produce compounds in which hydrogen abstraction by an  $11\beta$ -alkoxy radical ranges between the extremes of exclusive attack at either the 13- or the 10-methyl group. These variations are associated with the introduction of new trigonal centres, new 1,3-diaxial interactions, *etc.*, and in general the attendant conformational changes are too subtle to be gauged effectively by the use of molecular models. We now show that in such cases useful information regarding the likely mode of reaction of the alkoxy radical can be gleaned from a knowledge of the deshielding effects of the corresponding hydroxy-group.

There is good evidence that intramolecular hydrogen abstraction in the system  $\text{C-H}\cdots\text{O}^\cdot$  depends primarily

on the spatial orientation of the reacting centres,<sup>1,2</sup> whereas the same plus additional factors<sup>3</sup> have been discussed as making important contributions to long-range deshielding by hydroxy (and other) groups. Thus, although a complete correlation of the two phenomena is not to be expected, there are sufficient parallels to justify judicious comparisons. No particular significance is attached to the absolute value of the deshielding. Although in extreme cases this may be relevant,<sup>4</sup> in general we are primarily concerned with relative values for two similarly disposed groups within the same molecule. Photolysis of the nitrite of  $3\beta$ -acetoxy- $11\beta$ -hydroxy- $5\alpha$ -lanost-24-ene (I; R = OH) leads exclusively to 19-substituted products.<sup>5</sup> In keeping with this a comparison of the  $^1\text{H}$  n.m.r. spectrum of (I; R = OH) with that of  $3\beta$ -acetoxy- $5\alpha$ -lanost-24-ene<sup>6</sup> shows that the  $11\beta$ -hydroxy-group deshields the 10-methyl group to the greater extent (see Table). Irradiation of  $3\beta$ -acetoxy- $11\beta$ -hydroxy- $5\alpha$ -lanostane (I; R = OH, 24,25-dihydro) in the presence of lead tetra-acetate and iodine affords  $3\beta$ -acetoxy- $11\beta$ ,18-epoxy-19-iodo- $5\alpha$ -lanostane (II), the result of initial preferential attack of the alkoxy radical at the 10-methyl group, followed by attack at the 13-methyl group by a re-formed  $11\beta$ -alkoxy radical.<sup>7</sup>

In further support of our proposals we consider the photolysis of the nitrite of olean-12-ene- $11\beta$ -ol (III).<sup>8</sup>

<sup>5</sup> D. H. R. Barton, D. Kumari, P. Welzel, L. J. Danks, and J. F. McGhie, *J. Chem. Soc. (C)*, 1969, 332.

<sup>6</sup> R. B. Boar, D. A. Lewis, and J. F. McGhie, *J.C.S. Perkin I*, 1973, 1583.

<sup>7</sup> P. Roller and C. Djerassi, *J. Chem. Soc. (C)*, 1970, 1089.

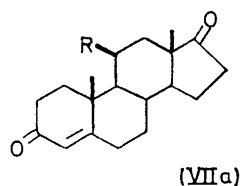
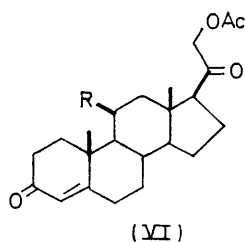
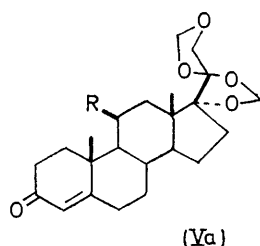
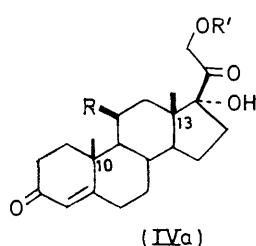
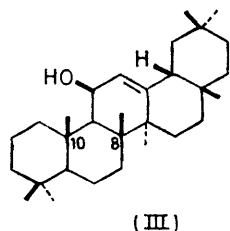
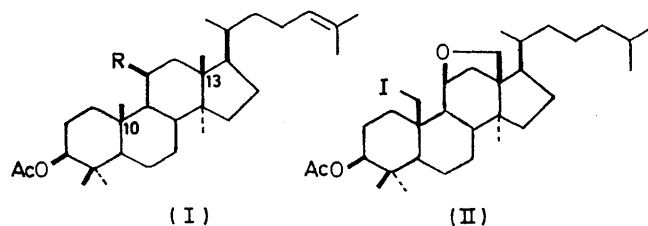
<sup>8</sup> D. H. R. Barton, E. F. Lier, and J. F. McGhie, *J. Chem. Soc. (C)*, 1968, 1031; E. F. Lier, Ph.D. Thesis, London, 1967.

<sup>1</sup> R. H. Hesse, *Adv. Free Radical Chem.*, 1969, **3**, 83.

<sup>2</sup> K. Heusler and J. Kalvoda, *Angew. Chem. Internat. Edn.*, 1964, **3**, 525.

<sup>3</sup> Perkin-Elmer NMR Quarterly, No. 12, 1974, p. 2 and references therein; L. M. Jackman and S. Sternhell, 'Applications of NMR Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon, Oxford, 1969, p. 72.

<sup>4</sup> H. Sugimoto, T. Tsuneno, and T. Masamune, *Tetrahedron Letters*, 1967, 4605; H. Sugimoto, N. Sato, and T. Masamune, *ibid.*, p. 1557.



b; 1,2-didehydro

Correlation of  $^1\text{H}$  n.m.r. spectral data for some steroids and triterpenoids and their  $11\beta$ -hydroxy-derivatives with known preferences for intramolecular hydrogen abstraction reactions

Compd.	$\tau$				$\tau_{\text{R}=\text{H}} - \tau_{\text{R}=\text{OH}}$		Hydrogen abstraction by an $11\beta$ -alkoxy radical from 13/10-methyl groups		Ref.
	13- $\text{CH}_3$		10- $\text{CH}_3$		13- $\text{CH}_3$	10- $\text{CH}_3$	Predicted	Observed	
	R = H	R = OH	R = H	R = OH					
(I)	9.229	8.998	9.069	8.789	0.231	0.280	10	10	5
(IVa; R' = H)	9.289	9.041	8.809	8.559	0.248	0.250	13 + 10		
(IVa; R' = Ac)	9.266	9.031	8.811	8.559	0.235	0.252	10		
(Va)	9.119	8.864	8.796	8.542	0.255	0.254	13 + 10	13 + 10	11
(VI)	9.281	9.050	8.807	8.554	0.231	0.253	10	10 > 13	12
(VIIa) *	9.06	8.83	8.76	8.50	0.23	0.26	10	13 only?	13
(IVb; R' = Ac)	9.257	9.003	8.768	8.534	0.254	0.234	13	13	11, 14
(Vb)	9.088	8.840	8.743	8.517	0.248	0.226	13	13	11, 14
(VIIb)	9.049	8.813	8.735	8.510	0.236	0.225	13	13	14
(VIIb) *	9.04	8.79	8.72	8.49	0.25	0.23			

\* Values taken from Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. and Pharm. Bull. (Japan)*, 1962, **10**, 338 for solutions in deuteriochloroform reported relative to cyclohexane ( $\tau$  8.56 at 60 MHz).

<sup>9</sup> N. S. Bhacca, D. D. Giannini, W. S. Jankowski, and M. E. Wolf, *J. Amer. Chem. Soc.*, 1973, **95**, 8421.

<sup>10</sup> D. L. J. Clive, *J.C.S. Chem. Comm.*, 1973, 695; K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Amer. Chem. Soc.*, 1973, **95**, 6137.

<sup>11</sup> M. Akhtar, J. M. Beaton, A. G. Hortmann, and D. H. R. Barton, *J. Amer. Chem. Soc.*, 1963, **85**, 1512.

This results in formation of the 25-oxime only, in line with the observation that in the  $^1\text{H}$  n.m.r. spectrum deshielding by the  $11\beta$ -hydroxy-group shifts the 10-methyl resonance by 0.46 p.p.m., but the 8-methyl resonance by only 0.27 p.p.m. downfield.

The Table summarises the  $^1\text{H}$  n.m.r. spectra of various steroids and their  $11\beta$ -hydroxy-derivatives, and indicates the general agreement between observed and predicted modes of attack. Future work will establish to what extent these trends can be quantified. It is already clear that this approach provides the basis for a useful and rapid probe of the effect that making other changes within the steroid nucleus is likely to have on intramolecular hydrogen abstraction reactions.  $^{13}\text{C}$  N.m.r. may prove an alternative method of probing the same problem since this technique is particularly sensitive to changes involving steric compression.<sup>9</sup>

We note that the method of determining deshieldings by comparing the n.m.r. spectrum of a compound with that of its hydroxy-derivative ceases to be valid if the introduction of the hydroxy-group causes any fundamental change in the conformation of the system.

Except for the dienone (Vb; R = H), compounds not already available were prepared by literature methods. This dienone was conveniently synthesised by treatment of the enone (Va; R = H) with benzeneselenenyl chloride, followed by oxidation with hydrogen peroxide.<sup>10</sup> Further details of this and related applications of organoselenium compounds will be reported subsequently.

#### EXPERIMENTAL

Solutions for n.m.r. spectroscopy were prepared by dissolving the compound (15 mg) in deuteriochloroform (0.2 ml). Where solubility did not permit this concentration, saturated solutions were used. Spectra were recorded at 90 MHz by use of a Perkin-Elmer R-32 instrument with field locked to tetramethylsilane as internal standard. Reproducibility was to within  $\pm 0.003$  p.p.m.

<sup>12</sup> D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.*, 1961, **83**, 4083.

<sup>13</sup> H. Reimann, A. S. Capomaggi, T. Strauss, E. P. Oliveto, and D. H. R. Barton, *J. Amer. Chem. Soc.*, 1961, **83**, 4481.

<sup>14</sup> D. H. R. Barton, M. Akhtar, and P. G. Sammes, *J. Amer. Chem. Soc.*, 1965, **87**, 4601.

$17\alpha,20$ :  $20,21$ -Bis(methylenedioxy)pregna- $1,4$ -dien- $3$ -one (Vb; R = H).— $17\alpha,20$ :  $20,21$ -Bis(methylenedioxy)pregn- $4$ -en- $3$ -one (Va; R = H) (200 mg) suspended in dry ethyl acetate (10 ml) was stirred at room temperature, and benzene-selenenyl chloride (108 mg) was added in portions over 30 min. After 5 h the clear, yellow solution was washed three times with water, then cooled in an ice-bath, and hydrogen peroxide (30%; 1 ml) in tetrahydrofuran (3 ml) was added. After 3 h the solution was washed with water, then evaporated, to yield starting material and the *dienone*, m.p. (from diethyl ether)  $200$ — $202^\circ$ ,  $[\alpha]_D -58^\circ$  ( $c$  0.95 in

$\text{CHCl}_3$ ),  $\nu_{\text{max}}$  1665, 1625, 1605, and  $1090\text{ cm}^{-1}$ ,  $\tau$  2.89 (1H, d,  $J$  10 Hz, 1-H), 3.75 (1H, dd,  $J$  10 and 1.5 Hz, 2-H), 3.90br (1H, s, 4-H), 4.79 and 4.95 (1H and 3H, respectively, s,  $2 \times \text{O}\cdot\text{CH}_2\cdot\text{O}$ ), 6.00 (2H, s, 21- $\text{H}_2$ ), 8.743 (3H, s, 19- $\text{H}_3$ ), and 9.088 (3H, s, 18- $\text{H}_3$ ) (Found: C, 71.4; H, 7.7.  $\text{C}_{23}\text{H}_{30}\text{O}_5$  requires C, 71.5; H, 7.8%).

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