Tetrahedron Letters No.10, pp. 1091-1099, 1966. Pergamon Press Ltd.
Printed in Great Britain.

THE CONFORMATION OF ESTERS AND THE "ACYLATION SHIFT". NMR EVIDENCE FROM PYRROLIZIDINE ALKALOIDS.

C. C. J. Culvenor

(Division of Organic Chemistry, C.S.I.R.O., Melbourne, Australia).

(Received 15 January 1966)

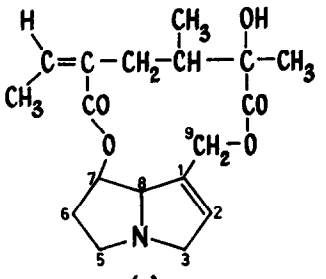
The greater deshielding of protons attached to the α-carbon atom of the alcohol moiety of esters (C^{α}), as compared with the same protons in the free alcohols, the so-called "acylation shift", is a well- known phenomenon in nuclear magnetic resonance spectroscopy[1]. In agreement with commonly quoted values, data obtained for a number of simple esters (Table 1) shows that the acylation shifts are essentially 1.0-1.15 p.p.m. for secondary alcohols, 0.45-0.60 p.p.m. for primary alcohols and only 0.2-0.3 p.p.m. for methanol. The physical basis of the shift has not previously been discussed although it is clearly associated with anisotropy effects of the ester system. Closer understanding has been hindered by lack of knowledge of the conformation of esters.

Senecionine (I) and other closely related 12-membered ring diesters of retronecine (II) are remarkable for the high degree of magnetic non-equivalence of the H9 protons which are the C^{α} protons of the primary ester system (Table 2; H9u is the upfield, H9d the downfield proton)[2]. They appear to constitute the first primary esters (esters being characterised by C^{α} cis to the carbonyl group, in contrast to lactones) whose conformation at C^{α} is essentially fixed and determinable.

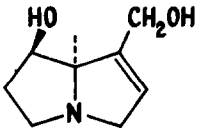
Alcohol	Chemical Shift of C^{α} Protons (δ,p.p.m.)	Ester	Chemical Shift of C^{α} Protons (δ,p.p.m.)	Acylation Shift (p.p.m.)
Methanol	3.35	Methyl formate	3.71	0.36
		Methyl acetate	3.60	0.25
		Methyl butyrate	3.60	0.25
		Methyl laurate	3.58	0.23
Primary alcohols				
Ethanol	3.59	Ethyl formate	4.17	0.58
		Ethyl acetate	4.06	0.47
		Ethyl propionate	4.07	0.48
		Ethyl n-butyrate	4.07	0.48
		Ethyl n-hexoate	4.06	0.47
		Ethyl iso-valerate	4.06	0.47
		Ethyl stearate	4.07	0.48
		Ethyl succinate	4.09	0.50
		Ethyl malonate	4.17	0.58
n-Butanol	3.53	n-Butyl lactate	4.14	0.61
Iso-Butanol	3.29	iso-Butyl acetate	3.77	0.48
iso-Hexyl alcohol	3.44	iso-Hexyl acetate	3.93	0.49
Benzyl alcohol	4.45	Benzyl acetate	5.02	0.57
		Benzyl propionate	5.04	0.59
		Benzyl stearate	5.18	0.73
Secondary alcohols				
Isopropanol	3.91	Isopropyl acetate	4.90	0.99
sec-Butanol	3.63	sec-Butyl acetate	4.75	1.12
Cyclohexanol	3.53	Cyclohexyl acetate	4.67	1.14

TABLE 1

Acylation Shifts of Alcohol C^{α} Protons (measured in 10% solutions in CCl_4 relative to internal TMS)



(I)



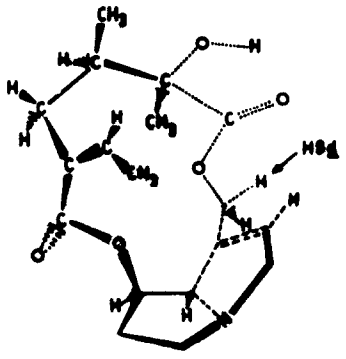
(II)

Alkaloid	Chemical Shifts (δ, ppm)		ΔH9 (ppm)	Mean H9 Shift (ppm)
	H9u	H9d		
(Retronecine (II))	4.25	4.25	-	4.25
Integerrimine	4.16	5.41	1.25	4.79
Jacobine	4.09	5.62	1.53	4.85
Jacozine	4.06	5.53	1.47	4.80
Retrorsine	4.07	5.46	1.39	4.77
Sceleratine	4.07	5.58	1.51	4.83
Senecionine (I)	4.02	5.49	1.47	4.76
Seneciphylline	4.04	5.44	1.40	4.74

TABLE 2

Chemical Shifts of H9 Protons in 12-Membered Ring Diesters of Retronecine

The conformation of senecionine can be defined as in the Fig. from consideration of the following data: planarity of the C-O-(CO)-C grouping in esters[3-8], preferred trans-planar orientation of the C=C-C=O group, hydrogen bonding of the C(OH)-C=O system[9], the relative magnitudes of the homoallylic and allylic coupling constants of the H9 protons (1.5-2.0 c/s for H9u and too small to be resolved for H9d)[2,10], and the crystal structure of the structurally related jacobine bromohydrin.[11] The oscillation permitted at C9 appears to be quite small. Proton H9d is almost coplanar

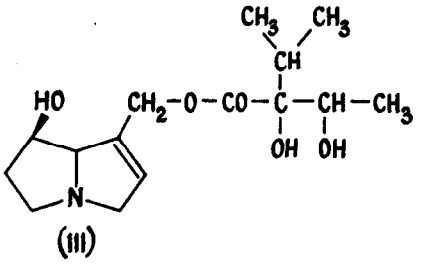


Conformation of Senecionine (The dotted lines indicate two groups of nearly coplanar bonds to which the H9d–C bond is common)

with the ester carbonyl group and thus in a region of intense deshielding; it is also nearly coplanar with the double bond of the pyrrolizidine ring and thus subject to further deshielding from this source. Proton H9u is in a region where it is neither deshielded nor shielded to any appreciable extent by either group. The difference in chemical shifts, ΔH9, gives a measure of the sum of the two deshielding effects and the largest values of ΔH9 in Table 2, c. 1.5 p.p.m., are believed to correspond to near maximum deshieldings. Calculation by the method of Yamaguchi et al.[12] gives a value of c. 0.5 p.p.m. for the deshielding of a C–H proton coplanar and cis to an adjacent double bond, leaving c. 1.0 p.p.m. for the deshielding of a CH–O–CO–R proton by the ester carbonyl group when the two are almost coplanar.

Two other aspects of the data in Table 2 are important. Firstly the mean of the H9u, H9d chemical shifts for each alkaloid lies in the δ4.74–4.85 region where are found also the chemical shifts of the H9 protons of retronecine esters in which these protons are magnetically equivalent (e.g.

the diastereoisomers, intermedine and lycopsamine (III), have δ_{H9} 4.78 and 4.81, respectively[13]). This region corresponds to a normal primary acylation shift, since the H9 protons in retronecine have δ4.25[2]. Magnetic non-



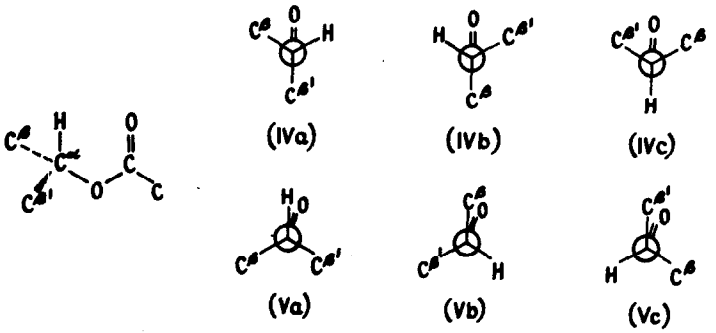
(III)

equivalence of the H9 protons is therefore the result of one proton being moved to lower field and the other proton being moved an equal amount to higher field, suggesting interference with an averaging process normally applicable. Secondly the H9u protons of senecionine and related alkaloids are similar in chemical shift to the H9 protons of retronecine itself (actually at slightly higher field). Here the main influences are only inductive effects and, with a weak additional deshielding operative in retronecine because the H9 protons have free rotation and spend some time in the plane of the double bond, it is apparent that the inductive effect of an ester group on C^{α} protons is not appreciably greater than that of a hydroxyl group.

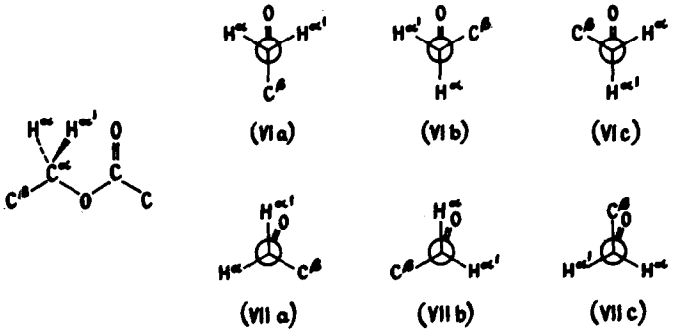
In the light of this evidence, the secondary acylation shift, 1.0-1.15 p.p.m., is seen to be consistent with a secondary ester conformation in which the C^{α} proton is in or near the plane of the ester group. Such a conformation is already strongly suggested by the available X-ray crystallographic data on secondary esters[14]. Interpretation of the 2:1 ratio between secondary and primary acylation shifts requires consideration of the possible conformations.

Secondary esters may have staggered conformations, (IVa), (IVb) and (IVc), or the eclipsed (Va), (Vb) and (Vc), there being an apparent prefer-

ence for eclipsing of C=O and C=C in aldehydes and butene[15,16]. The preferred forms will be (IVa), (IVb) and/or (Va); (Vb) and (Vc) are particularly improbable because of the very small approach distance between the carbonyl oxygen atom and an eclipsed C^{β} (c. 1.8Å).



Similarly the preferred forms of a primary ester will be the staggered (VIa) and/or the eclipsed (VIIa) and (VIIb); here, however, the other two staggered forms, (VIb) and (VIc), cannot be disregarded.



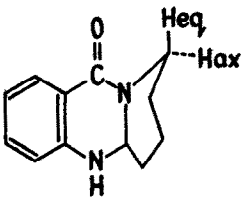
Considering staggered and eclipsed forms separately, it is seen that a 2:1 ratio between secondary and primary acylation shifts agrees precisely with the eclipsed conformations (averaging of (VIIa) and (VIIb) will cause

each C^{α} proton of primary esters to suffer half the deshielding experienced in the secondary ester (Va)) but not with the staggered conformations as literally interpreted. Averaging (VIb) and (VIc) would lead to half the deshielding effective on the C^{α} proton in (IVa), but predominance of (VIa) in primary esters would upset the ratio. However, if the unsymmetrical staggered forms, (IVa), (IVb), (VIb) and (VIc), are rotated to place the C^{α}–H bond closer to the plane of the carbonyl group than the C^{α}–C^{β} bond (i.e. approximating the eclipsed forms), consistency with a 2:1 ratio is possible. It is not unreasonable to expect deshielding of each C^{α} proton in (VIa) to be about half the value experienced in a near-eclipsed position.

Decision as to whether the lowest energy state of a primary ester is represented by the single staggered form (VIa) or the two eclipsed forms (VIIa) and (VIIb) will require measurements at very low temperatures. No significant changes in acylation shifts were noted for representative esters over the temperature range -40° to $+150^{\circ}$. In cases of magnetic non-equivalence of C^{α} protons in primary esters due to skewing of (VIa) or de-population of one of the forms (VIIa) and (VIIb), the resulting downfield shift of one proton and equal upfield shift of the other (c.f. Table 2) accords well with the eclipsed forms but is not inconsistent with the staggered form (VIa).

The acylation shift of methanol is lower than that of primary alcohols because three C^{α} protons now share the positions in the deshielding zone; the observed value, 0.23–0.36 p.p.m., one half to two-thirds the primary shift, is in agreement with expectation.

Similar arguments are applicable to CH–N–CO–R protons of amides for which model compounds are more readily available. In the amide (VIII), $\delta_{H\ ax} \sim 2.7$ and $\delta_{H\ eq.} \sim 4.6$, proton Heq being almost coplanar with the carbonyl group[17]. Allowing 0.4 p.p.m. for the differential shielding of axial and equatorial protons due to single bond anisotropies, the deshield-



(VIII)

ing by the carbonyl group of the nearly coplanar Heq must be c. 1.5 p.p.m., a value at least similar in magnitude to that found for similarly placed C^{α} protons of esters. Other similar examples of cyclic lactams exhibiting non-equivalent C^{α} protons were reported recently.[18]

ACKNOWLEDGEMENTS

The author is greatly indebted to Dr. S. R. Johns and Dr. J. A. Lamberton for discussion of conformational aspects and an early suggestion in regard to the amide (XI), and to Dr. A. McL. Mathieson for discussion of the X-ray data on secondary esters in advance of publication.

REFERENCES

1. L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy to Organic Chemistry", Pergamon Press, 1959; p. 55.
2. C. C. J. Culvenor and W. G. Woods, Australian J. Chem., 18, 1625 (1965).
3. J. M. O'Gorman, W. Shand and V. Schomaker, J. Amer. Chem. Soc., 72, 4222 (1950).
4. G. W. Wheland, Resonance in Organic Chemistry, Wiley and Sons, New York, 1955, p. 235.
5. J. Wilmshurst, J. Mol. Spectroscopy, 1, 201 (1957).
6. N. L. Owen and N. Sheppard, Proc. Chem. Soc., 1963, 264.

7. R. F. Curl, J. Chem. Phys., 30, 1529 (1959).

8. A. McL. Mathieson and J. C. Taylor, Tetrahedron Letters, No. 17, 590 (1961).

9. C. C. J. Culvenor and R. Dal Bon, Australian J. Chem., 17, 1296 (1964).

10. S. Sternhell, Revs. Pure Appl. Chem., 14, 15 (1964).

11. J. Fridrichsons, A. McL. Mathieson and D. J. Sutor, Acta Cryst., 16, 1075 (1963).

12. S. Yamaguchi, S. Okuda and N. Nakagawa, Chem. Pharm. Bull., 11, 1465 (1963).

13. C. C. J. Culvenor and L. W. Smith, unpublished data.

14. A. McL. Mathieson, Tetrahedron Letters, No. 46, 4137 (1965).

15. E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, "Conformational Analysis", Interscience, 1965; p. 19.

16. G. J. Karabatsos and N. Hsi, J. Amer. Chem. Soc. 87, 2864 (1965).

17. J. A. Lamberton and S. R. Johns, Australian J. Chem., 19, 151 (1966).

18. F. Bohlmann and D. Schumann, Tetrahedron Letters, No. 28, 2435 (1965).