Adina Alkaloids: the Structure of Adifoline

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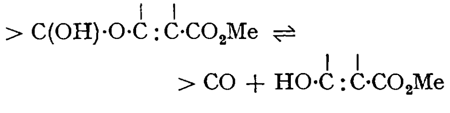
ONE of the alkaloids from the heartwood of *Adina cordifolia*, adifoline, m.p. > 350°, was previously investigated by Cross *et al.*, who showed that it was a β-carboline derivative and suggested the formula $C_{22}H_{20}N_2O_8$.[1] We have now determined the structure (1) for this alkaloid† on the basis of chemical and spectroscopic evidence, of which only the main points are outlined below.

Adifoline was shown to have the molecular formula‡ $C_{22}H_{20}N_2O_7$ and to contain one *C*-methyl and one *O*-methyl group; the latter was present in a methoxycarbonyl group since it could be removed by hydrolysis. Methylation of adifoline afforded trimethyladifoline, $C_{25}H_{26}N_2O_7$, whereas acetylation gave adifoline diacetate, $C_{26}H_{24}N_2O_9$, which was methylated to methyladifoline diacetate, $C_{27}H_{26}N_2O_9$. These reactions indicated a carboxy-group and two phenolic and/or enolic functions.

Reduction of adifoline with sodium borohydride gave a product which had lost a u.v. chromophore at 236 mμ (log ϵ 4·10) and no longer displayed two strong i.r. bands at 1640 and 1613 cm.$^{-1}$; subsequent methylation and acetylation yielded dimethyltetrahydroadifoline diacetate $C_{28}H_{32}N_2O_9$. On the other hand, the u.v. spectrum of trimethyladifoline was unaffected by sodium borohydride. This behaviour was consistent with the partial structure



$$>\mathrm{C(OH)\cdot O\cdot\overset{|}{C}:\overset{|}{C}\cdot CO_2Me} \rightleftharpoons >\mathrm{CO} + \mathrm{HO\cdot\overset{|}{C}:\overset{|}{C}\cdot CO_2Me}$$

since the β-alkoxy-$\alpha\beta$-unsaturated ester chromophore in adifoline can be destroyed by reduction of the enol, whereas in trimethyladifoline the enol form is protected as the methyl ether and cannot be reduced by borohydride.

The u.v. spectra of adifoline [$\lambda_{\max}$ (log ϵ): 234(4·61), 283(4·29), 362(3·68) mμ] and its derivatives all showed a bathochromic shift in acid

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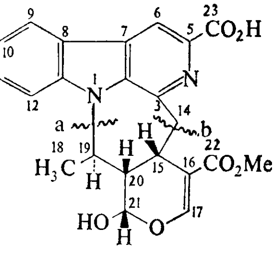
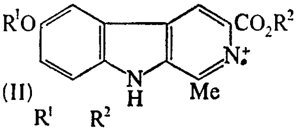
† Our alkaloid was identical with a sample of adifoline kindly supplied by Dr. T. J. King.

‡ All molecular formulae were determined by accurate mass measurement.

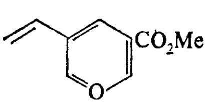
(I)



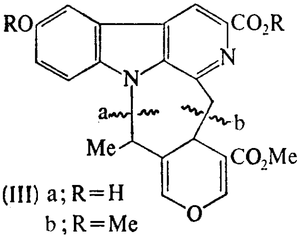
(II)



	R^1	R^2
a	H	H
b	Me	Me
c	Ac	H
d	Ac	Me



(IV)



(III) a; R=H
b; R=Me

solution and were suggestive of a substituted 3-carboxy-β-carboline chromophore. Support for this came from a strong peak at *m/e* 242 ($C_{13}H_{12}N_2O_3$) in the mass spectrum of adifoline which was attributed to ion (IIa) formed by cleavages (a) and (b) with hydrogen transfer; corresponding ions were displayed at *m/e* 270 (IIb) by trimethyladifoline, 284 (IIc) by adifoline diacetate, and 298 (IId) by methyladifoline diacetate. N.m.r. spectra indicated four aromatic protons whose chemical shifts and couplings were consistent with the β-carboline moiety of (I), except that the phenolic function could be at either C-10 or C-11 (*cf.* cordifoline[2]). Reduction of trimethyladifoline with lithium aluminium hydride afforded a compound whose u.v. spectrum [λ_{max} 233, 292 (sh), 299, 359 mμ] was practically superimposable on that of 7-methoxyharman,[3] thus demonstrating that the hydroxy-group is at C-10. Incidentally, this also proved that the substituent is in the same position in cordifoline, since a good correlation can be made between the u.v. and n.m.r. spectra of adifoline, cordifoline, adifoline diacetate, and cordifoline penta-acetate.

Adifoline was readily dehydrated to anhydroadifoline (IIIa), $C_{22}H_{18}N_2O_6$, m.p. 198—200°, which was methylated by diazomethane to dimethylanhydroadifoline (IIIb) $C_{24}H_{22}N_2O_6$. It was deduced that elimination of water from the hemiacetal had occurred to give an enol ether, since anhydroadifoline was unaffected by sodium borohydride. The presence of a methoxycarbonyl pyran system was indicated by u.v. and n.m.r. spectra and further supported by the mass spectrum. In addition to strong peaks at *m/e* 406(M^+) 362 ($M-CO_2$) and 242 (IIa) there was a major ion at *m/e* 165 ($C_7H_9O_3$) attributed to the pyrylium ion (IV). An ion at *m/e* 165 of similar

TABLE

Proton assignments from 100 *and* 220 *MHz. n.m.r. spectra in* $CF_3 \cdot CO_2H$

	Proton	Chemical shift (τ)	Multiplicity[a]	*J* (c./sec.)
Adifoline	H-6	0·90	s	—
	H-9	2·08	d	2
	H-11	2·41	q	9,2
	H-12	2·23	d	9
	H_a-14	5·76	q	16,10
	H_e-14	6·19	d	16
	H-15	6·63	q (br)	10,6
	H-17	2·07	-	—
	H_3-18	8·19	d	6
	H-19	5·50	m	11,6
	H-20	7·30	m	11,6,5
	H-21	3·23	d	5
	CO_2CH_3	6·16	s	—
Anhydro-adifoline	H_a-14	6·58	q	16,10
	H-14	5·44	d	16
	H-15	6·03	q	10,1
	H-17	1·94	d	1
	H_3-18	8·15	d	6
	H-19	5·14	q (br)	6
	H-21	2·56	s (br)	—
	CO_2CH_3	6·06	s	—
	H-6,9,11,12 as for adifoline.			

[a] s = singlet, d = doublet, q = quartet, m = multiplet, br = broadened.

intensity was given by dimethylanhydroadifoline but not by adifoline or trimethyladifoline.

Important clues to the structure were supplied by the observations that the n.m.r. spectrum of dimethylanhydroadifoline (in $CDCl_3$) was unchanged after shaking with D_2O, and the i.r. spectrum had no absorption in the 3000—4000 cm.$^{-1}$ region. Therefore, no NH or OH functions were present and the complete structure (I) could be deduced from the 100 and 220 MHz. n.m.r. spectra§ of adifoline and anhydroadifoline (in $CF_3{\cdot}CO_2H$). The more important data are summarised in the Table.

Multiplicities and coupling constants were determined with the use of benzene-induced solvent shifts to separate overlapping peaks and double irradiation where necessary, and proton assignments were confirmed by appropriate decoupling experiments. Thus in anhydroadifoline the C-18 methyl hydrogens are coupled to H-19, which is allylically coupled to H-21; H-21 is further broadened by a slight interaction with H-15; H-15 is coupled with H-17, but with only *one* hydrogen of the C-14 methylene group (H_a-14). Examination of a model indicated a dihedral angle of ~90° between H-15 and the pseudo-equatorial H_e-14 which would account for the lack of coupling. Finally, the hydrogens of the methylene group showed a strong geminal coupling in agreement with its presence in a relatively rigid ring system. This evidence is compatible with structure (IIIa) for anhydroadifoline.

An additional feature in the n.m.r. spectrum of adifoline is a proton designated as H-20 since it is coupled to H-15, H-19, and H-21, and this leads to structure (I). Furthermore, the observed coupling constants for H_a-14–H-15, H_e-14–H-15, H-15–H-20, H-20–H-19, and H-20–H-21 were compared with approximate values calculated from dihedral angles in Dreiding models and it was thus possible to assign the relative configuration shown for adifoline. The structure (I) is further substantiated by additional chemical and spectroscopic data which will be reported in detail in our full Paper.

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[1] A. D. Cross, F. E. King, and T. J. King, *J. Chem. Soc.*, 1961, 2714.
[2] R. T. Brown and L. R. Row, *Chem. Comm.*, 1967, 453.
[3] G. G. Doig, J. D. Loudon, and P. McClosky, *J. Chem. Soc.*, 1952, 3912.