Adirubine: a Novel Carboxy-indole Alkaloid

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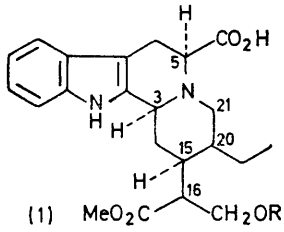
Summary Adirubine (**1a**), the first example of a new series of carboxy-alkaloids with the *Corynanthe* skeleton, has been isolated from *Adina rubescens* and its structure determined from chemical and spectral data.

THE isolation of cordifoline[1] and related carboxy-alkaloids[2,3] predicted the existence of a common precursor derived by condensation between tryptophan and secologanin (see preceding communication). This tetrahydrodesoxycordifoline (TDC) could be (a) a biogenetic cul-de-sac, (b) an alternative intermediate to vincoside[4] for some indole alkaloids, or (c) the progenitor of a novel range of acidic indole alkaloids in which the carboxy-group of tryptophan was retained.[5] The last possibility stimulated a search for members of this hypothetical tryptophan family, and we now report the discovery in *Adina rubescens* of the first example, adirubine, to which we have assigned the *Corynanthe* type structure (**1a**).

By a combination of gel permeation chromatography, gradient pH extraction, and preparative t.l.c. adirubine was isolated as the monoacetate, $C_{24}H_{30}O_6N_2$, m.p. 151—154°, $[\alpha]_D^{25}$ − 19° ($CHCl_3$). The u.v. spectrum indicated an indolic chromophore and carbonyl absorption at 1735 cm^{-1} and 3H singlets at τ 6·30 and 8·02 were consistent with CO_2Me and AcO functions respectively. The presence of an ethyl group was shown by a 3H triplet at τ 9·17. Treatment with diazomethane gave methyladirubine acetate, $C_{25}H_{32}O_6N_2$, $[\alpha]_D^{25}$ − 32° (MeOH), with an additional methoxy signal at τ 6·44. Both compounds had a 2H multiplet in the region τ 5·6—6·1 which was attributed to an acetylated primary alcohol since there was an upfield shift to τ 6·0—6·5 on deacetylation to methyladirubine, $C_{23}H_{30}O_5N_2$, $[\alpha]_D^{25}$ − 34° ($CHCl_3$). Reduction ($LiAlH_4$) of methyladirubine acetate afforded a triol, $C_{21}H_{30}O_3N_2$, and the deuteride a corresponding [$^2H_4$]triol, confirming the presence of three ester functions.

The mass spectra of adirubine derivatives and various model compounds (**2a**—**l**) showed clearly the basic tetracyclic *Corynanthe* structure and the positions of substituents (see Table).

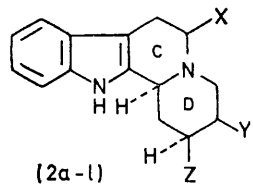
It was apparent that there were many similarities between the fragmentation patterns of adirubine derivatives (**2e**—**f**) and those of dihydrositsirikine (**2i**—**l**).[6] In particular both had ions (**3**) due to loss of the C-15 substituent and breakdown of ring D [(**4**) and (**5**)] in addition to the usual peaks at *m/e* 169 and 156. However, the presence in the former of major peaks at *m/e* 168 and 182 as opposed to 170 and 184 in the latter found an analogy in polyneuridine[7] where it



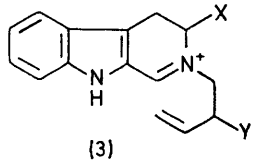
(1) MeO_2C CH_2OR

a; R = H

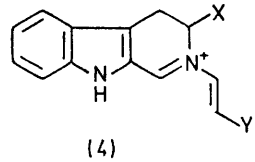
b; R = Ac



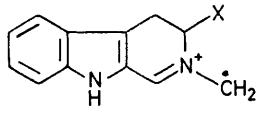
(2a-l)



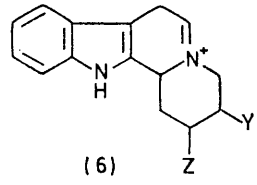
(3)



(4)



(5)



(6)

would readily aromatise. Identical behaviour was shown by methyladirubine, its acetate, and adirubine triol.

For confirmation that a group at C-5 would control the fragmentation in this way model compounds were synthesised. Heating of methyl L-tryptophanate and α-oxoadipic acid in acetic acid afforded a lactam, m.p. 176°, $[\alpha]_D$ + 198° ($CHCl_3$), which was smoothly reduced by diborane to the amino-ester (**2g**), $[\alpha]_D$ + 99° (MeOH), and by $LiAlH_4$ to the amino-alcohol (**2h**). In its mass spectra the ester was remarkably similar to methyladirubine with a base peak at $M - CO_2Me$ and other important ions at *m/e* 255, 223 ($M - CO_2Me - 2H$), 182, 169, 168, and 156; the alcohol was likewise analogous to adirubine triol.

Finally the ions (**4**) and (**5**) placed the ethyl group in adirubine at C-20. The unlikely alternative of C-21 was excluded firstly by the absence of any ion corresponding to (**5**) with retention of the ethyl group, and secondly by lack of the substantial $M - 29$ peak that might be expected if the ethyl were α to N_b like the C-5 substituent.

The c.d. spectrum of methyladirubine acetate displayed a positive Cotton effect between 300 and 250 nm and the absolute configuration at C-3 was thus readily established as α.[8] Since 15-H is almost invariably α one would expect a *cis* relationship between 3-H and 15-H and this was confirmed by the presence of Bohlmann i.r. bands at 2800, 2760, and 2735 cm^{-1} and the lack of any signal due to 3-H below τ 6·2 in its n.m.r. spectrum. On the assumption that adirubine is derived from L-tryptophan, it is likely that 5-H is also α, but the stereochemistry at C-16 and C-20 is unknown.

TABLE

	Substituents				*m/e* for ion[a]			
Structure (**2**)	X	Y	Z	M^+	(**3**)	(**4**)	(**5**)	(**6**)
a	CO_2H	Et	$MeO_2C{\cdot}CH{\cdot}CH_2OAc$	442	297	269	228	397
b	CO_2Me	"	"	456	311	283	242	397
c	CO_2CH_2D	"	"	457	312	284	243	397
d	CO_2Me	"	$MeO_2C{\cdot}CH{\cdot}CH_2OH$	414	311	283	242	355
e	CH_2OH	"	$HOCH_2CH{\cdot}CH_2OH$	358	283	255	?[b]	327
f	CD_2OH	"	$HOCD_2CH{\cdot}CH_2OH$	362	285	257	?[b]	329
g	CO_2Me	H	H	284	—	255	242	225
h	CH_2OH	"	"	256	—	?	?	225
i	H	Et	$MeO_2C{\cdot}CH{\cdot}CH_2OAc$	398	253	225	184	—
j	"	Et	$MeO_2C{\cdot}CH{\cdot}CH_2OH$	356	253	225	184	—
k	"	"	$HOCH_2CH{\cdot}CH_2OH$	328	253	225	184	—
l	"	CH_2OH	"	330	255	227	184	—

[a] Assignments were confirmed by accurate mass measurement; [b] Absent, but peaks were present 2 m.u. lower at 212 and 214 respectively corresponding to fully aromatised ions.

was diagnostic of an additional C–C bond in ring c. This could be correlated with the most striking difference which with adirubine acetate (**2a**), for example, was the ready loss of CO_2H to give the base peak at *m/e* 397, invariably accompanied by a smaller one due to loss of two more hydrogen atoms. The obvious inference was that the carboxy-group was attached to C-5 and cleavage was generating a favourable immonium ion (**6**), which in turn

We thus deduce the structure (**1b**) for adirubine acetate and (**1a**) for the naturally occurring adirubine, surely only the first of many congeners of the *Corynanthe–Strychnos* type. It will be of interest to see whether carboxy-representatives of the rearranged *Iboga* and *Aspidosperma* families will also be found.

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