Rearrangement of Catharanthine, Stemmadenine, and Tabersonine in Acetic Acid†

By R. T. BROWN, J. S. HILL, G. F. SMITH,* and K. S. J. STAPLEFORD
(*Department of Chemistry, The University of Manchester*, M13 9PL)
and J. POISSON, M. MUQUET, and N. KUNESCH
(*Faculté de Pharmacie de Paris, Paris-VIe*)

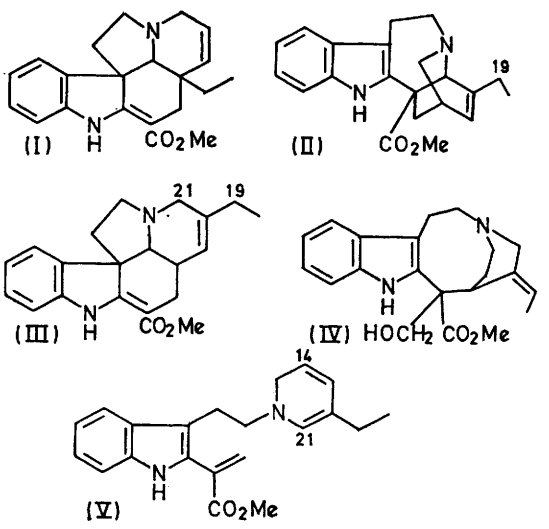
Summary Treatment of tabersonine with refluxing acetic acid under nitrogen yielded a new base, allocatharanthine (VI), and the derived (VII), but failed to produce detectable quantities of (±)-catharanthine or pseudocatharanthine, nor did similar treatment of stemmadenine afford any of these compounds.

SCOTT and QURESHI[1] reported the rearrangement in refluxing acetic acid of tabersonine (I) to (±)-catharanthine (II) (12%) and pseudocatharanthine (III) (28%), and of stemmadenine (IV) to (±)-tabersonine (12%), (±)-catharanthine (9%), and pseudocatharanthine (16%): these rearrangements were postulated to proceed by way of (V).

Such complex rearrangements, proceeding under simple conditions in relatively high yields, coupled with their obvious relevance to *in vivo* indole alkaloid transformations, are so remarkable and are of such great interest, that we decided to repeat them.

We report, after prolonged and careful study, our complete failure to detect *any* (II) or (III) in the products of the appropriate acetic acid treatment of (I), and any (I), (II), or (III) in the products of the same treatment of (IV).

Stemmadenine (IV; in 5—10 mg quantities) was heated in pure dry AcOH (a) in an evacuated sealed tube at 119°, (b) at reflux under N_2 in an oil-bath at 140°, and (c) at reflux in an oil-bath at 205—215°‡ over periods of time varying from 2—70 hr. In every case, the total ether-soluble bases had a pure indolic u.v. absorption with no



absorption at 320—330 nm, and by t.l.c. (see Table) could be seen to be completely free from (I), (II), and (III), the

† A part of this work concerning tabersonine was submitted by J. P. and M. M. as a preliminary communication at the Meeting on the Chemistry of Alkaloids, Manchester, April 1969.

‡ In our earlier experiments we used normal oil-bath temperatures of about 140°, but changed to temperatures of 200—210° on instruction from Professor Scott, to whom we are indebted for extensive unpublished information on the experimental conditions used in his laboratories.

appropriate regions remaining quite clear on spraying with ceric reagent even on heavy loading of the plate: added catharanthine (to an extent corresponding to a 1% yield) showed up as a clear blue spot. After 15 hr., the reaction mixture contained *ca.* 15% unchanged (IV) and *ca.* 50% *O*-acetyl-(IV); after 50 hr., 5% of (IV) was still present, together with *ca.* 55% *O*-acetyl-(IV).

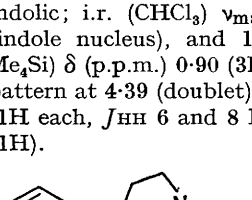
R_F values in various t.l.c. systems

	A	B	C	D
(I)	0·63	0·52	0·80	0·52
Dihydro-(I)	—	0·42	—	—
(II)	0·55	0·15	0·53	—
(III)	0·63	0·52	0·80	0·65
Dihydro-(III)	—	0·45	—	—
(IV)	0·15	—	—	—
O-Acetyl-(IV)	0·23	—	—	—
(VI)	—	0·12	0·36	—
Dihydro-(VI)	—	0·13	0·53	—
(VII)	—	0·20	0·53	—

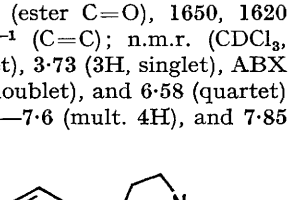
A: silica F/PhH, EtOAc, MeOH, 2:2:1.
B: silica F/$CHCl_3$, EtOAc, 9:1.
C: silica F/Et_2O.
D: silica F/$AgNO_3$/petroleum (40—60°), Et_2O, 2:1.

One of the reactions was carried out in [*O*-^{3}H] acetic acid, for one would then expect labelling of any (II) formed at C-19, and of (III) at C-19 and C-21: dilution analysis with (III) [total activity $1·89 \times 10^4$ d.p.m. from 8·1 mg (IV)] and a calculation based on the specific activity of (III) ($6·56 \times 10^7$ d.p.m./mg) formed from catharanthine in the same tritiated acetic acid, leads to an estimate of the maximum possible yield of (III) from (IV) of 4×10^{-3}%.

The refluxing acetic acid treatment (bath temp. 130°; 16 hr.) of tabersonine (I) was carried out on a large scale (318 mg.): the ether-soluble products (222 mg.) were isolated by column chromatography on silica, followed by preparative t.l.c. Neither catharanthine nor pseudocatharanthine was found, but, in addition to unchanged (I) (48%) and dihydro-(I) (vincadifformine) (14%), three closely related new compounds were found, the main one of which is an isomer of catharanthine, $C_{21}H_{24}O_2N_2$, to which the name allocatharanthine is given. This new base (17% yield; amorph; $[\alpha]_{578}$ + 63° $CHCl_3$), has a mass spectrum identical with that of catharanthine, and very similar t.l.c. behaviour. Structure (VI) is assigned to it on the above and following evidence: u.v. chromophore pure indolic; i.r. ($CHCl_3$) ν_{max} 1725 (ester C=O), 1650, 1620 (indole nucleus), and 1560 cm.$^{-1}$ (C=C); n.m.r. ($CDCl_3$, Me_4Si) δ (p.p.m.) 0·90 (3H, triplet), 3·73 (3H, singlet), ABX pattern at 4·39 (doublet), 6·13 (doublet), and 6·58 (quartet) (1H each, J_{HH} 6 and 8 Hz), 7·0—7·6 (mult. 4H), and 7·85 (1H).



(VI)

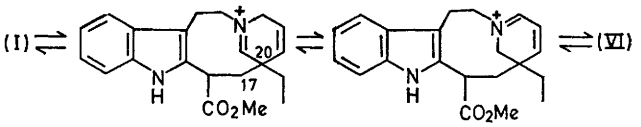


(VII)

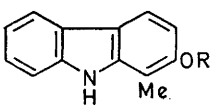
The other two new products isolated are dihydroallocatharanthine (15%) and acetoallocatharanthine (6%) (VII): the structure of the latter was assigned on spectroscopic arguments.

Tabersonine (I) was also heated in refluxing acetic acid at oil bath temperatures ranging from 190—205°§ for 16—50 hr: the pattern of products was found to be identical with that produced at bath temperatures of 130—140° by t.l.c. and mass-spectral analysis. Particular care was taken to analyse for (II) and (III) using analytical t.l.c. systems (see Table), and preparative t.l.c. followed by u.v. and mass-spectral analysis. Furthermore, a tabersonine (I) fraction which would have contained any pseudocatharanthine (III) was hydrogenated under conditions known to give the respective 15,20-dihydro-bases: only dihydro-(I) was detected by t.l.c.

The formation of (+)-allocatharanthine from tabersonine is an unexceptional reaction which corresponds mechanistically to a reversal of the catharanthine (II)–pseudocatharanthine (III) change,[2,3] *via* chanoimmonium ions as shown, and almost certainly does not involve a cleavage of the 17,20-bond.



Quite a different reaction was observed when tabersonine (I) was heated in the absence of solvent in an evacuated sealed tube (190°, 96 hr.): two products were isolated and identified as 2-hydroxy-1-methylcarbazole (VIIIa) and 2-methoxy-1-methylcarbazole (VIIIb) by m.p., u.v., and mass spectra. The formation of these compounds now must involve a C-17–C-20 cleavage. The later stages of the reaction sequence must parallel very closely those leading to 2-hydroxycarbazole from akuammicine.[4]



(VIII) (a, R = H; b, R = Me)

One final point which has a strong bearing on the work reported by Scott and Qureshi[3] concerns the catharanthine (II) → pseudocatharanthine (III) change. We find that, even after only 12 hr. reflux in AcOH under N_2, (II) is converted into other products to the extent of 99—99·5%: the main products are (III) (33%) and a mixture of dihydrobases (17%). The estimate of 0·5—1% of (−)- or (±)-(II) was arrived at by preparative t.l.c. analysis of the reaction mixture from 500 mg of (II). This seems to be incompatible with the isolation of (±)-(II) in yields of 5—12% from various reactions in refluxing acetic acid over periods of 16—72 hr.

Furthermore, catharanthine-free pseudocatharanthine (III), after 50 hr. in refluxing acetic acid under N_2, survived to the extent of about 40% and gave a whole range of products one of which was almost certainly catharanthine [(−) or (±)] and was estimated to be present to the extent of 1% at the most, and probably much less: this gives a strong indication of the reversibility of the change (II) ⇌ (III), but hardly supports the claim[3] that the change (III) → (II) is a synthetically useful process.

§ The same results have been obtained by Scott and Cherry by pyrolysis in xylene at 205° (personal communication).

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[1] A. A. Qureshi and A. I. Scott, *Chem. Comm.*, 1968, 945.
[2] M. Gorman, N. Neuss, and N. J. Cone, *J. Amer. Chem. Soc.*, 1965, **87**, 93.
[3] A. A. Qureshi and A. I. Scott, *Chem. Comm.*, 1968, 947.
[4] P. N. Edwards and G. F. Smith, *J. Chem. Soc.*, 1961, 1458.