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THE ZINC-ACETIC ACID REDUCTION OF RESERPINE AND OTHER TETRAHYDRO-β-CARBOLINE ALKALOIDS

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Abstract—It is shown that treatment of the tetrahydro-β-carboline alkaloids reserpine (**1**), 1,2-butano-1,2,3,4-tetrahydro-β-carboline (**10**) and ajmalicine (**13**) with zinc-acetic acid results in fission of the bond between the aliphatic N atom and the C atom joining it to the indole α-position. The products were identified by their spectra and in **1** and **10** by comparison of appropriate derivatives with those from Emde fissions of the corresponding alkaloid quaternary salts.

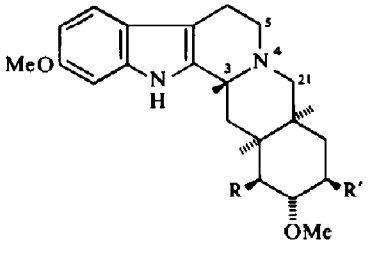
DURING investigations[1] of the mechanism of the C-3 epimerization of reserpine (**1**), we had cause to subject the alkaloid to prolonged treatment with zinc powder in refluxing acetic acid. The material thus obtained was a complex mixture containing isoreserpine (1, C-3 hydrogen α) and reserpine (in the equilibrium[1] proportions) and, as the only other crystalline component, a dihydroreserpine which we term 3,4-secoreserpine (**2**). Apart from reserpine and isoreserpine, 3,4-secoreserpine was the major component of the mixture, being obtained in high yield based on recovered reserpine and isoreserpine.

The molecular formula, $C_{33}H_{42}N_2O_9$, of the new base was established by its mass spectrum, in which the molecular ion occurred two mass units higher than that in the spectrum of reserpine. The UV absorption was very similar to that of reserpine which suggested that both chromophoric systems of the original base were intact. In order to be sure that the methoxy aromatic indole was still present, the second chromophoric system, the 3,4,5-trimethoxybenzoyl unit, was removed by methanolysis. Methyl 3,4-secoreserpate (**3**) thus obtained had UV absorption identical with that of methyl reserpate (**4**). Since these measurements showed that the two additional H atoms had not been added at any of the centres of unsaturation, it followed that one bond must have been broken during the formation of 3,4-seco-reserpine. That this bond was one of the three original bonds to the aliphatic nitrogen was shown by the formation, from 3,4-secoreserpine, of an N-4 acetyl derivative (**5**) by treatment with acetic anhydride-pyridine. Methyl 3,4-secoreserpate under the same conditions gave an O,N-diacetyl derivative (**6**). Both acetyl derivatives showed amide absorption (1640 and 1645 cm^{-1} respectively) in their IR spectra, were non-basic and displayed UV absorptions identical with those of 3,4-secoreserpine and methyl 3,4-secoreserpate respectively. It remained to establish that, of the three original bonds to the aliphatic nitrogen, C-3/N-4 had been cleaved during the formation of the dihydro compound. The NMR spectrum of 3,4-secoreserpine established the structure as shown in **2**. Either of the alternative modes of cleavage C-5/N-4 or C-21/N-4) would have given rise to dihydro species containing terminal Me groups. There was no signal corresponding to either a secondary or primary Me group in the NMR spectrum of 3,4-secoreserpine.

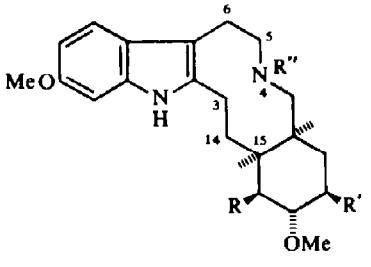
There are two features which are important for characterization in the mass spectra of 3,4-secoreserpine and its derivatives. Firstly the M − 1 peak, so characteristic[2] of tetrahydro-β-carboline alkaloids, is absent. The aliphatic nitrogen being no longer linked to C-3, cannot stabilize an ion formed by loss of an H atom from C-3. Secondly the ring opened compounds cleave readily in the mass spectrometer between C-5 and C-6 and between either C-3 and C-14 or C-14 and C-15. Their spectra thus show important groups of ions around *m/e* 186 and 174 represented by fragments (a) and (b) or minor variants (± hydrogen) thereof, which are not present to any significant extent in the spectra of reserpine, methyl reserpate or reserpine diol diacetate.

An attempt to establish a chemical correlation between the seco compound and reserpine, by re-oxidation was unsuccessful. Treatment of 3,4-secoreserpine with *t*-butyl hypochlorite gave material which had ill-defined UV absorption. The desired 7-chloroindolenine may have been present, but the subsequent desired intramolecular nucleophilic displacement, with the aliphatic nitrogen acting as a nucleophile,[3] did not take place. The reaction product was complex but TLC assay showed there to be no reserpine or isoreserpine.

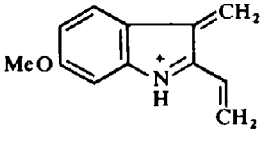
A chemical correlation was however achieved with the preparation, by a different route, of the di-O-acetate of 4-methyl-3,4-secoreserpine diol (7). This was firstly



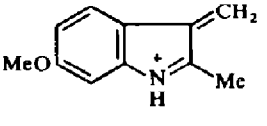
	R	R'
1:	MeO_2C	OCO-3,4,5-trimethoxyphenyl (TMP)
4:	MeO_2C	OH
9:	$HOCH_2$	OH



	R	R'	R''
2:	MeO_2C	OCOTMP	H
3:	MeO_2C	OH	H
5:	MeO_2C	OCOTMP	COMe
6:	MeO_2C	OCOMe	COMe
7:	$HOCH_2$	OH	Me
8:	MeO_2C	OCOTMP	CHO



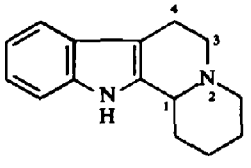
a



b

obtained by LAH reduction of 4-formyl-3, 4-secoreserpine (**8**) followed by acetylation. It was shown[4] recently that the benzylic bonds to the aliphatic N atoms in tetrahydro-β-carboline systems can be reductively cleaved by treatment of their quaternary salts with lithium in ammonia. Application of this reaction to the methiodide of reserpine diol (**9**) resulted in the formation of 4-methyl-3, 4-secoreserpine diol (**7**) the di-O-acetate of which was identical in all respects to that obtained from the zinc-acetic acid route. An attempt to convert reserpine methiodide in one step to 4-methyl-3,4-secoreserpine diol by treatment with LAH led only to reserpine diol (**9**) by displacement at the quaternary Me and reduction of the ester functions. No product resulting from hydride attack[5] at C-3 could be detected.

In order to obtain an estimate of the generality of the zinc-acetic acid cleavage process we have subjected two other representative tetrahydro-β-carboline alkaloids to the same conditions. 1,2-Butano-1,2,3,4-tetrahydro-β-carboline[6] (**10**) was cleaved in 50% yield (83% based on recovered starting material) to the N-2-acetyl derivative (**11**) of 1,2-seco-1,2-butano-1,2,3,4-tetrahydro-β-carboline. Here again a chemical correlation was achieved by Emde fission[4] of the ethiodide of 1,2-butano-1,2,3,4-tetrahydro-β-carboline. The resultant 2-ethyl-1,2-seco-1,2-butano-1,2,3,4-tetrahydro-β-carboline (**12**) was shown to be identical with the product of LAH reduction of 2-acetyl-1,2-seco-1,2-butano-1,2,3,4-tetrahydro-β-carboline (**11**) from the zinc-acetic acid route.



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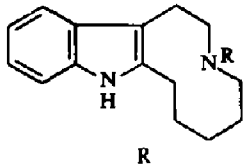
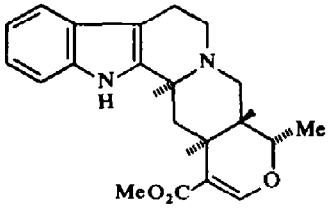


R

11: COMe
12: Et



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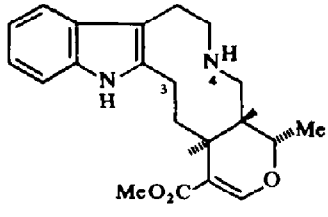

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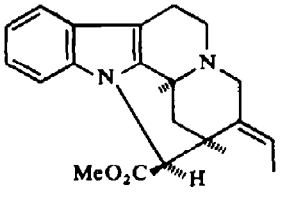

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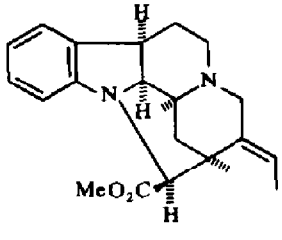

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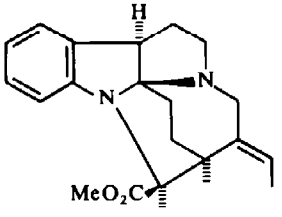
An interesting feature of the NMR spectra in deuteriochloroform of 3,4-secoreserpine (**2**) and 2-acetyl-1,2-seco-1,2-butano-1,2,3,4-tetrahydro-β-carboline (**11**) is the indication in each of two slowly interconverting conformations. In the former, two signals, integrating for three H atoms in all, were observed for the aliphatic methoxyl Me group at τ 6·39 and 6·46. In the latter, two signals integrating for three H atoms in all were observed at τ 7·93 and 8·19 for the 2-acetyl Me group. We suggest that these results indicate that two energetically distinguishable conformers of the 10-membered ring exist in deuteriochloroform solution in each case. When the spectrum of 2-acetyl-1,2-seco-1,2-butano-1,2,3,4-tetrahydro-β-carboline (**11**) was measured in d_6-DMSO it was found that at 140° the two acetyl signals (8·10 and 8·37) collapsed to a broad singlet at τ 8·24, an observation consistent with an increased ease of conformational interconversion at the higher temperature. We were



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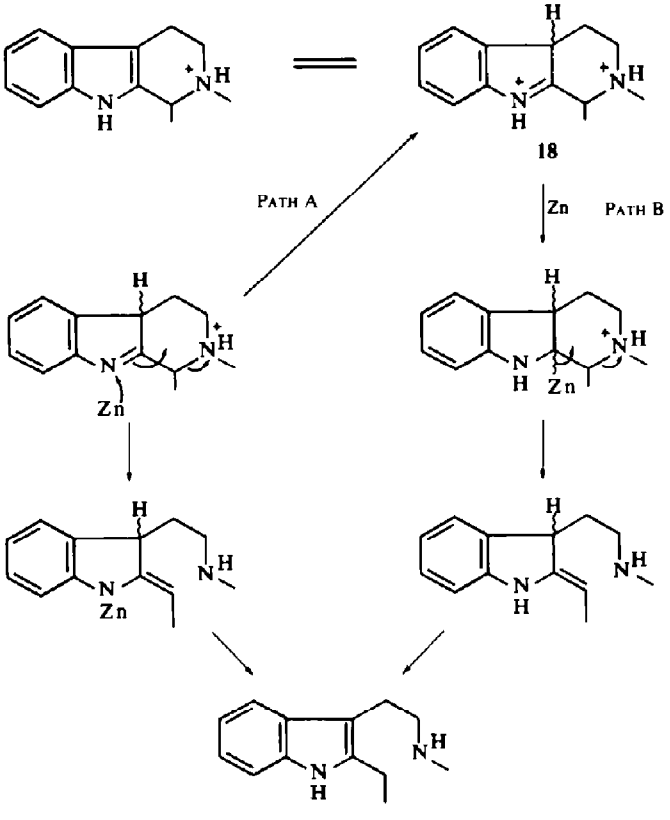

not able to observe an analagous change for 3,4-secoreserpine, since this compound in DMSO solution had only one Me signal for the aliphatic MeO at τ 6·63. The differing solvent properties of DMSO must strongly favour one conformer of the equilibrium observed in chloroform. It is noteworthy that the NMR spectrum of 4-acetyl-3,4-seco reserpine (**5**) in $CDCl_3$ shows no evidence of readily interconverting conformations.

Success in the fission of 1,2-butano-1,2,3,4-tetrahydro-β-carboline, the simplest tetracyclic analogue of reserpine indicated that no special activation (e.g. a MeO substituted indole) is necessary to allow fission. We accordingly treated ajmalicine (**13**) with zinc powder in refluxing acetic acid. A dihydro product was obtained which was clearly a 3,4-seco derivative (**14**) since its mass spectrum showed ions corresponding to (a) and (b) (lacking the MeO group) and had no M − 1 peak.

The zinc acetic acid cleavage reaction examined preliminarily here provides an alternative, apparently fairly general, to the several approaches[4-7] which have been recently developed to allow scission of the benzylic bond to N_b in tetrahydro-β-carboline systems. Such cleavages are of relevance for the synthetic interrelationship of tetrahydro-β-carboline alkaloids with the medium sized ring containing indole alkaloids such as picraphylline and quebrachamine. Recently Schmid *et al.* have observed a fission of the type under discussion during work on pycnanthine.[8] Zinc-hydrochloric acid reduction of pleiocarpamine (**15**) led to a mixture (the ratio depending on the quality of the zinc) of dihydropleiocarpamine (**16**) and isodihydro-pleicarpamine (**17**). This latter compound is the ring closed form, favoured in this case for steric reasons, of a dihydro-species derived by scission of the C-3/N-4 bond.

There are several reasonable ways to rationalise the cleavages under discussion. We believe that the best of these involves the assumption of an equilibrium concentration of a species formed by protonation[9] at the indole β-position. This indoleninium ion (**18**) could proceed *either* by *path A* which postulates an equilibrium concentration of free indolenine which then reacts with zinc at N_a or may complex with zinc at the indole α-position[10] (*path B*). Both routes are analagous to schemes suggested by Brewster[11] to explain the fission of suitable α-leaving groups during zinc treatment of ketones.

A more detailed examination of the mechanistic aspects of this cleavage reaction will be the subject of a further investigation.

EXPERIMENTAL

Mass spectra were measured by Dr. J. M. Wilson and his staff using A.E.I. MS9 and MS12 instruments. NMR spectra were determined using Varian A-60 and HR-100 spectrometers. TLC was carried out on silica gel "G" using PhH/EtOAc/MeOH (2/2/1).

Preparation of 3,4-*secoreserpine* (**2**). Reserpine (3·3 g) and Zn powder (3 g) were heated at reflux in AcOH (glacial, 50 ml) under N_2 for 2 days. The mixture was cooled, filtered and evaporated and the residue partitioned between K_2CO_3 aq and $CHCl_3$. The organic layer was dried and evaporated and the residue purified by chromatography over silica gel. Elution with $CHCl_3$–MeOH (9:1) gave 3,4-*seco reserpine* (**2**) (755 mg) which was crystallized from MeOH, m.p. 236–239°; ν_{max} ($CHCl_3$) 3450, 1710–1720 cm^{-1}, λ_{max} (EtOH) 220, 267, 295, mμ (ε 48,000, 15,700, 10,600), τ ($CDCl_3$) 1·95 (1H singlet, NH), 2·5–3·1 (5H, HAr), 6·05 (15H, 3 singlets, 5x CH_3O), 6·39 and 6·46 (3H, two singlets, CH_3OC-17), τ (d_6-DMSO) 6·63 (3H singlet, CH_3O·C-17), *m/e* 610 (M^+, 90%), 608 (100), 579 (4), 399 (4), 396 (5), 212 (6), 195 (18), 188 (4), 187 (4), 186 (4), 174 (10), (Found: Mol. wt. 610·288696; $C_{33}H_{42}N_9O_2$ requires: 610·289010).

Preparation of methyl 3,4-*seco reserpate* (3). MeONa (from Na (332 mg)) and 3,4-secoreserpine (108 mg) were refluxed in MeOH under N_2 for 2 hr. The soln was diluted with HCl aq and extracted with Et_2O. The dried ethereal extract was evaporated to give 3,4,5-trimethoxybenzoic acid (29 mg), m.p. 160–170°.

The aqueous soln was made basic with K_2CO_3 and extracted with Et_2O. The dried extract was evaporated and the residue crystallized from MeOH to give *methyl* 3,4-*secoreserpate* (3; 30 mg), m.p. 245–249°; ν_{max} (Nujol) 3345, 3330, 1755 cm^{-1}, λ_{max} (EtOH) 227, 273, 297 mμ (ε 35,200, 5170, 6620), *m/e* 416 (M^+, 100%), 401 (4), 385 (17), 384 (27), 242 (5), 241 (6), 228 (7), 200 (9), 188 (13), 187 (9), 186 (11), 174 (54), 161 (6), 160 (8), (Found: mol. wt. 416·229548; $C_{23}H_{32}N_2O_5$ requires: 416·231107).

Preparation of 4-*acetyl*-3,4-*secoreserpine* (5). 3,4-Secoreserpine (50 mg) was treated with Ac_2O (2·5 ml) and pyridine (2·5 ml) at room temp for 12 hr. The soln was evaporated *in vacuo* and the residue partitioned between K_2CO_3 aq and $CHCl_3$. The dried organic phase was evaporated to give 4-*acetyl*-3,4-*secoreserpine* (5; 46 mg), amorphous but homogeneous by TLC; ν_{max} ($CHCl_3$) 3460, 1710–1730, 1660 cm^{-1}, λ_{max} (EtOH) 225, 267, 296 mμ (ε 29,200, 13,980, 8820), τ ($CDCl_3$) 2·5 (1H, s, HN), 2·7–3·3 (5H, HAr), 6·15 (15H, 3 s, 5x CH_3O), 6·52 (3H, s, CH_3OC-17), 8·47 (3H, s, CH_3CO·N), *m/e* 652 (M^+, 100%), 620 (6), 608 (6), 441 (6), 440 (4), 426 (45), 226 (35), 212 (17), 211 (15), 200 (50), 195 (65), 186 (65), 174 (36), 160 (11), found for *m/e* 200 and 174: 200·107574, 174·091437; $C_{13}H_{14}NO$ and $C_{11}H_{12}NO$ require 200·107533, 174·09188, (Found: Mol. wt. 652·301302; $C_{35}H_{44}N_2O_{10}$ requires: 652·299573).

Preparation of O,N-*diacetyl methyl* 3,4-*secoreserpate* (6). Methyl 3,4-secoreserpate (3·2 mg) was treated exactly as above to give O,N-*diacetyl methyl* 3,4-*secoreserpate* (6) (1·2 mg), crystallized from MeOH, m.p. 306–309° (dec); ν_{max} (Nujol) 3370, 1740, 1715, 1640 cm^{-1}, λ_{max} (EtOH) 228, 272, 299 mμ (ε 36,200, 4760, 6250), *m/e* 500 (M^+, 100%), 456 (4), 441 (6), 428 (8), 270 (19), 201 (20), 200 (35), 188 (15), 187 (35), 186 (76), 174 (36), 173 (25), 160 (10), (Found: Mol. wt. 500·251256; $C_{27}H_{36}N_2O_7$ requires: 500·252244).

Oxidations with t-butyl hypochlorite. 3,4-Secoreserpine (34 mg) in CH_2Cl_2 was treated, at 0° with *t*-BuOCl (0·5 ml) and Et_3N (0·05 ml) in CH_2Cl_2. After 30 mins the soln was evaporated to give a brown gum which was partitioned between water and $CHCl_3$. The organic layer contained only starting material. The experiment was repeated but without Et_3N. After 75 min a brown oil (25 mg) was obtained which contained no detectable amount of reserpine or isoreserpine.

Preparation of 4-*formyl* 3,4-*secoreserpine* (8). 3,4-Secoreserpine (100 mg) was treated with Ac_2O (3 ml) and formic acid (3 ml) at room temp for 3 hr. The solvent was removed under vacuum and the residue partitioned between K_2CO_3 aq and $CHCl_3$. The organic phase gave 4-*formyl*-3,4-*secoreserpine* (8; 99 mg), amorphous but homogeneous by TLC; ν_{max} ($CHCl_3$) 1630 cm^{-1}, λ_{max} (EtOH) 230, 266, 295, mμ (ε 32,000, 14,200, 8800), τ ($CDCl_3$) 2·46 (1H, s, HN), 2·60 (1H, s, NCHO), 2·75–3·32 (5H, HAr), 6·2 (15H, 3 s, 5 x CH_3O), 6·32 (3H, s, CH_3OC-17), *m/e* 638 (M^+, 100%), 636 (18), 610 (22), 251 (11), 226 (9), 212 (36), 197 (14), 195 (64), 186 (26), 174 (14), 160 (9), 111 (100).

Preparation of diacetate of 4-*methyl*-3,4-*secoreserpine diol* (7). 4 Formyl-3,4-secoreserpine (60 mg) was reduced at reflux with LAH (500 mg) in THF for 14 h. The excess reagent was decomposed with the minimum of water, the soln filtered, dried and evaporated. The total product was treated with Ac_2O (2 ml) and pyridine (2 ml) at room temp for 12 hr. After evaporation of solvent, the residue was dissolved in HCl aq, washed with Et_2O, made basic with K_2CO_3 and extracted with $CHCl_3$. The organic phase was dried and evaporated and the residue (27 mg) crystallized from MeOH to give the *diacetate*, m.p. 183–188°; ν_{max} ($CHCl_3$) 3460, 1725 cm^{-1}, λ_{max} (EtOH) 227, 272, 297, mμ (ε 35,000, 5050, 6350), τ ($CDCl_3$) 6·26 (3H, s, CH_3 OC-11), 6·67 (3H, s, CH_3OC-17), 7·27 (3H, s, CH_3N), 8·02 (6H, s, 2xCH_3CO), *m/e* 586 (M^+, 100%), 441 (35), 428 (10), 415 (9), 312 (15), 300 (12), 251 (10), 238 (18), 200 (14), 187 (20), 186 (30), 174 (8), 173 (4), 161 (15), 160 (17), (Found: Mol. wt. 486·272915; $C_{27}H_{38}N_2O_6$ requires: 486·272969).

Lithium-ammonia fission of reserpine diol methiodide. Reserpine diol[12] methiodide (48 mg) was dissolved in 1-methoxy-2-propanol (0·15 ml) and liquid NH_3 (10 ml). Li (6 mg) was added and the soln stirred for 5 min until the blue colour had disappeared. The ammonia was evaporated and the residue treated with Ac_2O (2·5 ml) and pyridine (2·5 ml) at room temp for 12 hr. Evaporation of the solvent followed by partitioning between K_2CO_3 aq and $CHCl_3$ led to a residue (48 mg) which was crystallized from MeOH to give 9,12-*dihydro*-3,4-*secoreserpine diol diacetate* (6 mg), m.p. 174–176°; ν_{max} ($CHCl_3$) 3395, 1735, 1715, 1670 cm^{-1}, λ_{max} 220 mμ, *m/e* 488 (M^+, 100%), 487 (76), 486 (45), 473 (63), 441 (13), 430 (10), 312 (15), 300 (12), 188 (20), 186 (18), 176 (25), 174 (45), 173 (18), 160 (17), 144 (16), (Found: Mol. wt. 488·287027; $C_{27}H_{40}N_2O_6$ requires: 488·288619). Chromatography of the mother liquors by TLC on Al_2O_3 eluting with EtOAc, gave 3,4-*secoreserpine diol diacetate* (3 mg), crystallized from MeOH, m.p 184–188°, mixed m p. with the material prepared above by the Zn–AcOH route, 184–188°.

Preparation of reserpine diol diacetate. Reserpine diol[12] was acetylated with a mixture of Ac_2O and

pyridine and had m.p. 225–229°, *m/e* 470 (M^+, 100%), 469 (72), 477 (8), 409 (41), 265 (8), 251 (17), 214 (8), 200 (12), 199 (14), 186 (11), 174 (8).

Preparation of 2-*acetyl*-1,2-*seco*-1,2-*butano*-1,2,3,4-*tetrahydro*-β-*carboline* (**11**). 1,2-Butano-1,2,3,4-tetrahydro-β-carboline (200 mg) and Zn powder (3 g) were refluxed in AcOH (glacial 25 ml) for 5 days under N_2. The mixture was then filtered and evaporated and the residue partitioned between AcOH aq and $CHCl_3$. The dried $CHCl_3$ extract was evaporated to give the *amide* (**11**; 97 mg), crystallized from MeOH, m.p. 212–216°; ν_{max} (Nujol) 3230, 1620 cm^{-1}, λ_{max} (EtOH) 230, 285, 290 mμ (ε 25,300, 5920, 5400). τ ($CDCl_3$) 1·9 (1H, s, HN), 2·9 (4H, HAr), 7·93 (1·4H, CH_3CON), 8·19 (1·6H, CH_3CON), τ (d_6DMSO)[25] 8·1 (1H, CH_3CON), 8·37 (2H, CH_3CON), τ (d_6DMSO)[140] 8·24 (3H, s, CH_3CON), *m/e* 270 (M^+, 100%), 198 (14), 196 (15), 184 (15), 170 (40), 167 (64), 166 (25), 144 (55), 130 (10), 122 (28), 107 (20), (Found: Mol wt. 270·173204, $C_{17}H_{22}N_2O$ requires: 270·173195) Basification of the aqueous acidic phase and extraction with $CHCl_3$ gave starting material (83 mg)

Preparation of 2-*ethyl* 1,2-*seco*-1,2-*butano*-1,2,3,4-*tetrahydro*-β-*carboline* (**12**). 2-Acetyl-1,2-seco-1,2-butano-1,2,3,4-tetrahydro-β-carboline (11 mg) was reduced with LAH (50 mg) in refluxing THF (10 ml) for 2 hr. The excess reagent was decomposed with the minimum of water, the soln filtered, dried and evaporated to give an oil (9 mg) which was purified by TLC on Al_2O_3 eluting with EtOAc–C_6H_6 (9:1) to give-2-*ethyl*-1,2-*seco*-1,2-*butano*-1,2,3-*tetrahydro*-β-*carboline* (**12**; 5 mg), amorphous but homogenous by TLC, ν_{max} ($CHCl_3$) 3470 cm^{-1}, λ_{max} (EtOH) 230, 285, 290 mμ, *m/e* 256 (M^+, 65%), 255 (30), 198 (15), 162 (10), 160 (9), 157 (14), 144 (21), 143 (18), 130 (12), 128 (10), 111 (100), 98 (35), 84 (17), 72 (60), (Found: Mol wt. 256·193939; $C_{17}H_{24}N_2$ requires 256·193901).

Lithium-ammonia fission of 12-*butano*-1,2,3,4-*tetrahydro*-β-*carboline ethiodide*. The ethiodide, prepared in the usual way (23 mg, m.p. 350° dec) and 1-methoxy-2-propanol were treated with Li (3 mg) in liquid ammonia (10 ml). After 5 min the original blue colour had faded and further Li (2 mg) was added. After the ammonia had evaporated the residue was partitioned between K_2CO_3 aq and $CHCl_3$ and the organic phase separated, dried and evaporated. The residue (15 mg) was purified by TLC and the oil thus obtained shown to be identical with that obtained above, by TLC (several systems), UV and IR.

Preparation of 3,4-*secoajmalicine* (**14**) Ajmalicine (100 mg) and Zn powder (2 g) were refluxed in AcOH (glacial, 20 ml) for 5 hr. The soln was filtered and evaporated and the residue partitioned between K_2CO_3 aq and $CHCl_3$. The dried organic phase was evaporated to give a partially crystalline solid from which, by a combination of crystallization (MeOH) and TLC (silica; EtOAc C_6H_6, MeOH; 2·2:1) was obtained 3,4-secoajmalicine (25 mg), m.p. 195–200°; ν_{max} (Nujol) 1690 cm^{-1}, λ_{max} (EtOH) 227, 275, 284, 291 mμ (ε, 35,420), 5500, 5560, 4940), *m/e* 354 (M^+, 95%), 323 (8), 210 (20), 178 (13), 168 (18), 158 (100), 157 (45), 156 (40), 145 (60), 144 (95), 143 (60), 130 (40), 115 (35). (Found: C, 70·1; H, 6·7; N, 7·8%; $C_{21}H_{26}N_2O_3$ requires: C, 71·16; H, 7·39; N, 7·9%).

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