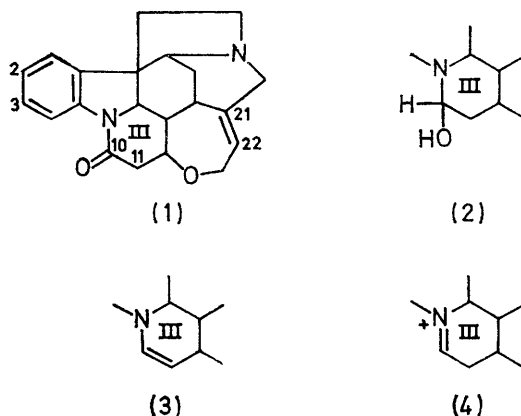


10,11-Didehydrostrychnidine

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Strychnine (1) was reduced by lithium aluminium hydride to a carbinolamine (2), which was so readily converted into the enamine, 10,11-didehydrostrychnidine (3), that it could not be isolated in pure form. In the presence of acid, the enamine readily dimerised.

WEYGAND and his collaborators¹ reduced *N*-methyl-anilides with lithium aluminium hydride (0.25 mol. equiv.), and hydrolysed the products (presumed carbinolamines) to obtain aldehydes. Galinovsky and his co-workers² similarly reduced 1-methyl-2-pyrrolidinone, and treated the intermediate (supposed carbinolamine) with acetonedicarboxylic acid to give hygrine and cuscohygrine. Reduction of strychnine (1) with an excess of lithium aluminium hydride yielded strychnidine.³ Like-



wise, dihydrobrucine gave dihydrobrucidine, and the two colubrines afforded the corresponding colubridines.⁴ However, brucine yielded 10,11-didehydrobrucidine,⁴ and it was suggested that this was the result of the low solubility of the complex formed with lithium aluminium hydride.

Reduction of strychnine with lithium aluminium hydride (0.25 mol. equiv.) in tetrahydrofuran yielded a product, which on t.l.c. (alumina; chloroform-methanol, 34 : 1) showed the presence of three components, R_F 0.93, 0.89, and 0.67, of which the two latter showed a colour reaction when the plate was sprayed with Brady's reagent. When this material was subjected to column chromatography, the first component eluted (R_F 0.93) was strychnine. This was followed by the component of R_F 0.89, a crystalline compound, m.p. 230–232°, which proved to be 10,11-didehydrostrychnidine (3). We were unable to obtain the component of R_F 0.67, even when more polar solvents were used for elution.

The identification of 10,11-didehydrostrychnidine followed from its spectra. The mass spectrum showed a

molecular ion peak at m/e 318 ($C_{21}H_{22}N_2O$), and the peak at 1621 cm^{-1} in the i.r. spectrum was attributed to the enamine C=C stretching frequency.⁵ In the n.m.r. spectra of strychnidine and 10,11-didehydrostrychnidine the olefinic proton at the 22-position gives rise to a poorly resolved triplet around τ 4.1. Both spectra are very similar in the aromatic region, but an additional peak at τ 3.05 in that of 10,11-didehydrostrychnidine is attributed to the α -proton of the enamine system, *i.e.* at position 10. Also a broad triplet at τ 4.85 in the spectrum of the didehydro-compound is absent in that of strychnidine, and is ascribed to the β -proton of the enamine system, *i.e.* at position 11.

In the n.m.r. spectrum of 10,11-didehydrostrychnidine in trifluoroacetic acid, the peaks at τ 3.05 and 4.85 were missing, but a broad peak was seen at τ 0.8. This is consistent with C-protonation to give the cation (4), in the spectrum of which the signal at τ 0.8 represents the proton at position 10 (*cf.* ref. 6). When, however, acetic acid was added to a solution of 10,11-didehydrostrychnidine in deuteriochloroform, no corresponding change in the n.m.r. spectrum occurred, the enamine group presumably not being sufficiently basic to be appreciably protonated under these conditions. Also, the change in u.v. spectrum on acidification of an ethanolic solution of the didehydro-base was less clearly defined than in the case of some enamines. Little change in the wavelengths of absorption maxima occurred, although the corresponding extinction coefficients did change (Table 1).

TABLE 1

	$\lambda_{max.}$	ϵ	$\lambda_{max.}$	ϵ	$\lambda_{max.}$	ϵ
Neutral solution	252	12,100	285	17,400	306	13,500
Acid solution	253	19,600	285	7400	308	8100

The compound of R_F 0.67, formed by reduction of strychnine, has not been isolated; it is probably the carbinolamine (2). When the reduction was performed with 1 mol. equiv. of lithium aluminium hydride, the crude product showed two spots on t.l.c., R_F 0.75 and 0.67. The mass spectrum of this crude product showed two molecular ion peaks, at m/e 336 and 320, corresponding to the carbinolamine (2) and strychnidine, respectively. However, when this mixture was subjected to column chromatography on alumina, it yielded 10,11-didehydrostrychnidine (R_F 0.89) and strychnidine (R_F 0.75) only. It therefore appears that the carbinolamine

¹ F. Weygand, G. Eberhardt, H. Linden, F. Schäfer, and I. Eigen, *Angew. Chem.*, 1953, **65**, 525.

² F. Galinovsky, A. Wagner, and R. Weiser, *Sitzungsber. Akad. Wiss. Wien*, 1951, Abt. 2B, **160**, 551.

³ P. Karrer, C. H. Eugster, and P. Waser, *Helv. Chim. Acta*, 1949, **32**, 2381.

⁴ S. P. Findlay, *J. Amer. Chem. Soc.*, 1951, **73**, 3008.

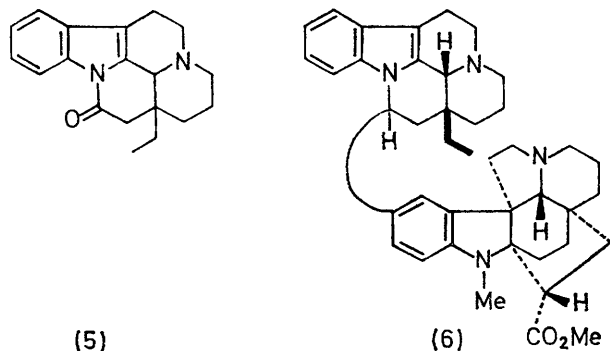
⁵ N. J. Leonard and V. W. Gash, *J. Amer. Chem. Soc.*, 1954, **76**, 2781.

⁶ H. Volz and H. H. Kiltz, *Tetrahedron Letters*, 1970, 1917; A. F. McDonagh and H. E. Smith, *J. Org. Chem.*, 1968, **33**, 8.

undergoes dehydration on chromatography on alumina to give 10,11-didehydrostrychnidine, and that both these compounds react with Brady's reagent. The i.r. spectrum of the crude product showed absorption at 3400 cm^{-1} (OH stretch), but no aldehyde stretching frequency, suggesting that the material of R_F 0.67 is predominantly the carbinolamine rather than the corresponding amino-aldehyde.

We also studied the reduction of strychnine with lithium diethoxyaluminium hydride,⁷ sodium bis-(2-methoxyethoxy)aluminium hydride,⁸ and lithium tri-*t*-butoxyaluminium hydride.⁹ The last failed to reduce strychnine, and the other two reagents offered no advantage over lithium aluminium hydride (see Table 2).

In an experiment using lithium aluminium hydride (1 mol. equiv.) which was allowed to proceed for several hours, a trace of a compound of R_F 0.64 was also formed.



This was not isolated in pure form, but the mass spectrum of the impure material showed a molecular ion peak at m/e 338, suggesting that the compound was tetrahydrostrychnine. Alcohols (rather than aldehydes)

by treatment with acid.¹⁰ Earlier, Clemo and King¹¹ obtained 10,11-didehydro-21,22-dihydrostrychnidine by reduction of dihydrostrychnine with sodium in liquid ammonia in the presence of methanol.

Treatment of the crude carbinolamine (2) with methanol saturated with hydrogen chloride gave an orange-coloured product, which was sparingly soluble in organic solvents, and of low mobility on t.l.c. It could therefore not be purified by chromatography, and appeared to be dimeric, its mass spectrum showing a molecular ion peak at m/e 636 [cf. molecular weight of the enamine (3) = 318]. In the presence of acid, the carbinolamine (2) could give rise to an equilibrium mixture of the enamine (3) and the iminium ion (4). The 10-position of the latter could then attack either the 11- or the 2-position of a second molecule to give a dimer. Findlay⁴ described mono- and di-hydrochlorides of didehydrobrucidine (3; OMe at positions 2 and 3) but as he apparently did not attempt to recover the base from these, it is conceivable that they could, in fact, be salts of a dimer, although positions 2 and 3 of the benzene ring are blocked by methoxy-groups. It is also uncertain as to whether the n.m.r. and u.v. spectra which we measured in trifluoroacetic acid and ethanolic hydrochloric acid, respectively, represent a monomer or a dimer. Clemo and King¹¹ also observed the instability of 10,11-didehydro-21,22-dihydrostrychnidine towards acids. Pleiomutine¹² (6) is an example of an alkaloid containing the proposed type of dimeric linkage.

EXPERIMENTAL

Merck aluminium oxide G (type E) was used in t.l.c.

Lithium aluminium hydride (1 g) was heated for 2 h under reflux with dry tetrahydrofuran (50 ml), and the cooled solution was filtered under nitrogen. The lithium

TABLE 2

Reduction of strychnine (1 g)

Reducing agent (mol. equiv.)	Temp. of mixing (°)	Reaction time* (h)	Strychnine (g)	Didehydrostrychnidine (g)	Strychnidine (g)
LiAlH ₄ (0.25) †	20	24	0.41	0.39	
LiAlH ₄ (0.33) †	-25	20	0.07	0.82	
LiAlH ₄ (0.50) †	20	24	0.23	0.65	
LiAlH ₄ (1.00) †	20	0.5		0.74	0.19
LiAlH ₄ (1.00) †	20	0.75		0.71	0.14
LiAlH ₄ (1.00) †	65	18		0.52	0.23
LiAlH ₂ (OEt) ₂ (1.00) †	65	17		0.70	0.16
LiAlH(Bu ^t) ₃ (1.00) †	20	60	0.92		
NaAlH ₂ (O-CH ₂ -CH ₂ -OMe) ₂ (1.00) §	81	42	0.06	0.76	0.10
NaAlH ₂ (O-CH ₂ -CH ₂ -OMe) ₂ (2.00) §	81	24		0.66	0.20

* In cases where the reaction time was >1 h, the mixture was boiled under reflux from the end of 1 h onwards. † In tetrahydrofuran. ‡ In benzene-ether. § In benzene.

are known to be formed by the reduction of certain anilides.¹

Reduction of eburnamonine (5) with lithium aluminium hydride gave two diastereoisomeric carbinolamines, which were converted into the enamine, eburnamenine,

⁷ H. C. Brown and A. Tsukamoto, *J. Amer. Chem. Soc.*, **1959**, **81**, 502.

⁸ M. Černý, J. Málek, M. Čapka, and Y. Chvalovský, *Coll. Czech. Chem. Comm.*, **1969**, **34**, 1033.

⁹ H. C. Brown and R. F. McFarlin, *J. Amer. Chem. Soc.*, **1958**, **80**, 5372.

aluminium hydride content of the filtrate was determined by measuring the volume of hydrogen evolved on decomposition by water, and the solution was then used immediately.

Reduction of Strychnine with Lithium Aluminium Hydride.—(a) A solution of lithium aluminium hydride (0.25 mol. equiv.) in tetrahydrofuran was added during 1 h to a stirred

¹⁰ M. F. Bartlett and W. I. Taylor, *J. Amer. Chem. Soc.*, **1960**, **82**, 5941.

¹¹ G. R. Clemo and T. J. King, *J. Chem. Soc.*, **1948**, 1661.

¹² D. W. Thomas, H. Achenbach, and K. Biemann, *J. Amer. Chem. Soc.*, **1966**, **88**, 1537.

solution of strychnine (1.0 g, 1 mol. equiv.) in dry tetrahydrofuran (30 ml) at 20°. The mixture was then heated under reflux for 23 h, cooled, and treated with saturated aqueous potassium sodium tartrate, and the organic layer was separated. The aqueous layer was extracted three times with tetrahydrofuran. The combined organic extracts were dried (Na_2SO_4) and the solvent was removed. The residual solid (0.86 g) was chromatographed on alumina (Hopkin and Williams Camag M.F.C.). Elution with benzene gave strychnine (0.41 g). Elution with benzene-chloroform (2 : 1) afforded 10,11-didehydrostrychnidine (0.39 g), m.p. 230—232° (from benzene) (Found: C, 79.1; H, 7.1; N, 8.9. $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}$ requires C, 79.1; H, 6.95; N, 8.8%); τ (CDCl_3) 4.85 (1H, t, J 6 Hz, enamine β -H, *i.e.* 11-H), 4.05 (1H, t, $J_{22,23}$ 6 Hz, olefinic 22-H), 2.6—3.5 (5H, m, aromatic protons and enamine α -H, *i.e.* 10-H), and 5.8—

8.8 (15H, m, remaining protons); τ ($\text{CF}_3\cdot\text{CO}_2\text{H}$) 3.38 (1H, m, olefinic 22-H), 1.9—2.5 (4H, m, aromatic protons), 0.80br (1H, 10-H of protonated enamine), and 4.9—8.5 (17H, m, remaining protons); ν_{max} 2850, 1621s, 1602, 1585, 1481s, 1237, 1112, 1036, 756s, and 733s cm^{-1} .

(b) In a similar experiment, using lithium aluminium hydride (1 mol. equiv.), with a reaction time of 0.75 h at 20°, chromatography of the crude product (0.88 g) gave 10,11-didehydrostrychnidine (0.71 g). Elution with chloroform yielded strychnidine, m.p. 256—257° (0.14 g), identical in i.r. spectrum and t.l.c. behaviour with an authentic sample; M^+ 320 ($\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}$).

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