# New Corynanthé Alkaloids from *Strychnos angustiflora*

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Three alkaloids isolated from *Strychnos angustiflora*, angustoline, angustine, and angustidine, have, respectively, the corynanthé structures (1) and (2), and the 21-norcorynanthé structure (5). They differ in the nature and position of side-chains on a fused pyridine ring. $^1$H N.m.r. long-range coupling data have been used in arriving at the structures. The biogenetic relationship between the alkaloids is discussed.

*Strychnos angustiflora* Benth. is a medicinal plant indigenous to South China. From the leaves have been isolated three orange-coloured alkaloids which have molecular formulae and electronic spectra (Table 1) (OH,NH), 1655 (–CO·N<), 1610, 1600 (conjugated aromatic ring), 810 (isolated H in pyridine), and 750 (disubstituted benzene) cm$^{-1}$. The 100 MHz n.m.r. spectrum † provided information on the nature of all

TABLE 1

U.v. maxima (nm) ($\log_{10}\varepsilon$ in parentheses) for solutions in ethanol

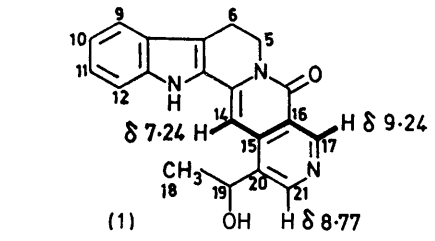
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Angustoline (1) | 221(4·49) | | 251(4·37) | 289(4·13) | 308(3·94) | 375(4·59) | 395(4·60) |
| Angustoline acetate (4) | 221(4·45) | | 252(4·20) | 290(3·11) | 301(3·88) | 378(4·58) | 397(4·59) |
| Angustine (2) | 220(4·54) | | 255(4·32) | 291(4·10) | 304(4·03) | 380(4·58) | 400(4·59) |
| Dihydroangustine (3) | 221(4·44) | | 252(4·15) | 290(3·90) | 300(3·81) | 375(4·46) | 395(4·48) |
| Angustidine (5) | 223(4·19) | 233(4·27) | 251(4·12) | 288(3·72) | 299(3·62) | 371(4·32) | 390(4·33) |

characteristic of a highly conjugated polycyclic skeleton. We propose the structures (1), (2), and (5), respectively, for these alkaloids: angustoline ($C_{20}H_{17}N_3O_2$), angustine ($C_{20}H_{15}N_3O$), and angustidine ($C_{19}H_{15}N_3O$).

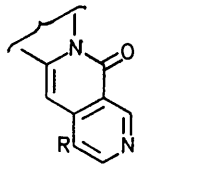
Angustoline absorbed in the i.r. (Nujol) at 3100—3400 17 hydrogen atoms in the molecule. The presence of the grouping $=\overset{|}{C}-CH(OH)\cdot CH_3$ was indicated by signals at δ 1·52 (3H, d, $J$ 6·4 Hz), 5·33 (1H, dq, $J$ 4·2 and 6·4 Hz), and 5·55 (1H, d, exchangeable). At δ 3·13 and 4·42 there were two 2H triplets ($J$ 6·7 Hz) which were assigned to the grouping $=\overset{|}{C}-CH_2-CH_2-\overset{|}{N}-$. The methylene group α to the nitrogen atom was not significantly deshielded in [$^2$H]trifluoroacetic acid compared to other

† Unless stated otherwise, n.m.r. spectra were measured at 100 MHz for solutions in [$^2H_6$]dimethyl sulphoxide and shifts (δ) are quoted in p.p.m. from internal tetramethylsilane; for full data see Table 2. Approximate $J$ values (in Hz) were calculated by first-order analysis.

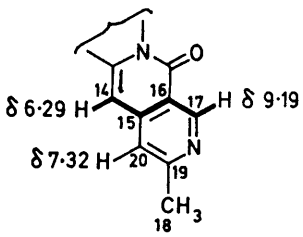
protons, suggesting that this nitrogen atom was non-basic.[1] In the low-field region were four 1H singlets at




(1)

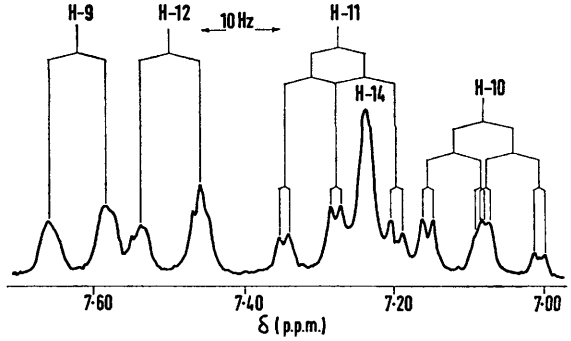


(2) R = $CH_2$:CH
(3) R = Et
(4) R = CH(OAc)Me




(5)

δ 11·81 (NH), 7·24, 8·77, and 9·24. The last two are reminiscent of signals due to protons α to nitrogen atoms in 5-substituted nicotinic acid derivatives such as dihydrogentianine (11) (δ 8·6 and 9·1),[2] gentianine (12),[3] and fontaphilline (13)[4] (δ 8·75 and 9·0). In both angustoline and the model compounds, the lower-field signal is to be assigned to the proton *ortho* to and hence deshielded by the carbonyl group. Finally, there was a 4H multiplet at δ 7·0—7·7 (Figure) due to four adjacent




Portion of 100 MHz n.m.r. spectrum of angustoline (1) [7% w/v in $(CD_3)_2SO$]

protons on a benzene ring. These signals, together with the NH singlet ($W_{\frac{1}{2}} \leqslant 3$ Hz) at δ 11·81, may be assigned to a 2,3-disubstituted indole system (*cf.* data for indole [5]).

The prevalent occurrence in *Strychnos* spp. of alkaloids incorporating a tryptamine unit is well documented.[6]

TABLE 2

$^1$H N.m.r. data

| Assignments | Angustoline (1) | Angustoline acetate (4) [a] | Angustine (2) [b] | Dihydro-angustine (3) | Angustidine (5) | Protonated angustoline (10) (in $CF_3{\cdot}CO_2D$) [c] |
|---|---|---|---|---|---|---|
| NH | 11·81 | 11·90 | 11·48 | 11·81 | 12·05 | |
| Indole H-9 | 7·62 (d, *J* 7·5) | | 7·63 (d, *J* 8) | 7·62 (d, *J* 7·5) | 7·62 (d, *J* 7·5) | |
| Indole H-10 | 7·08 (dt, *J* 1·4, 7·5) | 7·0—7·7 (m) | 7·17 (m) | 7·08 (dt, *J* 1·5, 7·5) | 7·08 (dt, *J* 1·5, 7·5) | 7·0—7·7 (m) |
| Indole H-11 | 7·28 (dt, *J* 1·4, 7·5) | | 7·37 (m) | 7·27 (dt, *J* 1·5, 7·5) | 7·26 (dt, *J* 1·5, 8) | |
| Indole H-12 | 7·49 (d, *J* 7·5) | | 7·49 (d, *J* 8) | 7·28 (d, *J* 7·5) | 7·47 (d, *J* 8) | |
| H-6 =C–$CH_2$– | 3·13 (t, *J* 6·7) [c] | 3·12 (t, *J* 6·5) | 3·17 (t, *J* 6·5) | 3·10 (t, *J* 6·5) | 3·10 (t, *J* 6·5) | 3·36 (t, *J* 7) |
| H-5 –N–$CH_2$– | 4·42 (t, *J* 6·7) [c] | 4·39 (t, *J* 6·5) | 4·42 (t, *J* 6·5) | 4·39 (t, *J* 6·5) | 4·38 (t, *J* 6·5) | 4·72 (t, *J* 7) |
| H-14 | 7·24 | 7·20 | 7·23 | 7·17 | 6·92 | 7·53 |
| H-21 | 8·77 | 8·69 | 8·59 | 8·49 | | 8·63 |
| H-20 | | | | | 7·32 | |
| H-17 | 9·24 | 9·27 | 9·25 | 9·14 | 9·19 | 9·58 |
| H-19 | 5·33 (dq, *J* 4·2, 6·4) [c] | 6·28 (q, *J* 6·5) | 7·25 (dd, *J* 18, 11·5) | 2·91 (q, *J* 7·5) | | 5·74 (q, *J* 6·5) [d] |
| H-18 | 1·52 (d, *J* 6·4, 3H) [c] | 1·67 (d, *J* 6·5, 3H) | 5·62 (dd, *J* 2, 11·5) 5·98 (dd, *J* 2, 18) | 1·30 (t, *J* 7·5, 3H) | 2·57 (3H) | 1·90 (d, *J* 6·5) |
| OAc | | 2·16 | | | | |
| OH | 5·55 (d, *J* 4·2) | | | | | |

[a] At 60 MHz. [b] Measured at 110°. [c] Coupling between H-5 and H-6, and between H-18 and H-19 demonstrated by double irridation. [d] Slowly shifted downfield by 1·0 p.p.m. due to trifluoroacetylation.

Taken with this consideration, the spectroscopic data for angustoline indicate partial structure (6), to which

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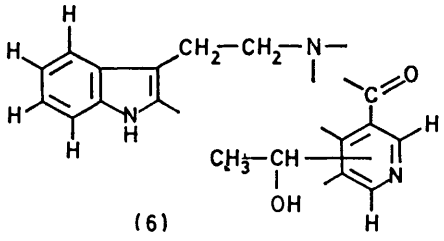
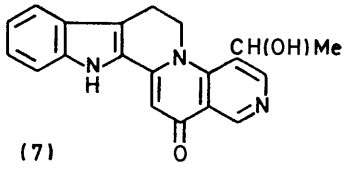
2C, 1H (responsible for the singlet at δ 7·24), and three units of unsaturated are to be added. The highly unsaturated nature of the molecule limits the possible structures to (1), (7), (8), and (9). Of these only (1) is compatible with n.m.r. decoupling data, which reveal (through narrowing of signals) the existence of two



(6)



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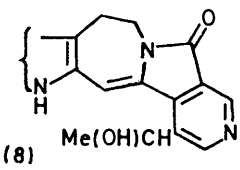

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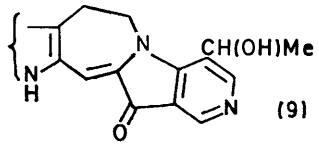

(9)

appreciable long-range couplings: (*a*) between protons resonating at δ 7·24 and 9·24; and (*b*) between the carbinol proton (δ 5·33) and an aromatic proton (δ 8·77). Coupling (*b*) (*ca.* 0·4 Hz) is benzylic in nature, and indicates [7] that the 1-hydroxyethyl side-chain is on the same ring as the proton resonating at δ 8·77. This is compatible with any of the structures (1) and (7)—(9). However coupling (*a*) (*ca.* 0·6 Hz) is accommodated only by structure (1). In this structure, the protons resonating at δ 9·24 and 7·24 are at the end of a planar zig-zag (and conjugated) chain [see (1), thickened lines], and long-range coupling of 0·4—2·0 Hz is expected.[7] We therefore propose structure (1) for angustoline.

Angustoline is a strong base which is protonated even by acetic acid. Thus dropwise addition of acetic acid to a solution of the alkaloid in methanol caused a progressive shift of the longest wavelength absorption peak from 395 to 439 nm. Both the basicity and the bathochromic shift may be accounted for by resonance stabilization of the protonated form [see (10)].

* For corresponding data for the model compound (12) see ref. 3.

† Corresponding data [2,8] ([$^2$H]chloroform) for the model compound (19) are δ 2·6, 7·05, and 9·05.

[7] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 330; S. Sternhell, *Quart. Rev.*, 1969, **23**, 236.

[8] Liang Xiao-trian, Yu De-quan, and Fu Feng-yung, *Sci. Sinica*, 1965, **14**, 869.

[9] V. Plouvier and J. Favre-Bonvin, *Phytochem.*, 1971, **10**, 1697.

[10] A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc.* (*C*), 1969, 1187, 1193.

The structure (2) of angustine follows readily. The n.m.r. spectrum is similar to that of angustoline, but with signals due to –CH(OH)Me replaced by those which may be assigned to an aryl-conjugated vinyl group (Table 2).* As expected, the electronic spectrum (Table 1) shows a slight bathochromic shift (*ca.* 5 nm) with respect to angustoline. On mild hydrogenation, angustine gave dihydroangustine (3), showing n.m.r. signals characteristic of an aromatic ethyl side-chain (Table 2). Correlation between angustoline (1) and angustine (2) was achieved by dehydration of the former with concentrated sulphuric acid, whereupon the latter was obtained in high yield. When angustoline or its acetate (4) was heated under nitrogen in refluxing collidine, dihydroangustine (3) was unexpectedly obtained.

We propose structure (5) for the third alkaloid, angustidine. Its n.m.r. spectrum differs from those of compounds (1)—(4) in that only one singlet assigned to an α-proton in pyridine is present (δ 9·19). The singlet near δ 8·7 (assigned to H-21 in angustoline) and signals due to a $C_2$ side-chain are absent. Instead there is an aromatic methyl singlet at δ 2·57 and an extra 1H singlet in the δ 6·9—7·4 region assigned to a β-proton on pyridine.† Appreciable long-range coupling was detected between the following pairs of signals: δ 9·19 and 6·92 [*ca.* 0·4 Hz, zig-zag path; see (5), thickened line], δ 9·19 and 7·32 (*ca.* 0·5 Hz, *para*-coupling), and δ 2·57 and 7·32 (*ca.* 0·5 Hz, benzylic). The latter pair of signals also exhibited a significant nuclear Overhauser effect (15% enhancement).

Angustoline and angustine are corynanthé-type alkaloids incorporating in the skeleton a tryptamine unit and a seco-loganin monoterpene unit closely related to the alkaloid gentianine (12). Gentianine has been shown in most but not all instances to be an artefact resulting from treatment of seco-iridoides [9] such as gentiopicroside (14), swertiamarin, (15), and sweroside (16) with ammonia. Angustoline and angustine might similarly be formed from glycoside mixtures related to vincoside lactam (17) or strictosamide (isovincoside lactam) (18),[10-12] which are in turn derived biogenetically from tryptamine and secologanin.[10,13] However, we found that when worked up in the absence of ammonia, the three alkaloids could nevertheless be obtained from the plant.

The biogenesis of angustidine might involve the loss of a carbon atom (C-21) from the seco-loganin portion of a corynanthé precursor [for numbering, see (1) and (5)]. An analogy for this process is provided by the reported isolation of gentianine (12), gentianidine (19), and gentioflavine (20) from *Erythraea centaurium* [14] and *Gentiana* spp.,[8,14] and of the former two from *Swertia japonica*.[2]

[11] K. T. D. de Silva, G. N. Smith, and K. E. H. Warren, *Chem. Comm.*, 1971, 905.

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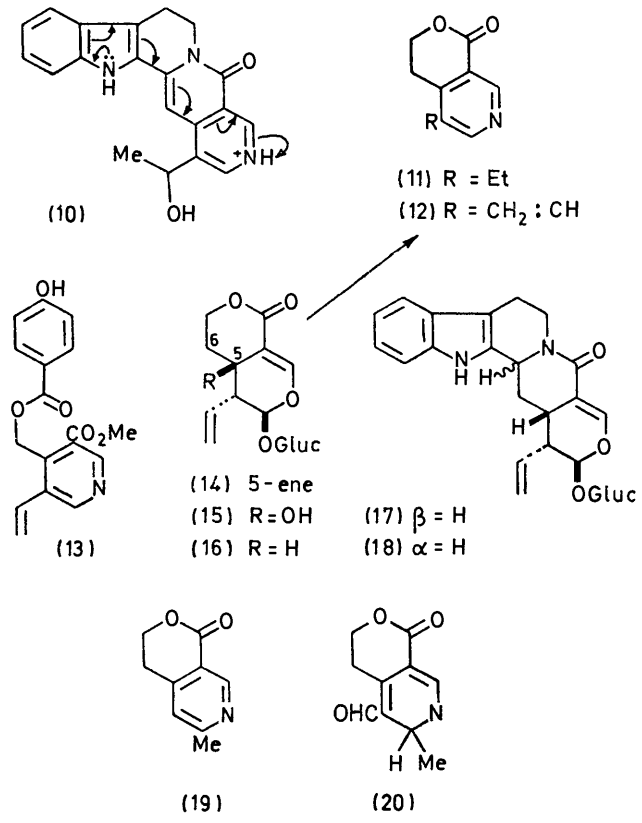
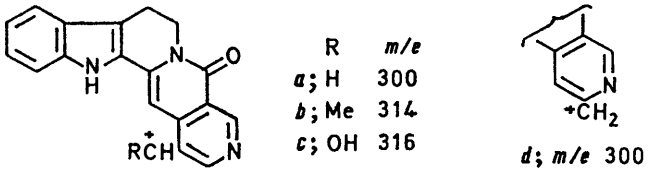
[14] N. Marekov and S. Popov, *Tetrahedron*, 1968, **24**, 1323; *Compt. rend. Acad. bulg. Sci.*, 1968, **21**, 435; N. Marekov, M. Arnaudov, and S. Popov, *ibid.*, 1970, **23**, 81; N. Marekov, L. Mondeshky, and M. Arnaudov, *ibid.*, p. 803.




The mass spectra of the alkaloids (1)—(4) serve mainly to confirm the nature of the side-chains. As expected, the base peaks correspond to the molecular ions, except for (4) which readily elimenates acetic acid. Pronounced β-cleavages giving rise to stable benzylic ions are observed. Thus loss of methyl and hydrogen from dihydroangustine (3) yields ions *a* (70%) and *b* (75%);




loss of methyl and hydroxy from angustoline (1) affords *c* (65%) and *b* (30%); loss of acetoxy from angustoline acetate (4) gives *b* (65%); and angustidine loses hydrogen to give *d* (80%). Except for angustine, α-cleavages of the side-chains occur to a fair degree, giving rise to ions at *m/e* 286 (5—25%).

## EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. Mass spectra were measured at 70 eV. Unless otherwise stated, i.r. spectra were determined for Nujol mulls.

*Isolation of Alkaloids.*—Ground air-dried leaves of *Strychnos angustiflora* (30 kg) were extracted at room temperature with light petroleum and then twice with methanol. To the methanolic extracts, concentrated *in vacuo* under nitrogen to 1 l, were added water (30 l), 10N-hydrochloric acid (1 l), chloroform (150 ml), and alumina (350 g). The mixture was shaken, and stored for 2 days. The acidic solution was decanted off, shaken with chloroform, and made alkaline with 50% sodium hydroxide. Extraction with chloroform and evaporation of the washed and dried chloroform extract gave a mixture which was chromatographed over alumina yielding the following pure alkaloids, listed in order of elution: (i) *angustidine* (5) (35 mg), yellow needles, m.p. 309—311° (from chloroform) (Found: $M^+$ 301·121. $C_{19}H_{15}N_3O$ requires *M*, 301·122), $\nu_{max.}$ 3100—3350, 1650, 1620, 1600, 1580, 805, and 745 $cm^{-1}$; (ii) *angustine* (2) (80 mg), obtained on re-chromatography as yellow plates from chloroform–methanol, m.p. >340° (Found: C, 72·7; H, 5·1; N, 12·3%; $M^+$, 313·121. $C_{20}H_{15}N_3O,H_2O$ requires C, 72·5; H, 5·2; N, 12·7%. $C_{20}H_{15}N_3O$ requires M, 313·122), $\nu_{max.}$ 3100—3300, 1650, 1610, 1580, 1150, 830, 815, and 740 $cm^{-1}$; (iii) *angustoline* (1) (300 mg), obtained on re-chromatography as yellow needles from chloroform–methanol, m.p. 310—314°, $[\alpha]_D$ −34° ($CHCl_3$) (Found: C, 72·5; H, 5·2; N, 12·7%; $M^+$, 331·131. $C_{20}H_{17}N_3O_2$ requires C, 72·5; H, 5·2; N, 12·7%; *M*, 331·132), $\nu_{max.}$ (dioxan) 1675, 1610, and 1595 $cm^{-1}$ [for $\nu_{max.}$ (Nujol) see Discussion section].

*Reactions of Angustine and Angustoline.*—Angustine (29 mg) in dioxan was hydrogenated in the presence of Adams catalyst to give *dihydroangustine* (3) (15 mg), m.p. 290—294° (from methanol) (Found: C, 72·3; H, 5·3; N, 11·9%; $M^+$, 315·138. $C_{20}H_{17}N_3O,H_2O$ requires C, 72·1; H, 5·7; N, 12·6%. $C_{20}H_{17}N_3O$ requires *M*, 315·137), $\nu_{max.}$ 3100—3500, 1640, 1605, 1575, 1135, 830, 820, 740, and 730 $cm^{-1}$.

Overnight treatment of angustoline with acetic anhydride–pyridine yielded *angustoline acetate* (4) (82%) as yellow needles from chloroform, m.p. 148—152° (Found: C, 65·9; H, 5·3; N, 10·2%; $M^+$ 373. $C_{22}H_{19}N_3O_3,1·5H_2O$ requires C, 66·0; H, 5·5; N, 10·5%. $C_{22}H_{19}N_3O_3$ requires *M*, 373), $\nu_{max.}$ 3100—3600, 1725, 1660, 1620, 1605, 1250, 815, and 735 $cm^{-1}$.

Treatment of either angustoline or angustoline acetate with refluxing collidine under nitrogen for 18 h gave a mixture from which dihydroangustine (3) (*ca.* 20%) could be separated by chromatography.

To angustoline (1) (7 mg) in anhydrous methanol (20 ml), concentrated sulphuric acid (6 ml) was added slowly and the mixture was refluxed for 2·5 h. Upon neutralization with aqueous potassium hydroxide and extraction with chloroform, angustine (2) was obtained in quantitative yield.

We thank Dr. S. W. Tam for determination of some of the mass spectra and the Merck Institute for Therapeutic Research for a grant.

[2/1420 *Received*, 19*th June*, 1972]