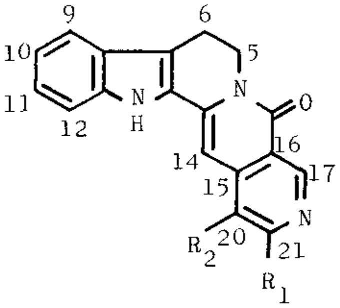
HETEROCYCLES, Vol 3, No 8, 1975

A TOTAL SYNTHESIS OF ANGUSTINE

Tetsuji Kametani,* Mitsuhiro Takeshita, Masataka Ihara,
and Keiichiro Fukumoto
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

A total synthesis of angustine (1) was accomplished via condensation of tryptamine with the lactone (5) which was prepared from 4-methyl-5-vinylnicotinonitrile (4), followed by cyclisation of the 7-azacarbostyril (8). Gentianine (6) was also synthesised by two routes from the nicotinonitrile (4).

In 1973, Cheung and his coworkers[1] isolated angustine (1), angustoline (2)[2] and angustidine (3)[3] from Strychnos angustiflora and their distribution in species of Mitragyna, Nauclèa, Uncaria



(1) R_1=H, R_2=$-\overset{19}{C}H=\overset{18}{C}H_2$

(2) R_1=H, R_2=$-CH(OH)CH_3$

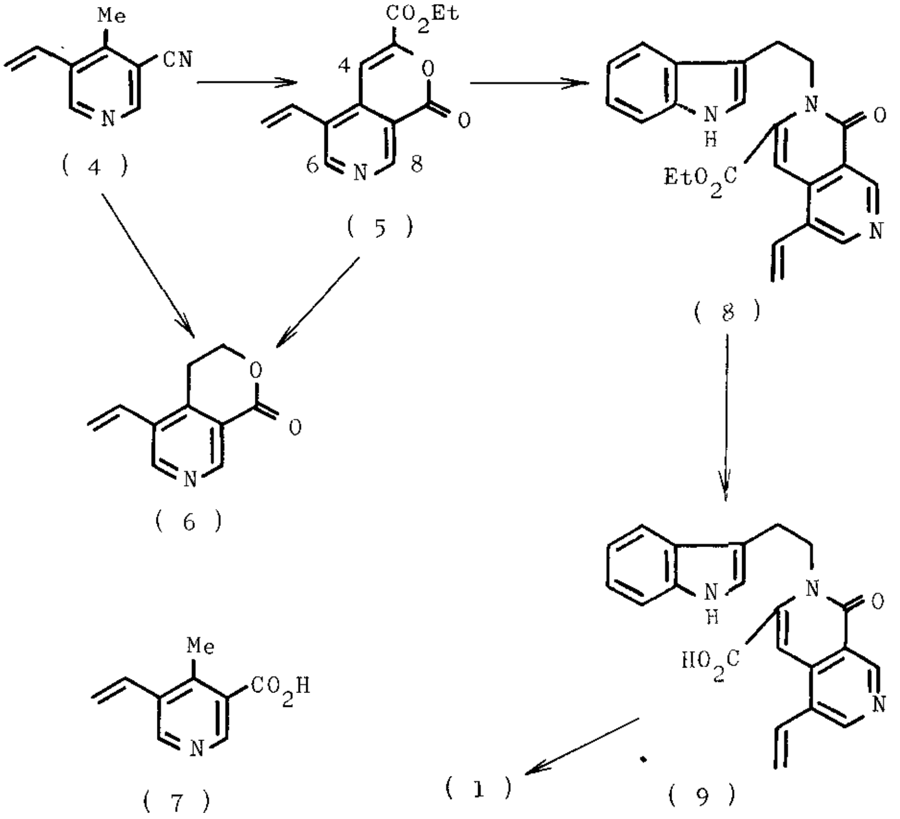
(3) R_1=Me. R_2=H

and *Strychnos* has recently been found.[4] They are *Corynanthé* type alkaloids incorporating in the skeletone a tryptamine unit and a secologanin monoterpene unit closely related to the alkaloid gentianine (6).[1] Therefore we are interested in the synthesis of angustine (1) using gentianine-like compound and here wish to report the total synthesis of angustine (1) and an alternative synthesis of gentianine (6).

Essentially based on Wenkert's method,[5] 4-methyl-5-vinylnicotinonitrile (4)[6] was condensed with ethyl oxalate in the presence of sodium hydride in benzene and *in situ* treated with diluted hydrochloric acid to give the lactone (5) in 76 % yield, m.p.120°, $\nu_{max}^{CHCl_3}$: 1740, 1720, 1640 and 1580 cm^{-1}; δ(CDCl$_3$): 1.43 (3H, t, *J* 7 Hz, $CH_2C\underline{H}_3$), 4.43 (2H, q, *J* 7 Hz, $C\underline{H}_2CH_3$), 5.76 (1H, dd, *J* 2 and 11.5 Hz, $-CH=C\underline{H}_2$), 5.89 (1H, dd, *J* 2 and 18 Hz, $-CH=C\underline{H}_2$), 7.06 (1H, dd, *J* 11.5 and 18 Hz, $-C\underline{H}=CH_2$), 7.62 (1H, s, C_4-H), 9.02 (1H, s, C_6-H), and 9.42 p.p.m. (1H, s, C_8-H); m/e : 245 (M^+). Heating the lactone (5) with sodium chloride in wet dimethylformamide[7] for 3 days, followed by purification of the product, gave colourless needles, m.p. 80 - 81°, ν_{max}^{KBr}: 1720 and 1621 cm^{-1}; δ (CDCl$_3$): 3.09 (2H, t, *J* 6 Hz, C_4-H), 4.55 (2H, t, *J* 6 Hz, C_3-H), 5.59 (1H, dd, *J* 2 and 11.5 Hz, $-CH=C\underline{H}_2$), 5.76 (1H, dd, *J* 2 and 18 Hz, $-CH=C\underline{H}_2$), 6.80 (1H, dd, *J* 11.5 and 18 Hz, $-C\underline{H}=CH_2$), 8.80 (1H, s, C_6-H), 9.11 (1H, s, C_8-H); m/e: 175 (M^+), which was identified as gentianine (6) by mixed melting point test and comparison with i.r. and n.m.r. spectra of the authentic sample. It was considered that the above reaction gave rise to the decarboxylation and then disproportionation. Gentianine (6) was furthermore synthesised by heating 4 with formalin in the presence of sodium hydrogen carbonate in water for 10 hr at 100°, followed by acid treatment.

Govindachari and his coworkers had prepared gentianine by the similar reaction with a nicotinic acid (7) derived from 4.[6]

Refluxing an equimolar amount of the above lactone (5) with tryptamine in acetic acid for 3 hr gave in 90 % yield the azaisocarbostyril (8), m.p. 145°, $\nu_{max}^{CHCl_3}$ 3480 (NH), 1720, 1670, and 1605 cm^{-1}; λ_{max}^{EtOH} (log ε): 335 (2.95), 290^{sh} (2.93), 280^{sh} (3.01) and 273 nm (3.02); m/e: 387 (M^+). The n.m.r. (δ in $CDCl_3$) spectrum showed an ethyl group at 1.25 (3H, t, J 7 Hz) and 4.03 (2H, q, J 7 Hz), two neighbouring methylne groups at 3.22 and 4.68 (each 2H, each t, J 7.5 Hz), methylene protons of a vinyl group at 5.59 (1H, dd, J 2 and 11.5 Hz) and 5.82 (1H, dd, J 2 and 18 Hz), α-proton of an indole ring at 6.89 (1H, d, J 1.5 Hz) and protons at C_6 and C_8 positions of an azaisocarbostyril ring at 8.56 (1H, s) and 9.45 p.p.m. (1H, s), respectively. Hydrolysis of 8 with ethanolic potassium hydroxide at room temperature, followed by heating the crude acid (9) with concentrated hydrochloric acid-glacial acetic acid (1 : 1 v/v) until the cease of the generation of carbon dioxide gave angustine (1) in 24 % yield from 8. During the reaction, a spontaneous dehydrogenation occured. Angustine (1) was also synthesised in 4 % yield by a direct treatment of 8 with concentrated hydrochloric aicd. Some values of chemical shifts of the synthetic angustine in the n.m.r. spectrum (δ in DMSO-d_6 at 25°) [4.38 (2H, t, J 7 Hz, C_5-H), 5.65 (1H, dd, J 2 and 11 Hz, C_{18}-H), 6.06 (1H, dd, J 2 and 18 Hz, C_{18}-H), 7.05 - 7.66 (5H, m, 4 x ArH and C_{14}-H), 8.80 (1H, s, C_{21}-H) and 9.20 p.p.m. (1H, s, C_{17}-H)] were slightly different from the previously reported data. Phillipson and his coworkers also found a slight difference between the observed chemical shifts of angustine and those reported data[1] and attributed them to a different operating temperature.[4] The u.v. [λ_{max}^{EtOH} (log ε): 400 (4.66), 380 (4.64), 304 (4.19), 292 (4.17), and 255 nm (4.32)], i.r. [ν_{max}^{Nujol} 3300 - 3100 (NH), 1640 (C=O), 1610, 1660, 1148, 830, 815 and 740 cm^{-1}] and mass [m/e 313 (M^+) (100 %)] spectra were identical with those of authentic sample. Thus, the total synthesis of angustine (1) has been accomplished.



ACKNOWLEDGEMENT We are grateful to Dr. T. R. Govindachari for a gift of gentianine, and to Dr. J. D. Phillipson for a providing of angustine.

REFERENCES

1 T. Y. Au, H. T. Cheung, and S. Sternhell, *J. C. S. Perkin I*, 1973, 13.

2 I. Ninomiya and T. Naito, *Heterocycles*, 1974, **2**, 607.

3 I. Ninomiya, H. Takasugi, and T. Naito, *J. C. S. Chem. Comm.*, 1973, 732; A. Shafiee and E. Winterfeldt, *Chem. Ber.*, 1974, **107**, 966.

4 J. D. Phillipson, S. R. Hemingway, N. G. Bisset, P. J. Houghlton, and E. J. Shellard, *Phytochemistry*, 1974, **13**, 973.

5 E. Wenkert, K. G. Dave, R. G. Lewis, and P. W. Sprague, *J. Amer. Chem. Soc.*, 1967, **89**, 6741.

6 T. R. Govindachari, K. Nagarajan, and S. Rajappa, *J. Chem. Soc.*, 1957, 2725.

7 A. P. Krapcho and A. J. Lovey, *Tetrahedron Letters*, 1973, 957.

Received, 12th June, 1975