(22) R. N. Castle and W. S. Seese, J. Org. Chem., 20, 987 (1955); G. N. Walker, J. Med. Chem., 8, 583 (1965).
(23) In CCl_4, this isomeric differentiation was not possible.
(24) F. Coletta, A. Gambaro, and L. Pasimeni, Gazz. Chim. Ital., 103, 265 (1973).
(25) J. H. Schauble, G. J. Walter, and J. G. Morin, J. Org. Chem., 39, 755 (1974).
(26) L. E. Friedrich and R. A. Cormier, J. Org. Chem., 35, 450 (1972).
(27) C. G. Kratchanov, Ts. D. Obretenov, and B. J. Kurtev, Synthesis, 263 (1972).
(28) S. Spasov, Tetrahedron, 25, 3631 (1969).

Studies on the Syntheses of Heterocyclic Compounds. 657.[1a] Total Synthesis of Angustine, Naucléfine, and Gentianine[1b]

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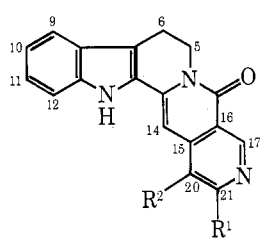
Condensation of 4-methyl-5-vinylnicotinonitrile (**7**) with ethyl oxalate, followed by acid hydrolysis, gave 3-ethoxycarbonyl-1-oxo-5-vinylpyrano[4,3-*c*]pyridine (**10**), which was heated in wet dimethylformamide to afford an unexpected product, gentianine (**6**). Gentianine (**6**) was also prepared directly from **7**. Condensation of **7** with ethyl formate yielded 3,4-dehydrogentianine (**16**). Treatment of the lactone (**10**) with tryptamine gave the 7-azaisocarbostyril (**14**), from which angustine (**1**) was synthesized by direct acid treatment or basic hydrolysis, followed by acidic cyclization. By the reaction of 3,4-dehydrogentianine (**16**) with tryptamine in acidic conditions, angustine (**1**) was also synthesized and naucléfine (**4**) was synthesized from nicotinonitrile (**17**) in a similar way.

In 1973, Cheng and his co-workers reported the isolation of angustine (**1**), angustoline (**2**), and angustidine (**3**) from *Strychnos angustiflora*.[2] Since then their distribution in species of *Mitragyna, Naucléa, Uncaria,* and *Strychnos* has been established.[3] Recently the related bases naucléfine (**4**) and nauclétine (**5**) were found in *Naucléa latifolia*.[4] Their

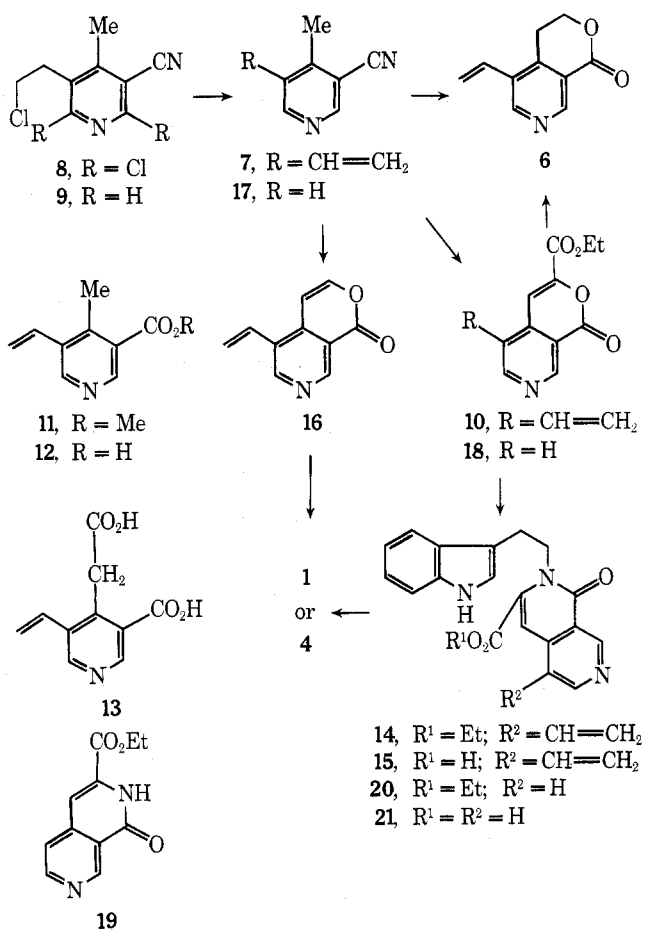


1, $R^1 = H$; $R^2 = -CH(19)=CH_2(18)$
2, $R^1 = H$; $R^2 = -CH(OH)Me$
3, $R^1 = Me$; $R^2 = H$
4, $R^1 = R^2 = H$
5, $R^1 = H$; $R^2 = COMe$

structures were assigned on the basis of spectral evidences and confirmed by the synthesis of angustoline (**2**),[5] angustidine (**3**),[6,7] and naucléfine (**4**).[4] Angustoline had been already converted into angustine (**1**).[2] It seemed worthwhile from a pharmacological point of view to investigate an effective synthesis of angustine and its derivatives. They are essentially *corynanthé* type alkaloids incorporating in their skeleton a tryptamine moiety and a secologanin monoterpene unit closely related to the alkaloid, gentianine (**6**).[2] We had therefore planned their synthesis using gentianine-like compounds and herewith describe biomimetic total syntheses of angustine (**1**) and naucléfine (**4**), and an alternative synthesis of gentianine (**6**).

According to a modified Govindachari procedure,[8] 4-methyl-5-vinylnicotinonitrile (**7**) was prepared via 2,6-dichloro-5-(2-chloroethyl)-3-cyano-4-methylpyridine (**8**) and 5-(2-chloroethyl)-4-methylnicotinonitrile (**9**). The nitrile **7** was condensed with ethyl oxalate in the presence of sodium hydride in benzene and in situ treated with diluted hydrochloric acid[9] to give the lactone **10**, mp 120 °C, in 76% yield.

Krapcho and Lovey had already carried out the decarboxylation of geminal diesters, β-keto esters, and α-cyano esters by heating in the presence of sodium chloride in wet dimethyl sulfoxide or wet dimethylformamide.[10] It was furthermore reported that even in the absence of sodium chloride, the reaction proceeded satisfactorily.[11,12] In expectation of a decarboxylation, the lactone **10** was heated with sodium chloride in wet dimethylformamide for 3 days and an unexpected product, mp 80–81 °C, *m/e* 175 (M^+), was isolated in 12% yield



after purification by column chromatography. The ir spectrum (in potassium bromide) of the product showed a carbonyl absorption at 1720 cm^{-1} and the NMR spectrum (δ in deuteriochloroform) revealed two neighboring methylene groups at 3.09 and 4.55 (each 2 H, each t, J = 6 Hz), a vinyl group at 5.59 (1 H, dd, J = 2 and 11.5 Hz), 5.76 (1 H, dd, J = 2 and 18 Hz), and 6.80 (1 H, dd, J = 11.5 and 18 Hz), and two aromatic protons at 8.80 and 9.11 ppm (each 1 H, each s). These spectral data suggested the product to be gentianine (**6**), which was also confirmed by direct comparison with an authentic sample.

When the lactone **10** was heated for 3 days in wet dimethylformamide in the absence of sodium chloride, the formation of gentianine (**6**) was also detected by gas chramotography. It is likely that decarboxylation and disproportionation occurred during the above transformation. The crude reaction product was treated directly with diazomethane and then carefully purified using silica gel column chromatography to afford methyl 4-methyl-5-vinylnicotinate (**11**) together with gentianine.

The formation of methyl 4-methyl-5-vinylnicotinate (**11**) was confirmed by a direct comparison with the authentic sample, prepared from the nitrile **7** via 4-methyl-5-vinylnicotinic acid (**12**). It was assumed that an aldehyde equivalent, formed by refluxing the dehydrolactone (**10**) in wet dimethylformamide, gave through disproportionation gentianine (**6**) and a derivative of the dicarboxylic acid (**13**), which was further decarboxylated to the nicotinic acid (**12**).

Gentianine (**6**) was furthermore synthesized by heating **7** with formalin in the presence of aqueous sodium bicarbonate solution for 19 h at 100 °C, followed by acid treatment. Govindachari and coworkers had previously prepared gentianine (**6**) by a similar reaction using the nicotinic acid analogue **12** derived from **7**.[8]

Refluxing the above lactone (**10**) with an equimolar amount of tryptamine in acetic acid for 3 h gave, in 90% yield, the azaisocarbostyril (**14**), the structure of which was confirmed by spectral evidence. The ester **14** was hydrolyzed with ethanolic potassium hydroxide at room temperature and the crude acid (**15**) obtained was then heated with a mixture (1:1 v/v) of concentrated hydrochloric acid and glacial acetic acid until no further generation of carbon dioxide could be detected. After chromatographic purification, angustine (**1**), mp >300 °C, was obtained in 23.5% overall yield from the ester **14**. Direct heating of **14** in a mixture of concentrated hydrochloric acid and acetic acid also gave angustine (**1**) in 8% yield. The uv, ir, and mass spectra of the synthetic compound were identical with those of natural angustine. The NMR spectrum (in dimethyl sulfoxide-d_6) at 110 °C was identical with that at the same temperature provided by Dr. Cheung. Taking the NMR spectra in the same solvent at room temperature and at 90 °C, some values of chemical shifts were considerably changed as predicted by Phillipson and coworkers.[3] Identity of the synthetic product with natural angustine (**1**) was further confirmed by high-pressure liquid chromatography.

Condensation of 4-methyl-5-vinylnicotinonitrile (**7**) with ethyl formate in the presence of sodium hydride in dry dimethyformamide or dry benzene at room temperature, followed by a treatment of the product with hydrochloric acid, gave dehydrogentianine (**16**). This pyrone was heated for 3 h with an equimolar amount of tryptamine in acetic acid to afford a mixture to which concentrated hydrochloric acid was added. Refluxing the resulting mixture for 10 h, followed by column chromatographic purification, afforded in 9.5% yield angustine (**1**).

Thereafter naucléfine (**4**) was synthesized according to the above sequence. 4-Methylnicotinonitrile (**17**)[13] was condensed with ethyl oxalate in the presence of potassium *tert*-butoxide in dry benzene and then treated with diluted hydrochloric acid to give the lactone **18** in addition to the naphthyridine **19**. The lactone **18** was converted into the azaisocarbostyril **20** by refluxing for 3 h with tryptamine in glacial acetic acid. After hydrolysis of **20** with ethanolic potassium hydroxide at room temperature, the crude acid **21** was heated for 7 days with a mixture of concentrated hydrochloric acid and glacial acetic acid to afford naucléfine (**4**) in 10% overall yield. Refluxing the azaisocarbostyril **20** with a mixture of concentrated hydrochloric acid and glacial acetic acid for 7 days also furnished naucléfine (**4**) in 15% yield. The uv, ir, NMR (in dimethyl sulfoxide-d_6), and mass spectra were superimposable with those of the natural product. The total syntheses of angustine (**1**) and naucléfine (**4**) have therefore been accomplished.

Experimental Section

All melting points are uncorrected. Uv spectra were measured with a Hitachi EPS-3 recording spectrometer, ir spectra with a Hitachi EPI-3 recording spectrometer, NMR spectra with a JEOL JNM-PMX-60 and JNM-PS-100 spectrometer, and mass spectra with a Hitachi RMU-7 spectrophotometer. The apparatus used for gas chromatography was a JEOL JGC-1100 equipped with a hydrogen flame ionization detector. High-pressure liquid chromatography was carried out with Waters Associated ALC-GDC 202,R401 instrument (6000 pumping system), with a 254-nm uv detector. The column (1 ft × 0.25 in.) was packed with μ-Bondapak C_{18} and elution was carried out with methanol–water (3:1 v/v) and flow rate of 1.5 ml/min.

5-(2-Chloroethyl)-4-methylnicotinonitrile (9). The trichloro compound 8 (48 g)[8] was hydrogenated for 6 h in methanol (300 ml) in the presence of sodium acetate (41 g) and 10% Pd/C (9.6 g) at room temperature under hydrogen (1 atm) until no more hydrogen had been absorbed. The resulting solution was filtered and the catalyst was washed with methanol. The combined filtrate and washings were evaporated. The residue was treated with aqueous sodium bicarbonate solution and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated to give a syrup, whose distillation at 147–149 °C (4 mm) afforded **9** (30.8 g, 88.7%) [lit.[8] bp 144–145 °C (3 mm)]: NMR (CCl_4) δ 2.48 (3 H, s, ArMe), 3.08 (2 H, t, J = 7 Hz, CH_2CH_2Cl), 3.67 (2 H, t, J = 7 Hz, CH_2CH_2Cl), 8.42 and 8.54 ppm (each 1 H, each s, 2 ArH).

4-Methyl-5-vinylnicotinonitrile (7). A mixture of the above nitrile (**9**, 4.8 g) and potassium hydroxide (1 g) in ethanol (10 ml) was stirred for 1 h at room temperature. After addition of water, the reaction mixture was extracted with ether. The extract was dried over Na_2SO_4 and evaporated to give a syrup whose distillation at 135–143 °C (10 mm) afforded **7** (3.0 g, 78%) [lit.[8] bp 98 °C (2 mm)]: NMR ($CDCl_3$) δ 2.55 (3 H, s, ArMe), 5.55 (1 H, dd, J = 11.5 and 2 Hz, $CH{=}CH_2$), 5.74 (1 H, dd, J = 18 and 2 Hz, $CH{=}CH_2$), 6.88 (1 H, dd, J = 18 and 11.5 Hz, $CH{=}CH_2$), 8.67 and 8.71 ppm (each 1 H, each s, 2 ArH).

3,4-Dihydro-3-ethoxycarbonyl-1-oxo-5-vinylpyrano[3,4-*c*]pyridine (10). To a solution of the preceding nitrile (**7**, 1 g) and ethyl oxalate (20 ml) in dry benzene (10 ml), 50% sodium hydride (400 mg) was added in small portions, and the mixture was stirred for 24 h under nitrogen at room temperature. With cooling, 10% hydrochloric acid was slowly added to the above resulting mixture, which was then washed several times with ether. The aqueous layer was made basic with 10% ammonia and extracted with chloroform. The chloroform layer was washed with water, dried over Na_2SO_4, and evaporated to give a powder, the recrystallization of which from ethanol afforded **10** (1.2 g, 76%) as pale yellow needles: mp 120 °C; ir ($CHCl_3$) 1740, 1720, 1640, and 1580 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (3 H, t, J = 7 Hz, CH_2CH_3), 4.43 (2 H, q, J = 7 Hz, CH_2CH_3), 5.67 (1 H, dd, J = 11.5 and 2 Hz, $CH{=}CH_2$), 5.89 (1 H, dd, J = 18 and 2 Hz, $CH{=}CH_2$), 7.06 (1 H, dd, J = 18 and 11.5 Hz, $CH{=}CH_2$), 7.62 (1 H, s, 4-CH), 9.02 (1 H, s, 6-CH), and 9.42 ppm (1 H, s, 8-CH); mass spectrum m/e 245 (M^+).

Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.73; H, 4.65; N, 5.70.

Gentianine (6). A. A mixture of the above lactone (**10**, 70 mg), sodium chloride (50 mg), and water (2 drops) in dimethylformamide (5 ml) was refluxed for 3 days in an oil bath. After cooling, followed by an addition of water, the resulting mixture was extracted with chloroform. The extract was dried over Na_2SO_4 and evaporated to leave a gum, which was chromatographed on silica gel. Benzene–methanol (100:0.5 v/v) eluate yielded a powder, the recrystallization of which from carbon tetrachloride gave gentianine (**6**, 7 mg, 12%), as colorless needles: mp 80–81 °C (lit.[8] mp 80–81 °C); ir ($CHCl_3$) 1720 and 1621 cm^{-1}; NMR ($CDCl_3$) δ 3.09 (2 H, t, J = 6 Hz, 4-CH_2), 4.55 (2 H, t, J = 6 Hz, 3-CH_2), 5.59 (1 H, dd, J = 11.5 and 2 Hz, $CH{=}CH_2$), 5.76 (1 H, dd, J = 18 and 2 Hz, $CH{=}CH_2$), 6.80 (1 H, dd, J = 18 and 11.5 Hz, $CH{=}CH_2$), 8.80 (1 H, s, 6-CH), and 9.11 ppm (1 H, s, 8-CH); mass spectrum m/e 175 (M^+).

B. A mixture of 4-methyl-5-vinylnicotinonitrile (**7**, 0.5 g), sodium bicarbonate (0.5 g), 27% formalin (0.7 ml), and water (7 ml) was heated for 10 h at 100 °C in a sealed tube. After cooling, the excess of formalin was distilled off. The mixture was acidified with 10% hydrochloric acid, washed with ether, and then basified with 10% ammonia. The basic material was extracted with ether and the extract was washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel with benzene–methanol (100:0.5 v/v) to give a powder, whose recrystallization from carbon tetrachloride afforded gentianine (**6**, 28 mg, 7.8%) as colorless needles, mp 81–82

°C. The ir (in $CHCl_3$), NMR (in $CDCl_3$), and mass spectra, and TLC and GLC (SE-30 and 1.6% OV-17) behaviors were identical with those of the product prepared by method A and authentic gentianine (6). A mixture melting point test with an authentic sample showed no depression.

Methyl 4-Methyl-5-vinylnicotinate (11) A. A mixture of 4-methyl-5-vinylnicotinonitrile (7, 1 g) and potassium hydroxide (3 g) in methanol was refluxed for 24 h. After cooling, the mixture was acidified to pH 5 with concentrated hydrochloric acid and then evaporated to dryness. The residue was extracted several times with methanol. The combined methanolic solution was saturated with hydrogen chloride gas and the mixture was refluxed for 5 h. After evaporation of the reaction mixture, the residue was extracted with chloroform, which was washed with 10% ammonia and water, dried over Na_2SO_4, and evaporated to give a brown residue, which was purified by sublimation at 80 °C (4 mm) to afford 11 (800 mg) as colorless needles: mp 46–47 °C; ir ($CHCl_3$) 1720 and 1645 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (3 H, s, ArMe), 3.90 (3 H, s, OMe), 5.46 (1 H, dd, J = 11.5 and 2 Hz, CH=C**H**$_2$), 5.63 (1 H, dd, J = 18 and 2 Hz, CH=C**H**$_2$), 6.93 (1 H, dd, J = 18 and 11.5 Hz, C**H**=CH$_2$), 8.66 and 8.90 ppm (each 1 H, each s, 2 ArH); mass spectrum m/e 177 (M^+).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.27; N, 7.91. Found: C, 67.35; H, 6.36; N, 7.88.

B. A mixture of the dehydrolactone 10 (70 mg) and water (2 drops) in dimethylformamide (5 ml) was refluxed for 3 days. After distillation of the solvents under reduced pressure, the residue was dissolved in methanol. An excess of diazomethane in ether was added to the above methanolic solution and the mixture was set aside for 16 h at room temperature. After the evaporation, the residue was chromatographed on silica gel. Benzene eluate gave 11 (2.5 mg) as colorless needles, mp 46–47 °C, which was identical with the authentic sample prepared as above with comparisons of the ir, NMR, and mass [m/e 177 (M^+)] spectra and chromatographic behaviors on TLC and GLC (SE-30). Benzene–methanol (99.5:0.5 v/v) eluate gave gentianine (2 mg) as colorless needles, mp 80–81 °C, whose ir and NMR spectra and chromatographic behaviors on TLC and GLC were identical with those of the authentic sample.

3-Ethoxycarbonyl-2-(β-3-indolylethyl)-5-vinyl-7-azaisocarbostyril (14). A solution of tryptamine (320 mg) and the lactone 10 (400 mg) in glacial acetic acid (10 ml) was refluxed for 3 h. After cooling, the solvent was distilled off. The residue was taken up in chloroform. The extract was washed with 10% ammonia and water and dried over Na_2SO_4. After evaporation of the solvent, the resulting powder was recrystallized from ethanol to give 14 (700 mg, 90%) as colorless needles: mp 145 °C; uv (EtOH) 335, 290 sh, 280 sh, and 273 nm (log ϵ 2.95, 2.93, 3.01, and 3.02); ir ($CHCl_3$) 3480 (NH), 1720 and 1670 (C=O), and 1605 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz, CH_2CH_3), 3.22 (2 H, t, J = 7.5 Hz, CH_2CH_2N), 4.03 (2 H, q, J = 7 Hz, OCH_2CH_3), 4.68 (2 H, t, J = 7.5 Hz, CH_2CH_2N), 5.59 (1 H, dd, J = 11.5 and 2 Hz, CH=C**H**$_2$), 5.82 (1 H, dd, J = 18 and 2 Hz, CH=C**H**$_2$), 6.89 (1 H, d, J = 1.5 Hz, indole α-H), 8.00 br (1 H, s, indole NH, disappeared with D_2O), 8.56 (1 H, s, 6-CH), and 9.45 ppm (1 H, s, 8-CH); mass spectrum m/e 387 (M^+).

Anal. Calcd for $C_{23}H_{21}N_3O_3 \cdot 0.25H_2O$: C, 70.45; H, 5.55; N, 10.72. Found: C, 70.79; H, 5.43; N, 10.79.

1-Oxo-5-vinylpyrano[3,4-c]pyridine (16). To a solution of 4-methyl-5-vinylnicotinonitrile (7, 1g) and ethyl formate (10 ml), 50% sodium hydride (400 mg) was added in portions and the mixture was stirred for 24 h at room temperature under nitrogen. After acidification with 10% hydrochloric acid, the aqueous solution was washed with ether, basified with 10% ammonia, and then extracted with chloroform. The chloroform extract was washed with saturated sodium chloride aqueous solution, dried over Na_2SO_4, and evaporated to give a gum, which was chromatographed on silica gel (30 g). Benzene eluate gave the starting material (400 mg) and dehydrogentianine (16) as a solid, the recrystallization of which from methanol–ether afforded colorless needles (150 mg, 21%): mp 119–120 °C; ir ($CHCl_3$) 1736, 1630, and 1580 cm^{-1}; NMR ($CDCl_3$) δ 5.65 (1 H, dd, J = 11.5 and 2 Hz, CH=C**H**$_2$), 5.74 (1 H, dd, J = 18 and 2 Hz, CH=C**H**$_2$), 6.99 (1 H, dd, J = 18 and 11.5 Hz, C**H**=CH$_2$), 6.70 (1 H, d, J = 6 Hz, C**H**=CHO), 7.48 (1 H, d, J = 6 Hz, CH=C**H**O), 8.95 and 9.48 ppm (each 1 H, each s, 2 ArH); mass spectrum m/e 173 (M^+).

Anal. Calcd for $C_{10}H_7NO_2$: C, 69.35; H, 4.07. Found: C, 69.14; H, 4.17.

Angustine (1). A. To a solution of the azaisocarbostyril 14 (600 mg) in ethanol (30 ml) a mixture of potassium hydroxide (98 mg) in ethanol (5 ml) was added and the resulting mixture was stirred for 6 h at room temperature. After acidification with 10% hydrochloric acid, the solvent was distilled off to give a syrup, to which glacial acetic acid (10 ml) and concentrated hydrochloric acid (10 ml) were added without purification. The mixture was then refluxed for 3 days until the cease of generation of carbon dioxide. After cooling the reaction mixture was made basic with 10% sodium hydroxide solution and then extracted several times with n-butyl alcohol. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave a gum, which was chromatographed on silica gel. Benzene–methanol (99.5:0.5 v/v) eluate gave a yellow powder, the recrystallization of which from chloroform–methanol gave angustine (1, 114 mg, 23.5%) as yellow plates: mp >300 °C (lit.[2] mp >340 °C and lit.[3] mp 283–284 °C dec); uv (EtOH) 400, 380, 304, 292, and 255 nm (log ϵ 4.66, 4.64, 4.19, 4.17, and 4.32); ir (Nujol) 3300–3100 (NH), 1640 (C=O), 1610, 1600, 1148, 830, 815, and 740 cm^{-1}; NMR (Me_2SO-d_6 at 25 °C)[16] δ 4.38 (2 H, t, J = 7 Hz, 5-CH_2), 5.65 (1 H, dd, J = 11.5 and 2 Hz, 18-CH), 6.05 (1 H, dd, J = 18 and 2 Hz, 18-CH), 7.05–7.66 (6 H, m, 4 ArH, 14- and 19-CH), 8.80 (1 H, s, 21-CH) and 9.20 ppm (1 H, s, 17-CH); mass spectrum m/e 313 (M^+) (100%). The uv, ir, and mass spectra, TLC,[13] and HPLC behaviors were identical with those of natural product.

B. A mixture of the azaisocarbostyril 14 (92 mg) and concentrated hydrochloric acid (2 ml) in glacial acetic acid (2 ml) was refluxed for 3 days until the cease of generation of carbon dioxide. After cooling, 10% ammonia was added to the reaction mixture, which was extracted several times with n-butyl alcohol. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave a gum, which was purified as above to afford angustine (1, 3 mg, 4%) as yellow plates, mp >300 °C, which was identical with angustine prepared by method A on spectral and TLC comparisons.

C. A solution of tryptamine (20 mg) and the dehydrogentianine 16 (28 mg) in glacial acetic acid (5 ml) was refluxed for 3 h. After an addition of concentrated hydrochloric acid (5 ml), the mixture was refluxed for 5 h. After cooling, 10% sodium hydroxide solution was added to the reaction mixture, which was extracted with n-butyl alcohol. The extract was washed with saturated sodium chloride aqueous solution, dried over Na_2SO_4, and evaporated to leave a gum, which was chromatographed on silica gel (1.5 g). Benzene–methanol (99.5:0.5 v/v) eluate gave a yellow powder, the recrystallization of which afforded angustine (1, 4.7 mg, 9.4%) as yellow plates, mp >300 °C, which was identical with angustine prepared by method A on spectral and TLC comparisons.

3-Ethoxycarbonyl-1-oxopyrano[3,4-c]pyridine (18). To a solution of 4-methylnicotinonitrile (17,[14] 300 mg) and ethyl oxalate (5 ml) in dry benzene (10 ml), potassium *tert*-butoxide (600 mg) was added in small portions and the mixture was stirred for 24 h under nitrogen. Under cooling with ice, 10% hydrochloric acid was added dropwise to the above mixture, which was then washed with ether. The aqueous layer was made basic with 10% ammonia and extracted with chloroform. The chloroform layer was washed with water, dried over Na_2SO_4, and evaporated to give a residue which was chromatographed on silica gel. The benzene–methanol (99.7:0.3 v/v) eluate afforded a powder, which was recrystallized from ethanol to give 18 (54 mg, 10%) as colorless needles: mp 138–139 °C; ir ($CHCl_3$) 1740, 1720, 1630, and 1575 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (3 H, t, J = 7 Hz, CH_2CH_3), 4.83 (2 H, q, J = 7 Hz, CH_2CH_3), 7.33 (1 H, s, 4-CH), 7.36 (1 H, d, J = 6.5 Hz, 5-CH), 8.91 (1 H, d, J = 6.5 Hz, 6-CH), and 9.46 ppm (1 H, s, 8-CH).

Anal. Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.16; H, 4.24; N, 6.40.

The benzene–methanol (99.5:0.5 v/v) eluate gave a powder which was recrystallized from ethanol to afford the naphthyridine 19 (58 mg, 10%) as colorless needles: mp 232–234 °C (lit.[15] mp 229–230 °C); ir ($CHCl_3$) 3350 (NH), 1718, 1664, and 1592 cm^{-1}; NMR ($CDCl_3$) δ 1.51 (3 H, t, J = 7 Hz, CH_2CH_3), 4.46 (2 H, q, J = 7 Hz, CH_2CH_3), 7.02 (1 H, s, 6-CH), and 9.56 ppm (1 H, s, 8-CH).

Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.28; H, 4.83; N, 12.68.

3-Ethoxycarbonyl-2-(β-indolylethyl)-7-azaisocarbostyril (20). A solution of tryptamine (296 mg) and the above lactone 18 in glacial acetic acid (10 ml) was refluxed for 3 h. After cooling, the solvent was distilled off to give a residue, which was taken up in chloroform. The extract was washed with 10% ammonia and water, dried over Na_2SO_4, and evaporated to afford a powder, which was recrystallized from ethanol to yield 20 (550 mg, 82%) as colorless needles: mp 158–159 °C; ir ($CHCl_3$) 3460 (NH), 1720, 1650, and 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (3 H, t, J = 7 Hz, CH_2CH_3), 3.23 (2 H, t, J = 7.5 Hz, CH_2CH_2N), 4.00 (2 H, q, J = 7 Hz, CH_2CH_3), 4.70 (2 H, t, J = 7.5 Hz, CH_2CH_2N), 6.89 (1 H, d, J = 1.5 Hz, indole α-H), 8.68 (1 H, d, J = 5.6 Hz, 6-CH), and 9.68 ppm (1 H, s, 8-CH).

Naucléfine (4). A To a solution of the azaisocarbostyril 20 (320 mg) in ethanol (10 ml), a solution of potassium hydroxide (53 mg) in ethanol (10 ml) was added and the resulting mixture was stirred for 6 h at room temperature. After acidification with 10% hydrochloric

acid, the solvent was evaporated to leave the acid **21** as a gum to which a mixture of acetic acid (5 ml) and concentrated hydrochloric acid (5 ml) was added. The mixture was refluxed for 7 days until carbon dioxide had ceased to be evolved. After being allowed to stand overnight, crystals formed were collected by filtration and then suspended in chloroform. The chloroform suspension was shaken with 10% ammonia, washed with water, and dried over Na_2SO_4. Evaporation of the chloroform yielded a powder, which was recrystallized from methanol to give naucléfine (**4**, 26 mg, 10%) as yellow needles, mp 285–290 °C (lit.[4] mp 285–290 °C), whose uv [(EtOH) 390, 372, 300, 290, 250, and 220 nm], ir [(KBr) 3500 (NH), 1650 (C=O), 1610 and 1538 cm^{-1}], NMR [(Me_2SO-d_6) δ 4.92 (2 H, t, J = 7 Hz, 5-CH_2), 6.96–7.70 (6 H, m, indole aromatic protons and 14- and 20-CH), 8.56 (1 H, d, J = 6.5 Hz, 21-CH), and 9.25 (1 H, s, 17-CH)] spectra were superimposable on those of natural product.

B. A mixture of the azaisocarbostyril **20** (300 mg), concentrated hydrochloric acid (5 ml), and glacial acetic acid (5 ml) was refluxed for 7 days after standing overnight. Crystals formed were collected and worked up as above to give naucléfine (**4**, 28 mg, 15%) as yellow needles, mp 285–290 °C, which was identical with the above product prepared by method A.

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References and Notes

(1) (a) Part 659: T. Kametani et al., *Heterocycles*, **4**, 1223 (1976). (b) Part of this work reported as a preliminary communication: T. Kametani, M. Takeshita, M. Ihara, and K. Fukumoto, *Heterocycles*, **3**, 607 (1975).
(2) T. Y. Au, H. T. Cheung, and S. Sternhell, *J. Chem. Soc., Perkin Trans. 1*, 13 (1973).
(3) J. D. Phillipson, S. R. Hemingway, N. G. Bisset, P. J. Houghton, and E. J. Shellard, *Phytochemistry*, **13**, 973 (1974).
(4) F. Hotellier, P. Delaveau, and J. L. Pousset, *Phytochemistry*, **14**, 1407 (1975).
(5) I. Ninomiya and T. Naito, *Heterocycles*, **2**, 607 (1974).
(6) I. Ninomiya, H. Takasugi, and T. Naito, *J. Chem. Soc., Chem. Commun.*, 732 (1973).
(7) A. Shafflee and E. Winterfeldt, *Chem. Ber.*, **107**, 966 (1974).
(8) T. R. Govindachari, K. Nagarajan, and S. Rajappa, *J. Chem. Soc.*, 2725 (1957).
(9) E. Wenkert, K. G. Dave, R. G. Lewis, and P. W. Sprague, *J. Am. Chem. Soc.*, **89**, 6741 (1967).
(10) A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 957 (1973).
(11) A. P. Krapcho, E. G. E. Jahngen, Jr., and A. J. Lovey, *Tetrahedron Lett.*, 1091 (1974).
(12) C. L. Liotta and F. L. Cook, *Tetrahedron Lett.*, 1095 (1974).
(13) J. D. Phillipson and S. R. Hemingway, *J. Chromatogr.*, **105**, 163 (1975).
(14) J. M. Bobbitt and D. A. Scola, *J. Org. Chem.*, **25**, 560 (1960).
(15) D. J. Sheffield and K. R. H. Wooldridge, *J. Chem. Soc., Perkin Trans. 1*, 2506 (1972).
(16) NMR (Me_2SO-d_6 at 90 °C) δ 4.49 (2 H, t, J = 7 Hz, 5-CH_2), 5.73 (1 H, dd, J = 11.5 and 2 Hz, 18-CH), 6.90 (1 H, dd, J = 18 and 2 Hz, 18-CH), 8.87 (1 H, s, 21-H), and 9.26 (1 H, s, 17-CH).

A Novel Cleavage of Aryl Benzyl Ethers and Allyl Aryl Ethers by Sodium Bis(2-methoxyethoxy)aluminum Hydride. An Alternative Synthesis of Pentazocine

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Refluxing with sodium bis(2-methoxyethoxy)aluminum hydride in xylene causes an effective cleavage of benzyl or allyl ether. Using this reaction, pentazocine (**10**) was synthesized as follows. Hydrogenolysis of 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-benzazocin-4-one (**11**) with palladium on charcoal, followed by condensation of the resulting secondary amide (**12**) with dimethylallyl bromide gave the *N,O*-bis(dimethylallyl) compound (**15**), which yielded pentazocine (**10**) on refluxing with sodium bis(2-methoxyethoxy)aluminum hydride in xylene. The conversion of 3-benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocinium bromide (**17**) into pentazocine was examined under various conditions.

Although several examples of the hydrogenolysis of various types of organic compounds using complex metal hydrides have been reported, there are few synthetic applications.[1-3] Since sodium bis(2-methoxyethoxy)aluminum hydride, commercially available, has many advantages over other complex metal hydrides, the hydrogenolysis with sodium bis(2-methoxyethoxy)aluminum hydride have been studied. In this paper we now wish to report effective cleavages of aryl benzyl ethers or allyl aryl ethers with sodium bis(2-methoxyethoxy)aluminum hydride and alternative synthetic methods of pentazocine (**10**), a nonnarcotic analgesic, applying this reagent.

Debenzylation of the compounds having a methoxyl group at a vicinal carbon with sodium bis(2-methoxyethoxy)aluminum hydride proceeded more smoothly than that of the benzyl ether on monooxygenated aryl group. Thus, refluxing of 4-benzyloxybenzaldehyde (**1**) with an excess of the reagent in xylene for 6 h gave mainly 4-benzyloxybenzyl alcohol (**2**), and *p*-cresol (**3**) was obtained as a sole product by the same treatment as above for 60 h. On the other hand, when 4-benzyloxy-3-methoxybenzaldehyde (**4**) was refluxed with an excess of sodium bis(2-methoxyethoxy)aluminum hydride in xylene, creosol (**6**) was formed together with a small amount of 4-benzyloxy-3-methoxybenzyl alcohol (**5**) after 6 h, and creosol (**6**) was homogeneously obtained after 10 h. Treatment of 10-benzyloxy-5,6,13,13a-tetrahydro-2,3,11-trimethoxy-8*H*-dibenzo[*a,g*]quinolizine (**7**)[4] under the same conditions for 6 h caused the cleavage of the benzyl ether to afford the phenolic tetrahydroprotoberberine (**8**)[4] in an excellent yield (Scheme I).