UNUSUAL REARRANGEMENT REACTION OF QUEBRACHAMINE DERIVATIVE CATALYZED BY CYANIDE ANION

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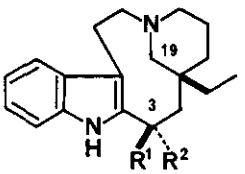
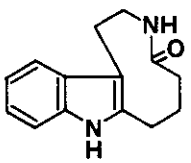
Abstract - Cyanation of trimethylammonium salt 8 with potassium cyanide afforded 3-cyano derivatives 9a and 9b accompanied by a significant amount of unexpected rearrangement product 10. The structure of 10 was established by single X-ray crystallographic analysis.

Quebrachamine and related alkaloids which have unique nine-membered ring system in the molecule were biogenetically close to aspidosperma alkaloids. Recently, we had established usefulness of the nine-membered lactam 3 which had been readily available by the photoisomerization.[1] Application of this reaction to the natural product syntheses had been performed by us to synthesize strychnos, aspidosperma, eburnamine,[1] and schizozygane alkaloids.[2] Especially, aspidosperma alkaloids and quebrachamine (1)[3] had been synthesized from 19-oxoquebrachamine (4). To extend this method to the syntheses of vincadine (2)[4] and re-



1; $R^1 = R^2 = H$
2; $R^1 = COOCH_3$, $R^2 = H$



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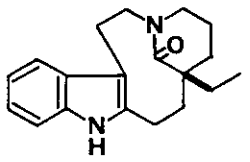

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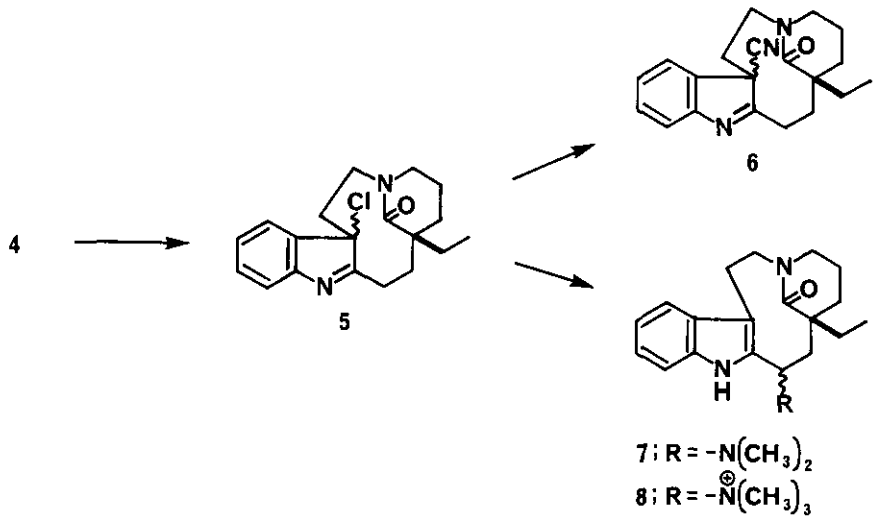
lated alkaloids, introduction of methoxycarbonyl group to the C(3)-position of quebrachamine skeleton has been investigated.

In our knowledge, Buchi's chloroindolenine method[5] is only one practical method to introduce cyano function to the α-carbon of C(2) of indoles. Oxoquebrachamine 4 reacted with tert-butyl hypochlorite to give the unstable chloroindolenine 5. Treatment of crude 5 with potassium cyanide afforded 6 (mp 197-199°C) in 59% yield and none of the 3-cyano compounds were detected. Similar structure was suggested[6] in the reaction of quebrachamine (1) with cyanogen bromide in refluxing chloroform. Ultraviolet spectrum of 6 indicated typical indolenine absorption (λ_{max}264 nm, λ_{min}240 nm) and on infrared spectrum, nitrile absorption was observed at 2260 cm^{-1}.



Isomerization of 6 to 9 (KCN, CH_3CN, reflux, 1 h) was unsuccessful under these conditions merely to give 4 in 80% yield. Alternatively, Wilson's modification[7] to the 2-ethylindole derivative was applied to our system. Indolenine 5 reacted with dimethylamine to give 3-dimethylamino-19-oxoquebrachamine (7) in 91% yield. Althrough, stereochemistry of this compound is not determined yet, 7 was homogeneous on high resolution NMR spectrum. Treatment of 7 with excess methyl iodide afforded ammonium salt 8 in 76% yield. Compound 8 was refluxed for 24 h in acetonitrile with potassium cyanide in the presence of 18-crown-6 gave stereoisomers of 3-cyano-19-oxoquebrachamine 9a, 9b, and unexpected product 10 in 17%, 17%, and 19% yield, respectively. Structures of 9a and 9b were consistent with desired 3-cyano-19-oxoquebrachamine (9). Structure of 10 was tentatively

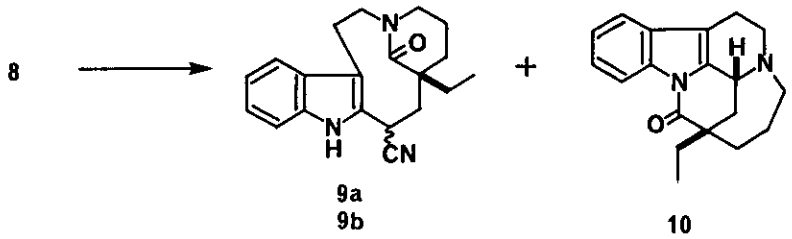


Table 1. Reaction of 8 with potassium cyanide

Entry	Temperature(°C)	Time(h)	Products(%) 9a	9b	10	Total yield(%)
1	82	24	17	17	19	53
2	50	1	0	45	38	83
3	50	37	14	27	30	71
4	rt	13.5	5	52	31	88
5	rt	24	6	48	31	85

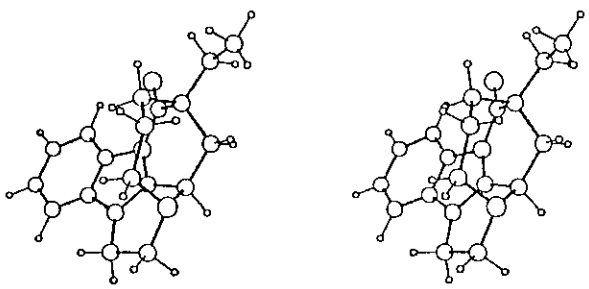
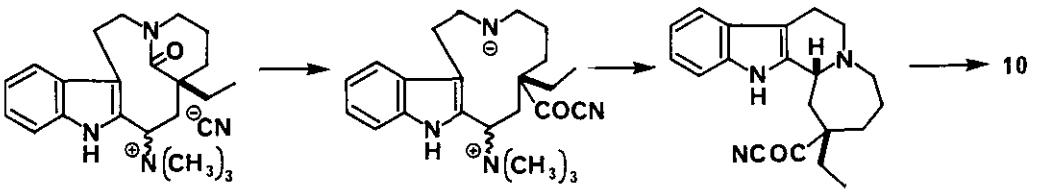


Table 2 Final fractional coordinates of the non-H atoms for 10

Atom	x	y	z	Atom	x	y	z
C(1)	0.55787	0.13254	0.23449	C(12)	0.92704	0.32840	0.26964
C(2)	0.35966	0.09904	0.20138	C(13)	1.03311	0.33743	0.34866
C(3)	0.25770	0.15299	0.14561	C(14)	1.17559	0.24968	0.36721
C(4)	0.35001	0.23930	0.12237	C(15)	0.83181	0.34621	0.40187
C(5)	0.54854	0.27436	0.15347	C(16)	0.84160	0.28552	0.47248
C(6)	0.64794	0.21934	0.20906	C(17)	0.78036	0.18034	0.46256
C(7)	0.70075	0.09792	0.29485	C(18)	1.17737	0.42785	0.35072
C(8)	0.86903	0.16031	0.30278	C(19)	1.27177	0.45544	0.42830
C(9)	0.67768	0.01790	0.35016	N(1)	0.84224	0.23746	0.25350
C(10)	0.85926	0.02420	0.41392	N(2)	0.95235	0.11971	0.43078
C(11)	1.05044	0.15613	0.36090	O(1)	0.89986	0.39414	0.22664

assigned by spectral data, namely, characteristic absorptions of ultraviolet spectrum (λ_{max}240, 273 nm) of N-acylindole were observed. On NMR spectrum, broad singlet proton was observed at 4.36 ppm, which could be methine proton neighbor to nitrogen. This conclusion was finally established by X-ray analysis.[8]



11 12

Reaction mechanism of this unusual rearrangement shown in the Scheme could be conceivable. The strained amide bond of the nine-membered lactam 8 was cleaved by cyanide anion to give twelve membered intermediate 11, followed by transannular cyclization afforded 12, and finally, reactive α-oxonitrile 12 cyclized to provide 10. This reaction was performed under various conditions summarized in Table 2. The best yield was obtained at room temperature for 13.5 h (entry 4) and longer reaction time (entry 5) or higher temperature (entry 1, 3) is not required. The formation ratio of 9 and 10 seems not to be related to the reaction conditions. Kinetically major isomer 9b is taken to be isomerized to 9a at 50°C (entry 2, 3). Confirmation of the stereochemistry of 9a, and 9b and application of the present result to the synthesis of vincadine (2) are in progress.

EXPERIMENTAL

Melting points were determined on a Yamato M-P melting point apparatus and are uncorrected. Infrared spectra were recorded on JASCO IRA-2 diffraction grating spectrometer and ultraviolet spectra were measured on Shimazu UV-240 spectrometer. Mass spectra were taken on JEOL-D300 spectrometer. Nuclear magnetic resonance spectra were determined on JEOL FX-100 (100 MHz) or FX-200 (200MHz) spectrometers. Chemical shifts were reported in ppm down field from internal tetramethylsilane on δ scale. Coupling constants (J) were recorded in Hertz, and abbreviations used were as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatographic separations were performed on Merck silica gel (70-325 mesh ASTM). Preparative TLC were carried

out on Merck silica gel GF_{254}(Type 60) or Merck alumina GF_{254}(Type 60). All reactions were carried out under argon atmosphere.

Cyanoindolenine 6

To a solution of 19-oxoquebrachamine (4) (50 mg, 0.169 mmol) and trietylamine (26 µl) in methylene chloride (10 ml) was added dropwise a solution of tert-butylhypchlorite (20 µl, 0.177 mmol) in carbon tetrachloride (0.7 ml) at -78°C. The mixture was stirred at the same temperature for 10 min and then warmed to room temperature. After removal of solvent, the crude chloroindolenine 5 reacted with potassium cyanide (110 mg, 1.69 mmol) in acetonitrile (10 ml) in the presence of catalytic amount of 18-crown-6 (1,4,7,10,13,16-hexacyclooctadecane) at room temperature for 24 h. To complete the reaction the mixture was heated at 60°C for 2 h. After being cooled, the mixture was diluted with methylene chloride, washed with water, and dried over sodium sulfate. After removal of the solvent, the residue was purified by preparative TLC (silica gel, ethyl acetate : hexane = 1 : 2) gave 6 (32 mg, 59%), accompanied by 4 (7 mg, 14%). Compound 6: mp 197-199 °C (from ethyl acetate); IR (nujol) 2260, 1650 cm^{-1}; Mass spectrum m/z 321 (M^+) (base peak); NMR ($CDCl_3$) δ0.88 (t, J=7.0 Hz, 3H), 1.24-2.24 (m, 7H), 2.38-3.36 (m, 7H), 3.50-3.90 (m, 2H), 7.20-7.75(m, 3H), 7.60-7.76 (m, 1H). Anal. calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07%. Found: C, 74.91; H, 7.36; N, 12.83%.

Reaction of 6 with Potassium Cyanide

A mixture of 6 (11 mg, 0.034 mmol) and potassium cyanide (5 mg, 0.077 mmol) in acetonitrile (3 ml) was refluxed in the presence of catalytic amount of 18-crown-6. The reaction was monitored by TLC (silica gel, ethyl acetate : hexane = 1 : 1). After being refluxed for 1 h, the reaction was quenched as described above to give 4 (8 mg, 80%).

3-(N,N-Dimethylamino)-19-oxoquebrachamine 7

To a solution of chloroindolenine 5 (started from 30 mg of 4) in methylene chloride was diluted with methanol (1 ml). Dry dimethylamine was bubbled slowly at -15°C for 15 min. The reaction mixture was allowed to stand at room temperature overnight. After removal of the low boiling compounds, the residue was purified by preparative TLC (alumina, ethyl acetate : hexane = 2 : 1) to give 7

(31 mg, 91%) as a white powder; IR (nujol) 3450, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (t, J=7.0 Hz, 3H), 1.08-1.41 (m, 1H), 1.6-2.1 (m, 7H), 2.21 (s, 6H), 2.58-3.0 (m, 3H), 3.02-3.43 (m, 2H), 3.66-3.96 (m, 1H), 4.14-4.56 (m, 1H), 6.98-7.40 (m, 3H), 7.40-7.60 (m, 1H), 8.05 (dr s, 1H); high resolution mass spectrum, Anal. calcd for $C_{21}H_{29}N_3O$ 339.2305; Found 339.2310.

Ammonium Salt 8

A sample of 7 (111 mg, 0.327 mmol) was treated with methyl iodide (0.22 ml, 3.60 mmol) in 30 ml of ethyl acetate at room temperature for 20 h. The precipitated salt was collected by filtration to give 8 (119 mg, 76%) as a yellowish powder; IR (nujol) 3200, 2370, 1630 cm^{-1}; mass spectrum m/z 422 [M^+-$(CH_3)_3N$], 339 (M^+-CH_3I), 58 (base peak).

Cyanation of 8

To a solution of 8 (55 mg, 0.114 mmol) in acetonitrile (4 ml) was added potassium cyanide (74 mg, 1.14 mmol) and 18-crown-6 (65 mg, 0.246 mmol). The mixture was stirred at room temperature for 24 h. After removal of the solvent, water (10 ml) and methylene chloride (20 ml) were added to the residue. The organic layer was seperated and aqueous layer was extracted with methylene chloride (10 ml x 3). The extracts were combined and washed, dried, and concentrated. The residue was purified by preparative TLC (silica gel, ethyl acetate : hexane = 1 : 2) to obtain 9a (2 mg, 6%); Rf=0.25; mp 243-244°C (colorless prisms from ethyl acetate); IR ($CHCl_3$) 3440, 2240, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (t, J=7.0 Hz, 3H), 1.20-1.52 (m, 2H), 1.55-1.94 (m, 5H), 2.13 (dd, J=13.6, 12.0 Hz, 1H), 2.48 (dd, J=13.6, 5.2 Hz, 1H), 2.67 (ddd, J=13.0, 12.0, 6.0 Hz, 1H), 2.7-2.9 (m, 1H), 2.94 (dd, J=14.2, 6.0, 1H), 3.49 (ddd, J=14.2, 12.0, 7.6 Hz, 1H), 4.25 (dd, J=13.0, 7.6 Hz, 1H), 4.55 (dd, J=12.0, 5.2 Hz, 1H), 7.1-7.35 (m, 3H), 7.41 (d, J=7.0 Hz, 1H), 7.60 (d, J=7.0 Hz, 1H), 8.36 (br s, 1H); high resolution mass spectrum; Anal. calcd for $C_{20}H_{23}N_3O$ 321.1840; Found 321.1836; and 9b (17 mg, 48%); Rf=0.12; mp 254-255 °C (white powder from ethyl acetate); IR ($CHCl_3$) 3440, 2240, 1618 cm^{-1}; NMR ($CDCl_3$) δ0.80 (t, J=7.0 Hz, 3H), 1.15-2.15 (m, 6H), 2.25 (d, J=13.0 Hz, 1H) 2.50 (dd, J=13.0, 10.0 Hz, 1H), 2.78 (br t, J=15.0 Hz, 2H), 3.06 (br t, J=13.0 Hz, 1H), 3.36 (br d, 13.0 Hz, 1H), 3.78 (br t, J=13.0 Hz, 1H), 4.02 (d, J=10.0 Hz, 1H), 4.43 (t, J=13.0 Hz, 1H), 7.07-7.40 (m, 3H), 7.53 (d, J=7.0 Hz, 1H), 8.03 (br s, 1H); high resolution mass spectrum; Anal. calcd

for $C_{20}H_{23}N_3O$ 321.1840; Found 321.1835. The most polar band was eluted with chloroform - methanol (4 : 1) gave 10 (10 mg, 31%); mp 117-118 °C (colorless *prisms from ethyl acetate*); IR ($CHCl_3$) 1680, 1610 cm^{-1}; UV (EtOH) λ_{max}240, 273 nm (N-acylindole); NMR ($CDCl_3$) δ1.03 (t, J=7.0 Hz, 3H), 1.2-3.70 (m, 14H), 4.36 (br s, 1H), 7.1-7.6 (m, 3H), 8.25-8.34 (m, 1H). Anal. calcd for $C_{19}H_{22}N_2O$ C, 77.52; H, 7.53; N, 9.52%. Found: C, 77.17; H, 7.65; N, 9.29%.

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8) Compound 10 crystallized in space group $P2_1/c$ with cell dimensions a=6.049 (9) Å, b=14.0216 (58) Å, c=17.9036 (116) Å, β=91.80 (4)°, D_{calcd}=1.288 g/cm^3 for Z=4. The structure was solved by direct methods using MULTAN and Fourier techniques, and all atoms (including hydrogens) were refined by block-diagonal least squares using 2084 observed (out of 2194 unique) data to final R-factor=0.057.

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