SYNTHESIS OF ALKALOIDS, CLEISTOPHOLINE, OXYLOPINE (ISOURSULINE), AND URSULINE

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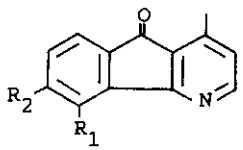
Abstract ——— Synthesis of alkaloids, cleistopholine, oxylopine (isoursuline), ursuline, and related compounds by application of a method for constructing cycloalkenopyridines was described and the synthesis revealed that the structure of oxylopine should be revised to 6-hydroxy-5-methoxyonychine from 5-hydroxy-6-methoxyonychine.

Previously, we reported[1] the synthesis of the compound, 1-methyl-4-azafluoren-9-one (1), corresponding to the structure of onychine (the revised structure by us[1] and A. Cavé's group[2]) occurring in Onychopetalum amazonicum (Annonaceae), by application of the synthetic method for constructing cycloalkenopyridines from oxime O-allyl ethers of cycloalkanones.

In this paper, we report the synthesis of onychine related compounds, cleistopholine (2)[3,4] from Cleistopholis patens, oxylopine[5] (isoursuline[6]) (3), and ursuline (4)[6,7] from Oxandra xylopioides, by using the above method for constructing cycloalkenopyridines. And also this paper deals with the structure of oxylopine which should be revised to 6-hydroxy-5-methoxyonychine from 5-hydroxy-6-methoxyonychine.

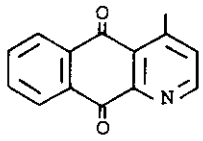
Treatment of β-tetralone (5) with O-crotylhydroxylamine (6) in ethanol in the presence of sodium acetate gave oxime O-crotyl ether (7) in 97% yield. Thermolysis of the ether (7) in the sealed glass tube under air at 180°C (bath temperature) for 24 h yielded 1-methylbenzo[f]quinoline (8) (15%) and 3-methylbenzo[f]quinoline



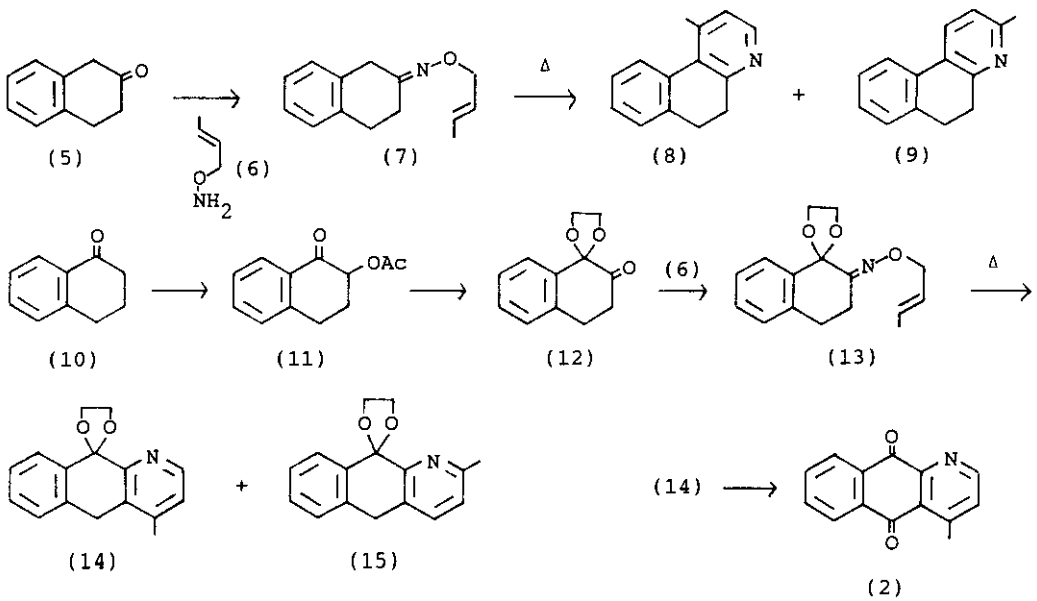
(1) R_1=R_2=H

(3) R_1=OH, R_2=OMe

(4) R_1=OMe, R_2=OH



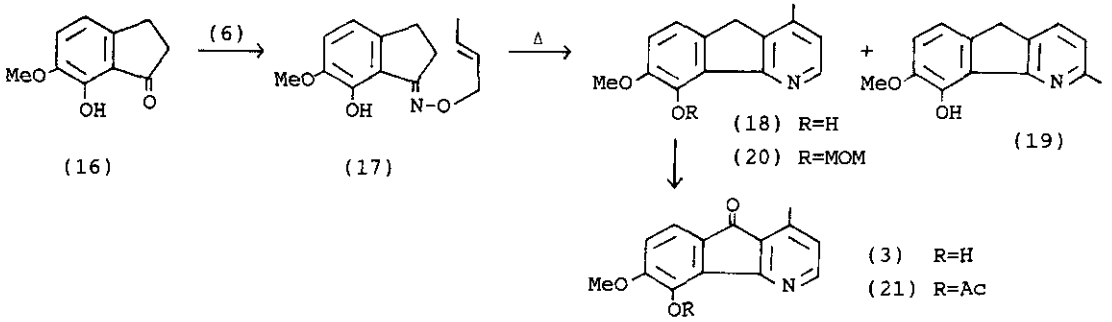
(2)

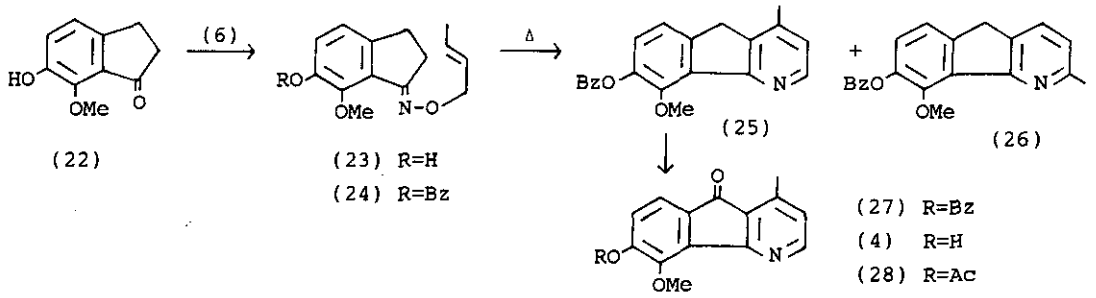


(9) (10%)[8]. The objective benzo[g]quinoline derivative could not be gained, so instead of (5) 1,2-naphthoquinone derivative (12) was synthesized. Oxidative acetylation of α-tetralone (10) with lead tetraacetate afforded 2-acetoxy-α-tetralone (11) (85%). Ketalization of (11) with ethylene glycol followed by deacetylation and oxidation with pyridinium chlorochromate in the presence of sodium acetate produced (12)[9] in 50% yield from (11). Condensation of keto-ketal (12) with O-crotylhydroxylamine (6) in the usual way gave the oxime (13)[10] in 75% yield. Heating of the ether (13) at 160°C (bath temperature) for 20 h afforded 4-methylbenzo[g]quinoline (14) (8%) and 2-methylbenzo[g]quinoline (15) (5%) (recoverd material (13) 60%)[11,12]. Oxidation of (14) with Jones reagent in acetone gave the target compound, cleistopholine (2)[13,14] in 60% yield. Spectroscopic

properties of cleistopholine showed good identity with those described literature[3, 4], confirming the synthesis of cleistopholine.

Treatment of 7-hydroxy-6-methoxyindanone (16) prepared from isovanillin and malonic acid[15], with crotylhydroxylamine (6) afforded oxime (17)[16] in 93% yield. Thermolysis of oxime (17) at 170°C (bath temperature) for 20 h produced 5-hydroxy-6-methoxy-1-methyl-4-azafluorene (18) (35%) and 5-hydroxy-6-methoxy-3-methyl-4-azafluorene (19) (8%)[17] (recovered (17) 18%). After methoxymethylation of (18), oxidation of (20) with potassium permanganate followed by demethoxymethylation with sulfuric acid-acetic acid gave 5-hydroxy-6-methoxyonychine (3)[18] in 75% yield from (18). The ^{1}H-nmr spectral data of synthetic (3) revealed nonidentity with those of oxylopine (see Table). Furthermore, the ^{1}H-nmr spectrum of O-acetyl derivative (21) prepared from (3), showed signals having different chemical shift concerning methyl protons of methoxy and acetyl groups (see Table). In order to make the discrepancy clear, the synthesis of the isomer, 6-hydroxy-5-methoxyonychine was made. Oxime O-crotyl ether (24)[19], prepared from 6-hydroxy-7-methoxyindanone (22) by condensation with (6) followed by benzylation of the hydroxyl group, was subjected to the thermal rearrangement in the same manner for 3 h to give





1-methylazafluorene (25) (28%) and 3-methylazafluorene (26) (5%)[20] (recovered (24) 20%). Oxidation of (25) with potassium permanganate followed by debenzylation with acid gave 6-hydroxy-5-methoxyonychine (4)[21] in 65% yield from (25). ^{1}H-Nmr spectral data of (4) and its O-acetyl derivative (28) exhibited good agreement with those of oxylopine and O-acetyloxylopine from Oxandra xylopioides[5] (see Table). Based on the above results, it is highly plausible that the structure of oxylopine should be revised to (4) from (3), but the direct comparison of our synthetic specimen with oxylopine has not been carried out.

The ^{1}H-nmr and ir spectra of 5-hydroxy-6-methoxyonychine (3), 6-hydroxy-5-methoxyonychine (4), and O-acetyl derivatives (21) and (28) were identical with those of isoursuline, ursuline, and those O-acetyl derivatives[22].

Table Comparison of the ^{1}H-nmr spectral data of synthetic compounds, (3), (4), (21), and (28) with those described in the literatures.

oxylopine [5]	(3)	(4)	ursuline [6,7]	isoursuline [6]
2.63 (Me,s)	2.63 (Me,s)	2.63 (Me,s)	2.64 (Me,s)	2.61 (Me,s)
4.21 (OMe,s)	3.99 (OMe,s)	4.20 (OMe,s)	4.20 (OMe,s)	3.98 (OMe,s)
6.94 (7-H,d, J=7.9Hz)	6.80 (7-H,d, J=8Hz)	6.94 (7-H,d, J=8Hz)	6.96 (7-H,d, J=7.5Hz)	6.80 (7-H,d, J=8Hz)
6.95 (2-H,d, J=5.7Hz)	6.93 (2-H,d, J=5.5Hz)	6.95 (2-H,d, J=5.5Hz)	6.98 (2-H,d, J=5Hz)	6.94 (2-H,d, J=5.5Hz)
7.45 (8-H,d, J=7.9HZ)	7.29 (8-H,d, J=8Hz)	7.44 (8-H,d, J=8Hz)	7.46 (8-H,d, J=7.5Hz)	7.29 (8-H,d, J=8Hz)
8.47 (3-H,d, J=5.7Hz)	8.30 (3-H,d, J=5.5Hz)	8.47 (3-H,d, J=5.5Hz)	8.50 (3-H,d, J=5Hz)	8.31 (3-H,d, J=5.5Hz)
O-acetyl-oxylopine [5]	(21)	(28)	O-acetyl-ursuline [6,7]	O-acetyl-isoursuline [6]
2.38 (COMe,d)	2.49 (COMe,s)	2.38 (COMe,s)	2.36 (COMe,s)	2.49 (COMe,s)
2.64 (Me,s)	2.63 (Me,s)	2.64 (Me,s)	2.64 (Me,s)	2.61 (Me,s)
4.08 (OMe,s)	3.96 (OMe,s)	4.10 (OMe,s)	4.09 (OMe,s)	3.94 (OMe,s)
6.95 (2-H,d, J=5.8Hz)	6.98 (2-H,d, J=5Hz)	6.98 (2-H,d, J=5.5Hz)	6.96 (2-H,d, J=5.5Hz)	6.95 (2-H,d, J=5Hz)
7.05 (7-H,d, J=7.5Hz)	6.95 (7-H,d, J=8Hz)	7.10 (7-H,d, J=8Hz)	7.10 (7-H,d, J=8Hz)	6.93 (7-H,d, J=8.2Hz)
7.48 (8-H,d, J=7.5Hz)	7.64 (8-H,d, J=8Hz)	7.50 (8-H,d, J=8Hz)	7.50 (8-H,d, J=8Hz)	7.61 (8-H,d, J=8.2Hz)
8.48 (3-H,d, J=5.8Hz)	8.43 (3-H,d, J=5Hz)	8.51 (3-H,d, J=5.5Hz)	8.52 (3-H,d, J=5.5Hz)	8.41 (3-H,d, J=5Hz)

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8. (8) Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600, 1585. ^{1}H-Nmr ($CDCl_3$) δ: 2.66 (3H, s, Me), 2.88 and 3.02 (2H each, m, CH_2×2), 7.12 (1H, d, J=5Hz, 2-H), 7.32 (3H, m, 7,8,9-H), 7.67 (1H, dd, J=7.5, 2Hz, 10-H), 8.29 (1H, d, J=5Hz, 3-H). Ms m/z: 195 (M^+).
(9) Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600, 1575. ^{1}H-Nmr ($CDCl_3$) δ: 2.59 (3H, s, Me), 3.05 (4H, m, CH_2×2), 7.13 (1H, d, J=7.5Hz, 2-H), 7.32 (3H, m, 7,8,9-H), 7.70 (1H, d, J=6.5Hz, 10-H), 7.93 (1H, d, J=7.5Hz, 1-H). Ms m/z: 195 (M^+).

9. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (C=O). Ms m/z: 204.0782 (M^+, calcd for $C_{12}H_{12}O_3$, 204.0785).

10. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (C=N). ^{1}H-Nmr ($CDCl_3$) δ: 1.62 (3H, d, J=7Hz, Me), 4.18 (4H, s, OCH_2CH_2O), 4.55 (2H, m, OCH_2), 5.67 (2H, m, CH=CH). Ms m/z: 273 (M^+).

11. (14) Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1610. ^{1}H-Nmr ($CDCl_3$) δ: 2.86 (3H, s, Me), 7.30 (1H, d, J=4Hz, 3-H), 7.60 (2H, m, 7,8-H), 8.09 (1H, m, 6-H), 8.45 (1H, m, 9-H), 8.83 (1H, d, J=4Hz, 2-H). Ms m/z: 253.1102 (M^+, calcd for $C_{16}H_{15}NO_2$, 253.1102).
(15) Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600. ^{1}H-Nmr ($CDCl_3$) δ: 2.93 (3H, s, Me), 7.34 (1H, d, J=8.5Hz, 3-H), 7.58 (2H, m, 7,8-H), 8.04 (1H, dd, J=7.5, 2.5Hz, 6-H), 8.28 (1H, d, J=8.5Hz, 4-H), 8.43 (1H, d, J=7.5Hz, 9-H). Ms m/z: 253.1086 (M^+, calcd for $C_{16}H_{15}NO_2$, 253.1102).

12. Thermolysis of oxime (13) at 180-200°C (bath temperature) gave (14) (7%),

1-methylbenzo[f]quinoline (M^+: 193) (7%), and 3-methylbenzo[f]quinoline (M^+: 193) (6%) (recovered material 15%).

13. mp: 190-193°C. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695, 1680, 1600. ^{1}H-Nmr ($CDCl_3$) δ: 2.92 (3H, s, Me), 7.52 (1H, d, J=5Hz, 3-H), 7.86 (2H, m, 6,7-H), 8.29 (1H, m, 5 or 8-H), 8.40 (1H, m, 8 or 5-H), 8.93 (1H, d, J=5Hz, 2-H). Ms m/z: 223.0647 (M^+, calcd for $C_{14}H_9NO_2$, 223.0633).
14. Treatment of crotonaldehyde N,N-dimethylhydrazone with naphthoquinone in acetonitrile for 40 h produced cleistopholine in 50% yield. The spectral data and the tlc behaviour of it showed good agreement with those of synthetic cleistopholine.
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16. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (C=N). Ms m/z: 247.1203 (M^+, calcd for $C_{14}H_{17}NO_3$, 247.1207).
17. (18) ^{1}H-Nmr ($CDCl_3$) δ: 2.39 (3H, s, Me), 3.72 (2H, s, CH_2), 3.96 (3H, s, OMe), 6.96 (3H, m, 2,7,8-H), 8.32 (1H, d, J=5.5Hz, 3-H). Ms m/z: 227.0944 (M^+, calcd for $C_{14}H_{13}NO_2$, 227.0944).
(19) ^{1}H-Nmr ($CDCl_3$) δ: 2.61 (3H, s, Me), 3.80 (2H, s, CH_2), 3.97 (3H, s, OMe), 6.99 (3H, m, 2,7,8-H), 7.69 (1H, d, J=8Hz, 1-H). Ms m/z: 227.0933 (M^+, calcd for $C_{14}H_{13}NO_2$, 227.0944).
18. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. Ms m/z: 241.0734 (M^+, calcd for $C_{14}H_{11}NO_3$, 241.0737).
19. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (C=N). Ms m/z: 337.1666 (M^+, calcd for $C_{21}H_{23}NO_3$, 337.1676).
20. (25) Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600, 1575. ^{1}H-Nmr ($CDCl_3$) δ: 2.41 (3H, s, Me), 3.73 (2H, s, CH_2), 4.14 (3H, s, OMe), 7.01 (1H, d, J=5Hz, 2-H), 7.03 (1H, d, J=8Hz, 7-H), 7.20 (1H, d, J=8Hz, 8-H), 8.60 (1H, d, J=5Hz, 3-H). Ms m/z: 317.1400 (M^+, calcd for $C_{21}H_{19}NO_2$, 317.1414).
(26) Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1590, 1570. ^{1}H-Nmr ($CDCl_3$) δ: 2.45 (3H, s, Me), 3,76 (2H, s, CH_2), 4.31 (3H, s, OMe), 6.99 (1H, d, J=8Hz, 2-H), 7.18 (1H, d, J=8Hz, 7-H), 7.44 (7H, m, aromatic-H). Ms m/z: 317.1431 (M^+, calcd for $C_{21}H_{19}NO_2$, 317.1414).
21. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470, 1710. Ms m/z: 241.0730 (M^+, calcd for $C_{14}H_{11}NO_3$, 241.0737).
22. We are indebted to Professor A. Cavé and Dr. F. Roblot for their generous supplies of the copies of ^{1}H-nmr and ir spectra of ursuline, O-acetylursuline, isoursuline, and O-acetylisoursuline.

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