STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS. PART 808.†
TOTAL SYNTHESIS OF (±)-O-METHYLTUBULOSINE

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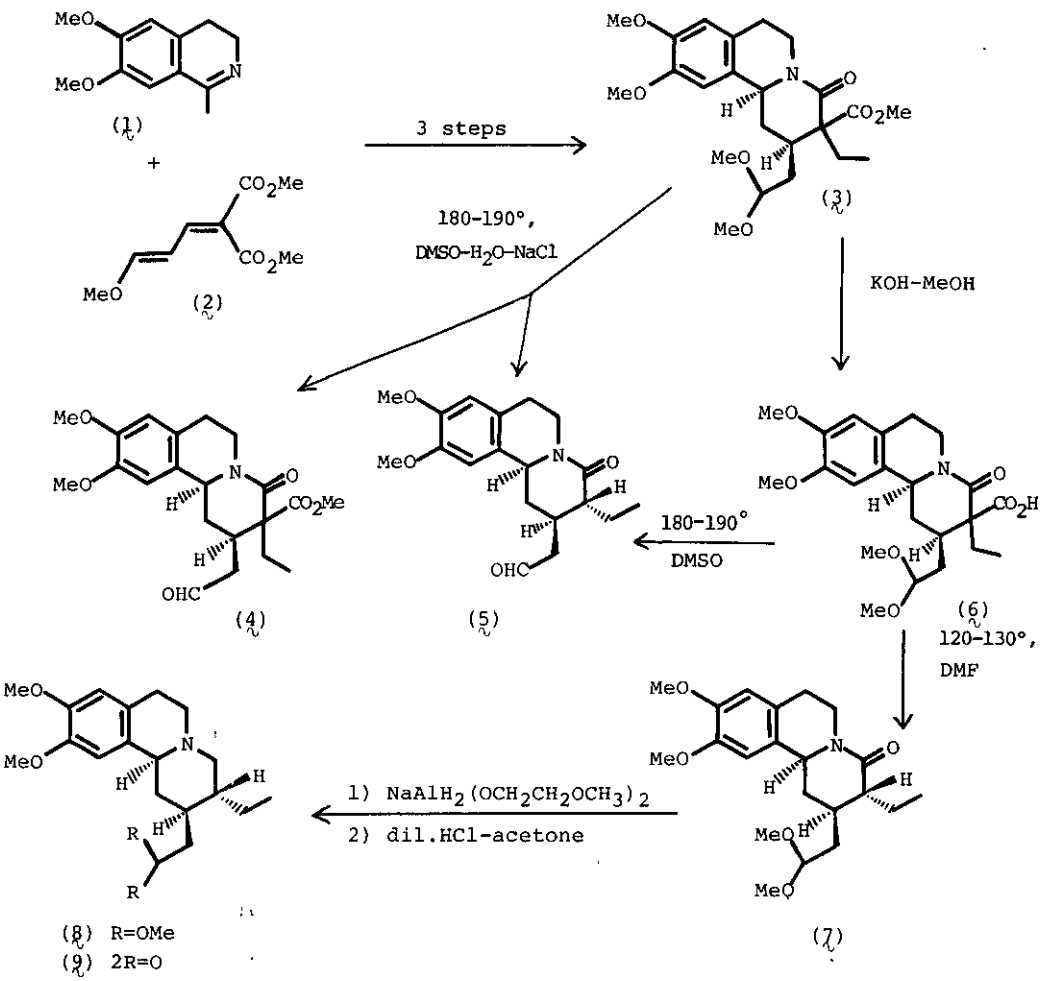
Abstract —— Pictet-Spengler condensation of (±)-4-oxoprotoemetine (5) with 5-methoxytryptamine (10) in acetic acid gave (±)-4-oxo-O-methyltubulosine (12a) which was converted to (±)-O-methyltubulosine (13a) by reduction with sodium bis(2-methoxyethoxy)-aluminium hydride. Modified syntheses of (±)-4-oxoprotoemetine (5) and (±)-protoemetine (9) are also described.

Recently we reported the syntheses of (±)-emetine[1] and (±)-tubulosine[2] (15) by Pictet-Spengler reaction of the corresponding amines with (±)-4-oxoprotoemetine (5), which was synthesized by condensation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (1) and dimethyl 3-methoxyallylidenemalonate (2) followed by several steps. In a continuation of this study we have developed a shorter route to (±)-4-oxoprotoemetine (5) and have further converted it to (±)-O-methyltubulosine (13a), which is expected to possess antitumor activity.[3]

Demethoxycarbonylation of 3-ethyl-1,2,3,6,7,11b-hexahydro-9,10-dimethoxy-3-methoxycarbonyl-2-(β,β-dimethoxyethyl)-4-oxobenzo[a]quinolizine (3)[1] was attempted by heating at 180 - 190°C in a mixture of dimethyl sulfoxide and water, in the presence of sodium chloride.[4] However the unexpected aldehyde (4) was the main product obtained, together with a small amount of (±)-4-oxoprotoemetine (5). Deacetalization occurred smoothly by heating in dimethyl sulfoxide in the absence of water and the salt. Demethoxycarbonylation required more severe conditions than deacetalization, but longer reaction time or higher temperature produced a tarry product. Heating the acetal carboxylic acid (6)[1] for 1 hr at 180 - 190°C in dry dimethyl sulfoxide gave (±)-4-oxoprotoemetine (5) stereoselectively and in excellent yield.

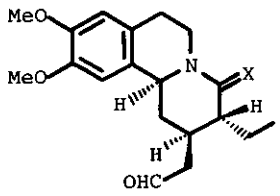
On condensation with 5-methoxytryptamine (10), in acetic acid for 2 days, (±)-4-


MeO
MeO
N
(1)
+
CO2Me
CO2Me
MeO
(2)
3 steps
O
H
CO2Me
(3)
180-190°,
DMSO-H2O-NaCl
KOH-MeOH
CO2Me
OHC
(4)
(5)
180-190°
DMSO
CO2H
(6)
120-130°,
DMF
(7)
1) NaAlH2(OCH2CH2OCH3)2
2) dil.HCl-acetone
R
(8) R=OMe
(9) 2R=O

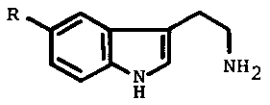
oxoprotoemetine (5) afforded (±)-4-oxo-O-methyltubulosine (12a) and its isomer (12b) in a ratio of 4 : 1, which were separable by silica gel column chromatography. Reduction of each lactam (12a and 12b) with sodium bis(2-methoxyethoxy)aluminium hydride (Red-al) gave corresponding amines (13a and 13b). IR, NMR, and mass spectra, and TLC behavior of 13a were identical to those of (-)-O-methyltubulosine derived from (-)-tubulosine[5] donated by Prof. Szántay. The structure of 13b was supported by the NMR spectrum, which exhibited one of the methoxyl group resonances at high field,[6] and by the mass spectrum, m/e 489 (M^+).

Pictet-Spengler reaction using (±)-protoemetine (9), prepared by reduction of the acetal (7)[1] with sodium bis(2-methoxyethoxy)aluminium hydride followed by deacetalization of the resulting amine (8) in a mixture of dilute hydrochloric acid and acetone, was also tried. (±)-Protoemetine (9) was rather unstable compared to (±)-4-oxoprotoemetine (5) so that condensation of 9 with tryptamine (11), in acetic acid for 2 days at room temperature, formed (±)-deoxytubulosine (14a) and its isomer (14b) in poor yield.

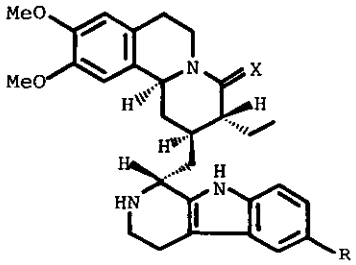
Thus we have established an efficient method for the synthesis of tubulosine derivatives *via* (±)-4-oxoprotoemetine (5).



(5) X=O
(9) X=H_2

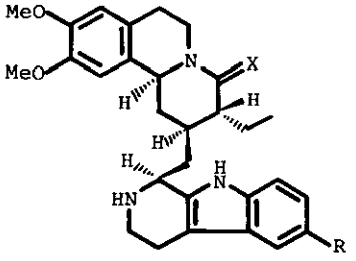


(10) R=OMe
(11) R=H



(12a) R=OMe, X=O
(13a) R=OMe, X=H_2
(14a) R=H, X=H_2
(15) R=OH, X=H_2

+



(12b) R=OMe, X=O
(13b) R=OMe, X=H_2
(14b) R=H, X=H_2

EXPERIMENTAL

All melting points were determined with a Yanaco micromelting point apparatus and are uncorrected. Infrared spectra were taken with a Hitachi 215 spectrophotometer. Nuclear magnetic resonance spectra were measured with a JEOL JNM-PMX-60 instrument using tetramethylsilane as internal standard. Mass spectra were taken with Hitachi M-52 and JEOL JMS-OlSG-2 spectrometers.

3-Ethyl-2-formylmethyl-1,2,3,6,7,11b-hexahydro-9,10-dimethoxy-3-methoxycarbonyl-4-oxobenzo[a]quinolizine (4) and (±)-4-Oxoprotoemetine (5). —— A solution of 3-ethyl-1,2,3,6,7,11b-hexahydro-9,10-dimethoxy-3-methoxycarbonyl-2-(β,β-dimethoxyethyl)-4-oxobenzo[a]quinolizine (3)[1] (76 mg) in DMSO-H_2O (10 ml-7μl) was stirred with NaCl (10 mg) at 180 - 190°C for 2 hr. After addition of benzene, the mixture was washed with water, dried (Na_2SO_4), and evaporated to give a brown oil which was subjected to silica gel column chromatography. Elution with CH_2Cl_2-MeOH (200 : 1 v/v) gave the ester (4) (56 mg) as a yellowish oil, IR $\nu_{max}^{CHCl_3}$ 1720 (C=O), 1625 cm^{-1} (C=O); NMR ($CDCl_3$)δ 0.90 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 3.67 (3H, s, CO_2Me), 3.89 (6H, s, 2 x OMe), 6.65 (2H, s, 2 x ArH), 9.84 (1H, s, CHO); MS m/e 389 (M^+). Calcd. for $C_{21}H_{27}NO_5$ M^+: m/e 389.1837. Found: 389.1824. Further elution with the same solvent mixture gave (±)-4-oxoprotoemetine (5) (5 mg) which was shown to be identical to an authentic sample.[1]

(±)-4-Oxoprotoemetine (5). —— A solution of 3-carboxy-3-ethyl-1,2,3,6,7,11b-hexahydro-9,10-dimethoxy-2-(β,β-dimethoxyethyl)-4-oxobenzo[a]quinolizine (6)[1] (22 mg) in dry DMSO (5 ml) was stirred for 1 hr at 180 - 190°C. After addition of benzene, the mixture was washed with water, dried (Na_2SO_4), and evaporated to give a brown oil. Purification with silica gel column chromatography, using benzene-AcOEt (1 : 1 v/v) as an eluent, afforded (±)-4-oxoprotoemetine (5) (17 mg) as a yellowish oil.

(±)-Protoemetine (9). —— To a stirring solution of (±)-3α-ethyl-1,2α,3β,6,7,11bα-hexahydro-9,10-dimethoxy-2-(β,β-dimethoxyethyl)-4-oxobenzo[a]quinolizine (7) (105 mg) in dry benzene (5 ml) was added 70 % Red-al in toluene (1 ml) under ice-cooling, and the mixture was stirred for 1 hr at room temperature. The excess Red-al was decomposed by addition of 10 % NaOH solution and the organic layer was separeted. The aqueous layer was extracted with benzene. The combined organic layer was washed with water, dried (Na_2SO_4), and evaporated to give a brown oil which was purified by silica gel column chromatography. Elution with CH_2Cl_2-MeOH (100 : 1 v/v) afforded the acetal (8) (90 mg) as a yellowish oil, IR $\nu_{max}^{CHCl_3}$ 2700 - 2850 cm^{-1} (trans-quinolizine); NMR ($CDCl_3$)δ 0.78 - 1.17 (3H, m, $CH_2\underline{CH_3}$), 3.35 (3H, s, OMe), 3.38 (3H,

s, OMe), 3.90 (6H, s, 2 x OMe), 6.60 (1H, s, ArH), 6.78 (1H, s, ArH); MS m/e 363 (M^+). A solution of the above acetal (8) (63 mg) in a mixture of 3 % HCl (3 ml) and acetone (3 ml) was stirred for 1 hr at room temperature. After evaporation of the acetone, the remaining aqueous layer was basified with solid $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a brown oil which was purified by silica gel column chromatography. Elution with CH_2Cl_2-MeOH (100 : 1 v/v) afforded (±)-protoemetine (9)[7] (50 mg) as a yellowish oil, IR $\nu_{max}^{CHCl_3}$ 1725 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.80 - 1.16 (3H, m, $CH_2\underline{CH}_3$), 3.91 (6H, s, 2 x OMe), 6.70 (1H, s, ArH), 6.77 (1H, s, ArH), 10.00 (1H, t, J = 1 Hz, CHO); MS m/e 317 (M^+).

(±)-4-Oxo-O-methyltubulosine (12a) and Its Isomer (12b). — A mixture of (±)-4-oxoprotoemetine (5) (180 mg) and 5-methoxytryptamine (10) (105 mg) in AcOH (10 ml) was stirred for 2 days at room temperature. After evaporation of the solvent the residue was basified with saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a caramel which was subjected to silica gel column chromatography. Elution with $CHCl_3$-MeOH (50 : 1 v/v) gave the comound (12a) (190 mg) as a caramel, IR $\nu_{max}^{CHCl_3}$ 3510 (NH), 1625 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7 Hz, $CH_2\underline{CH}_3$), 3.86 (9H, s, 3 x OMe), 6.60 - 7.30 (5H, m, 5 x ArH), 9.26 (1H, bs, NH); Calcd. for $C_{30}H_{37}N_3O_4$ M^+ : m/e 503.2782. Found: 503.2749. Further elution with the same solvent mixture gave the stereoisomer (12b) (49 mg) as a caramel, IR $\nu_{max}^{CHCl_3}$ 3510 (NH), 1620 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7 Hz, $CH_2\underline{CH}_3$), 3.53 (3H, s, OMe), 3.82 (6H, s, 2 x OMe), 6.34 - 7.20 (5H, m, 5 x ArH), 8.62 (1H, bs, NH); Calcd. for $C_{30}H_{37}N_3O_4$ M^+: m/e 503.2782. Found: 503.2736.

(±)-O-Methyltubulosine (13a). — To a stirring solution of the above compound (12a) (135 mg) in benzene (20 ml) was added 70 % Red-al in toluene (1 ml) under ice-cooling and the mixture was stirred for 1 hr at room temperature. The excess Red-al was decomposed by addition of 10 % NaOH solution. The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic layer was washed with water, dried (Na_2SO_4), and evaporated to give a yellow solid which was recrystallized from MeOH to afford 13a as colorless needles (75 mg), mp 146 - 148°C, IR $\nu_{max}^{CHCl_3}$ 3510 cm^{-1} (NH); NMR ($CDCl_3$) δ 0.77 ∿ 1.16 (3H, m, $CH_2\underline{CH}_3$) 3.86 (9H, s, 3 x OMe), 6.60 - 7.16 (5H, m, 5 x ArH), 7.81 (1H, bs, NH); MS m/e 489 (M^+); Anal. Calcd. for $C_{30}H_{39}N_3O_3 \cdot H_2O$; C, 70.97; H, 8.14; N, 8.28. Found: C, 70.59; H, 7.89; N, 8.19.

(±)-O-Methylisotubulosine (13b). — Reduction of the compound (12b) (47 mg) in the

same manner as above gave a yellow oil which was purified by HPLC [Hitachi gel 3011, MeOH-CH_3CN (3 : 1 v/v)] to afford 13b (26 mg) as a caramel, IR $\nu_{mas}^{CHCl_3}$ 3510 cm^{-1} (NH); NMR ($CDCl_3$) δ 0.80 - 1.17 (3H, m, $CH_2\underline{CH}_3$), 3.61 (3H, s, OMe), 3.86 (3H, s, OMe), 3.89 (3H, s, OMe), 6.44 - 7.83 (5H, m, 5 x ArH); MS m/e 489 (M^+); Calcd. for $C_{30}H_{39}N_3O_3$ M^+: m/e 489.2991. Found: 489.3014.

(±)-Deoxytubulosine (14a) and Its Isomer (14b). —— A mixture of (±)-protoemetine (9) (50 mg) and tryptamine (11) (35 mg) in AcOH (10 ml) was stirred for 2 days at room temperature. After evaporation of the solvent the residue was basified with saturated $NaHCO_3$ solution and extraced with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a solid which was recrystallized from $CHCl_3$-MeOH to afford 14a (20 mg) as colorless needles which were identical (by comparison of spectral data and TLC behaviors) to an authentic sample.[2] Evaporation of the mother liquid gave a reddish caramel which was purified by alumina column chromatography, using $CHCl_3$ as eluent, to give a yellow solid. Recrystallization from CH_2Cl_2-Et_2O afforded 14b (5 mg) as colorless needles, mp 214 - 215°C, IR $\nu_{max}^{CHCl_3}$ 3530 cm^{-1} (NH); NMR ($CDCl_3$) δ 0.70 - 1.20 (3H, m, $CH_2\underline{CH}_3$), 3.63 (3H, s, OMe), 3.94 (3H, s, OMe), 6.56 (1H, s, ArH), 6.69 (1H, s, ArH), 7.13 - 7.76 (4H, m, 4 x ArH), 8.33 (1H, bs, NH); MS m/e 459 (M^+); Calcd. for $C_{29}H_{37}N_3O_2$ M^+: m/e 459.2883. Found: 459.2838.

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