SYNTHESIS OF THE IPECAC ALKALOIDS FROM NORCAMPHOR

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A general Route to the Ipecac Alkaloids from norcamphor(8) has been developed. Alkylation of the bicyclic lactone(9), obtained from norcamphor(8), gave the endo-isomer(10), exclusively, which was converted in four steps to the key intermediate(14). The compound(14), thus obtained, was transformed into (±)-protoemetine (2) and (±)-protoemetinol(3) via two different routes.

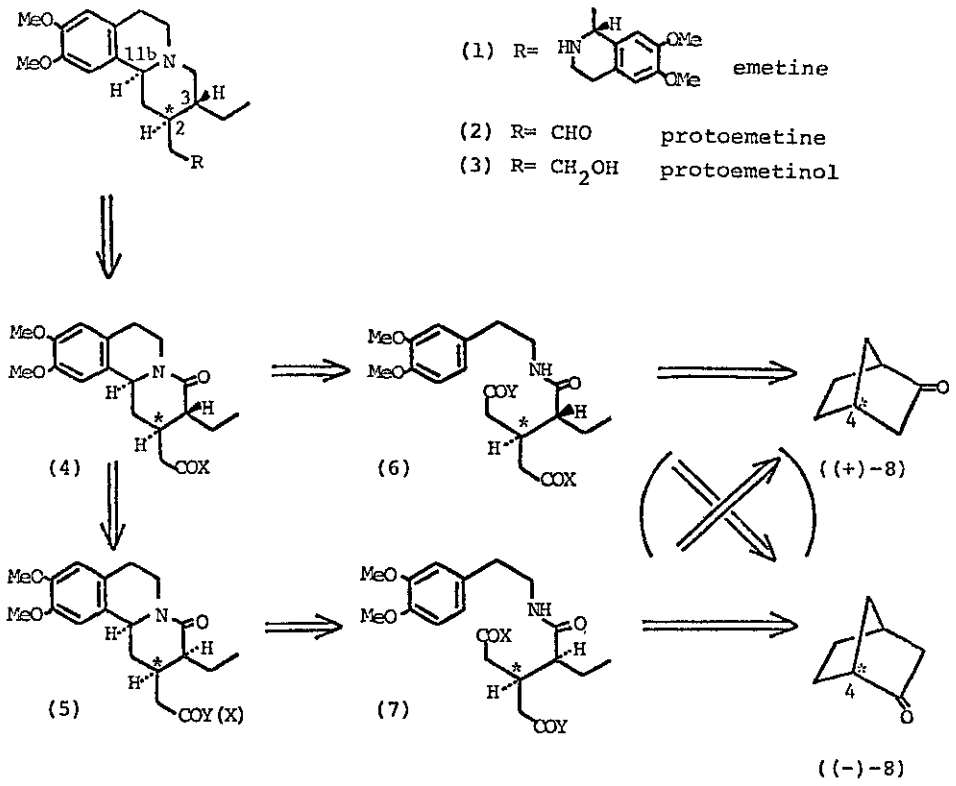
INTRODUCTION

The syntheses of the Ipecac alkaloids constitute one of the most intensively studied classes of natural products owing to the pharmacological properties of their parent compound, emetine(1)[1], and some of these are so efficient as to discourage further effort to develop an alternative synthesis. However, we felt that an alternative approach would be promising if it can provide not only the Ipecac alkaloids, but also a number of other alkaloids such as the Corynanthe type indole alkaloids in optically active forms. With the intention of establishing the enantioselective synthesis, we investigated the diastereoselective approach to the Ipecac alkaloids, (±)-protoemetine(2) and (±)-protoemetinol(3), as the preliminary study[2].

As the starting material of our present study, we chose (±)-norcamphor(8). Since both (+)- and (-)-enantiomers of norcamphor(8) have been prepared enantioselectively[3], we assumed that the enantioselective synthesis of the alkaloids should be realized using an appropriate enantiomer provided (±)-norcamphor(8) could have been transformed diastereoselectively into (±)-protoemetine(2) and (±)-protoemetinol (3) without having epimerized at the pivotal chiral center(C-4 of (8)).

We envisioned the lactam(4) to be the penultimate intermediate in the enantioselective synthesis which might be derived from either (+)(or (-))-norcamphor(8) via the amide(6) or(-)(or (+))-norcamphor(8) via the amide(7)(enantiomer of (6))

through the epimerization[4,5] at the C-3 center of the lactam(5). In order to materialize this intention, we undertook the investigation into the possibilities of synthesizing the Ipecac alkaloids from (±)-norcamphor(8) via the key intermediates corresponding to the enantiomeric amides, (6) and (7).



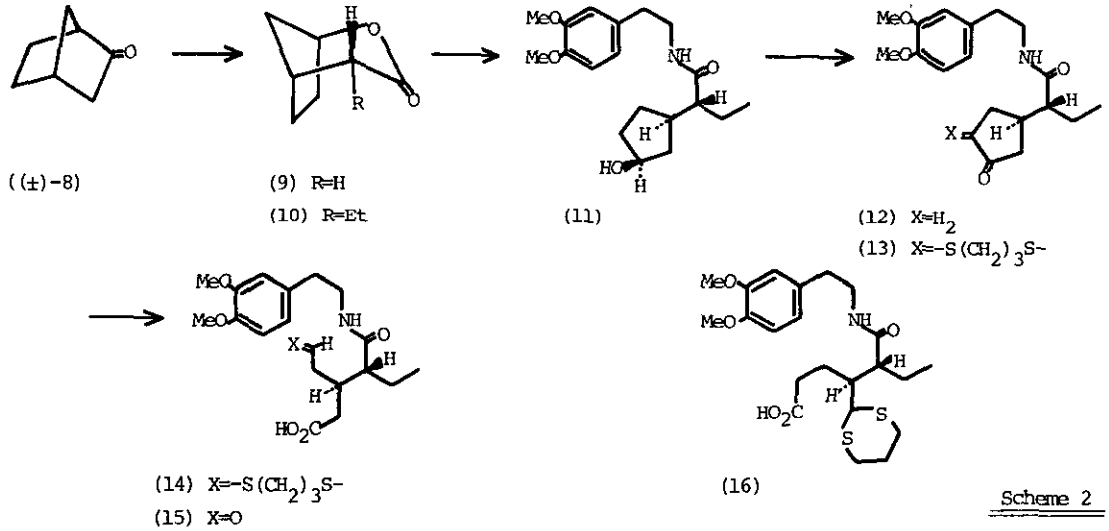
Scheme 1

RESULTS AND DISCUSSION

Our first task was to synthesize the key intermediates corresponding to the amides, (6) and (7), from (±)-norcamphor(8). Norcamphor(8)[6] gave the δ-lactone(9)[7] exclusively on treatment with m-chloroperbenzoic acid or peracetic acid both in satisfactory yield. Alkylation of the lactone(9) with ethyl bromide in the presence of lithium diisopropylamide in tetrahydrofuran containing hexamethylphosphoramide at -78°C gave the endo-ethyllactone(10) stereoselectively in 71% yield, though

the actual stereochemistry could not be determined at this stage. Condensation of the ethyllactone(10) with homoveratrylamine at 180 °C gave the crystalline amide(11) in 76% yield, which was oxidized with Jones reagent to afford the crystalline keto-amide(12) in 90 % yield.

Treatment of the compound(12) with pyrrolidine in boiling benzene gave the corresponding enamine which was immediately treated with trimethylene dithiotosylate[8,9] in boiling acetonitrile containing triethylamine to furnish the crystalline α-diketone monothioketal(13) regioselectively in 58 % overall yield. *Cleavage of the α-diketone monothioketal*(13) to the amido-acid(14) equivalent to the key compound(6) was accomplished without incident by the general procedure of Marshall and Seitz[10,11]. Thus, treatment of (13) with potassium hydroxide in tert-butyl alcohol at 60 °C allowed facile cleavage of the α-diketone monothioketal bond leading to quantitative formation of the acid(14) preserving the amide group. *Its ^{1}H-nmr spectrum* showed a one-proton triplet at δ4.00(J=6.0Hz) ppm due to the proton at C-2 center of the dithiane group substituted with a methylene residue, and hence possible formation of the unwanted alternative(16) could be eliminated.



((±)-8) (9) R=H (10) R=Et (11) (12) X=H$_2$ (13) X=-S(CH$_2$)$_3$S- (14) X=-S(CH$_2$)$_3$S- (15) X=O (16)

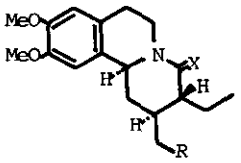
Scheme 2

Having constructed the key intermediate(14), we initially attempted hydrolysis of its dithiane group to give the aldehyde(15) leaving the stereochemistry of the ethyl group uncertain. Exposure of (14) to methyl iodide in aqueous acetonitrile at reflux temperature, according to the method by Fetizon and Jurion[12], funished none of the desired aldehyde(15), but two lactam-acids,(17) and (22), *in yields of*

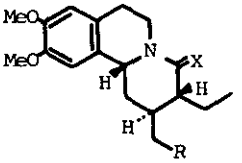
30 and 60 %, directly. The spontaneous cyclization may be initiated by the action of the acidic by-product (presumably hydriodic acid) generated in the hydrolysis on the initially formed aldehyde(15). The intramolecular Pictet-Spengler type cyclization under these hydrolytic conditions would be of general use since we encountered a similar intramolecular cyclization in the indole system in the course of the syntheses of some indole alkaloids[13]. When the reaction was performed at room temperature only the latter(22) was formed exclusively though longer reaction time was required. Since no interconversion between two lactams occurred under the basic conditions[4,5](NaH, DMF, reflux) as well as the cyclization conditions[12], it is apparent that the stereoisomerism observed took place not in the later stage, but in the cyclization stage. Consequently, they could be assigned to be enantiomers at the 11b-center both with thermodynamically more stable trans 2(H)/3(H) configuration.

Of the two lactams, structure of the minor one showing the same melting point as that reported by Burgstahler and Bithos[14] was unambiguously confirmed to be (17) by converting it into the known amino-ester(19) and (±)-protoemetinol(3). Thus, esterification of the former lactam(17) with methanolic hydrogen chloride afforded the methyl ester(18), which on treatment with phosphorus oxychloride in boiling benzene, followed by reduction with sodium borohydride,[15,16] gave the amino-ester(19) in 55 % overall yield via the chloro-iminium intermediate(31a). The amino-ester(19) obtained was identical in all respects with an authentic sample prepared through the different route[17]. In formal sence an alternative total synthesis of (±)-emetine(1) has been achieved at this stage since (19) has been shown to give (1) via a three step sequence[1b,17]. On reduction with lithium aluminum hydride, the minor lactam (17) afforded (±)-protoemetinol(3) in 95 % yield, which was identical with an authentic sample prepared from the authentic amino-ester(19).

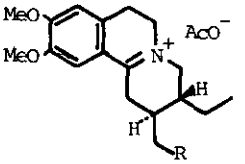
On the other hand, the ester(23) obtained from the latter lactam(22) was similarly converted into the isomeric amino-ester(24) in 53 % overall yield via the chloro-iminium intermediate(29a). The amino-ester(24), on sequential dehydrogenation with mercuric acetate and reduction with sodium borohydride allowed the inversion at the 11b-center via the dehydro-base(27) leading to a formation of the isomeric amino-ester(19) in 63% overall yield, which was identical with that obtained from the isomeric lactam(17). At this point stereochemical relationship between the two lactams was unambiguously established and consequently the stereochemistry of the ethyl group on the bicyclic lactone(10) has now been rigorously assigned as shown.



(17) R=CO_2H, X=O
(18) R=CO_2Me, X=O
(19) R=CO_2Me, X=H_2
(20) R=  , X=H_2
(21) R=CHO, X=O



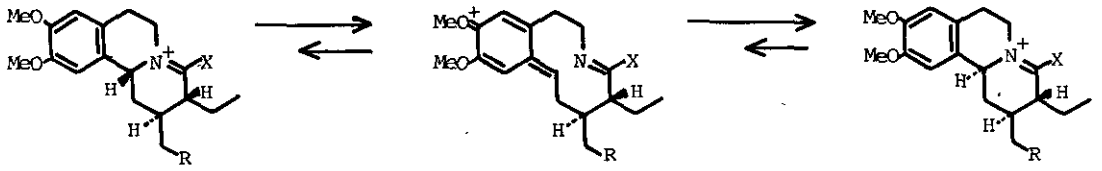
(22) R=CO_2H, X=O
(23) R=CO_2Me, X=O
(24) R=CO_2Me, X=H_2
(25) R=CH_2OH, X=H_2
(26) R=CHO, X=O



(27) R=CO_2Me
(28) R=CH_2OAc

Scheme 3

Interestingly, the amino-ester(19) could be directly obtaind in 31 % yield with 16 % of the 11b-epimer(24) when the ester(23) was treated with an exess of phosphorus oxychloride at 110 °C without using any solvent, followed by reduction with sodium borohydride. We assumed that the isomerization observed was brought through an intervention of a transient B/C seco intermediate(30a) wherefrom thermodynamically more stable compound(31a) with α-11b(H) configuration was produced (Scheme 4). Similar isomerization was also observed when the major lactam(22) was reduced with lithium aluminum hydride in boiling tetrahydrofuran giving 12% yield of the inverted product, (±)-protoemetinol(3), along with 83% yield of the corresponging amino-alcohol(25), presumably through (30b) and (31b). The 11b-epimer(25) obtained as the major product was transformed into (±)-protoemetinol(3) in 61% overall yield via (28) through a four-step sequence. Thus, (25) on sequential acetylation, dehydrogenation, reduction, and saponification furnished (±)-protoemetinol(3). We may now assume that the Ipecac alkaloids with natural configuration could be obtained from (+)-norcamphor(8).



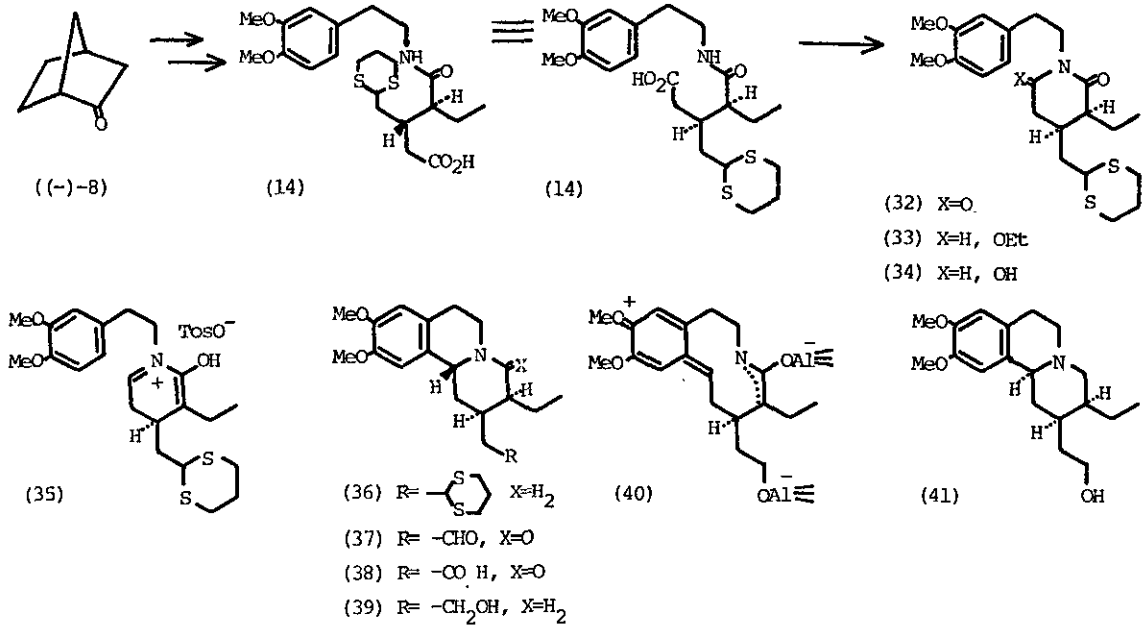
(29)

(30) a) series: R=CO_2Me, X=Cl
b) series: R=CH_2OAl^- , X=OAl^-

(31)

Scheme 4

As a potential chiral route to the Ipecac alkaloids from (+)-norcamphor(8) has now been established, we next investigated an alternative diastereoselective synthesis of the alkaloids with the intention of using (-)-norcamphor(8) as starting material(Scheme 5). The amide(14), corresponding to the key intermediate(7) from (-)-norcamphor(8), was heated at 200 °C for 7 h to furnish the glutarimide(32) in 88 % yield. Reduction of the imide(32) with sodium borohydride in cold aqueous ethanol at pH 8-10[18] allowed site-selective reduction to give the ω-ethoxylactam (33) in quantitative yield. The product(33) on treatment with p-toluenesulfonic acid in boiling benzene furnished three lactams, (42), (43), and (44), in yields of 24, 20, and 24 %. On the other hand, the corresponding ω-hydroxylactam(34) obtained from (32) using diisobutylaluminum hydride[19] at -65 °C gave two lactams, (42) and (44), in yields of 36 and 6 % under the same conditions. Although there is no appropriate interpretation for these differences, the observed site-selectivity in both reductions is noteworthy as the preferential reduction of the more hindered carbonyl under the former conditions has been reported in the succinimide series by Speckamp[20]. Because of insusceptibility of these three lactams to the acidic conditions employed in the cyclization stage as well as to the basic conditions[4,5], epimerization at the C-3 center could take place prior to cyclization probably through a conjugated iminium intermediate(35).

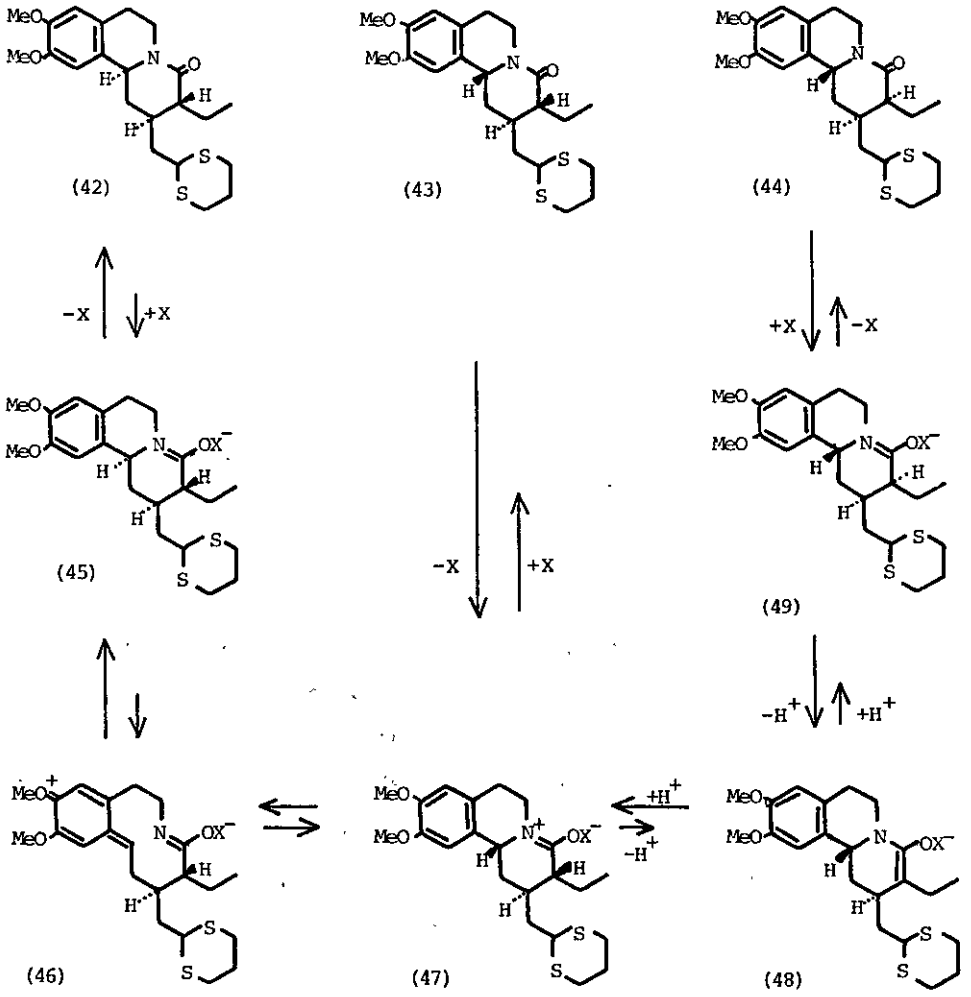


Scheme 5

Structures of the three lactams were determined by transformation into the known compounds respectively. Reduction of (42) with lithium aluminum hydride in boiling tetrahydrofuran gave the amine(20) in 56 % yield. Exposure of the hydrochloride of (20) to an excess of methyl iodide in aqueous acetonitrile at room temperature effected the hydrolysis of the dithiane group without affecting the tertiary nitrogen[21] to give (±)-protoemetine(2), quantitatively, whose ^{1}H-NMR and IR spectra were identical with those of an authentic material obtained by an entirely different route[22]. (±)-Protoemetine(2) obtained was converted into (±)-protoemtinol(3) in 79 % yield by reduction with sodium borohydride in methanol. Furthermore, the lactam(42) was transformed into the known lactam-acid(17) in 61 % overall yield via the aldehyde(21). Namely, (42) gave the acid (17) through the aldehyde(21) on hydrolysis with an excess of methyl iodide in aqueous acetonitrile at room temperature, followed by oxidation with silver oxide in the presense of sodium hydroxide. The second isomeric lactam(43) was similarly converted into the known lactam-acid(22) in 62 % overall yield via the aldehyde(26) by the hydrolysis with methyl iodide in aqueous acetonitrile, followed by oxidation with silver oxide. Similarly the third lactam(44) furnished the corresponding acid(38) via the aldehyde (37) though no stereochemical information could be available by these transformations. Interestingly, the aldehyde(37), formed in 95 % yield from (44), furnished three isomeric compounds, two known, (±)-protoemetinol(3) and its 11b-isomer(25), and one unknown(39) in yields of 34, 48, and 14 % on reduction with lithium aluminum hydride. The third amino-alcohol(39) possessing the stereochemistry of the parent lactam(44) was inverted at the C-11b center to give the fourth amino-alcohol(41) by sequential acetylation(Ac_2O), dehydrogenation($Hg(OAc)_2$), reduction ($NaBH_4$), and hydrolysis(NaOH)[23]. The structure of (41) was confirmed by comparison with an authentic material obtained through the established route[4,5]. The stereoselectivity in the transformation of (39) into (41) through the dehydro-base has been observed and confirmed in the related systems by Openshaw and Whittaker[23]. Concomitant formation of the isomerized amino-alcohols, (3) and (25),during the reduction may be explained again in terms of an intervention of a B/C seco intermediate(40) inducing epimerization at both the C-11b and the C-3 centers.

With anticipation of isomerization into the thermodynamically more stable isomer via a B/C seco intermediate(46), the third lactam(44) was treated with a Lewis acid in benzene solution at room temperature. The expected reaction did really take place using aluminum chloride which allowed complete conversion of (44) into the isomeric

(42) after having stirred for 20 h and the reaction was found to proceed more readily with boron trifluoride etherate leading to a quantitative formation of (42) within 2 h. Examination of the reaction by thin-layer chromatography revealed an evident initial formation of the second lactam(43), which was gradually converted into (42). The reaction, however, seemed to proceed through more complex way involving participation of the dithiane group since the lactam(18) possessing the methoxycarbonyl group in place of the dithiane group did not change under the same conditions or more forcing conditions.



Scheme 6

In any event, our intention of using (-)-norcamphor(8) in an enantioselective synthesis has been potentially achieved since all of the lactams, (42), (43), and (44), have been proven to be convertible in the Ipecac alkaloids as shown.

CONCLUSIONS

The foregoing describes a potentially general approach to the enantioselective synthesis of the Ipecac alkaloids starting from both (+)- and (-)-enantiomers of norcamphor(8). More importantly, the method may be extensible to a large number of the Corynanthe-type indole alkaloids including various medicinally useful compounds. Application to the enantioselective synthesis of the Ipecac alkaloids and extensions[24~27] of the present methodology are under investigation.

EXPERIMENTAL SECTION

Melting points were determined on a Yanagimoto MP-S2 apparatus and are uncorrected. Infrared absorption spectra were recorded on a Shimadzu IR 400 instrument, and Proton magnetic resonance spectra, for deuteriochloroform solutions, were recorded on JEOL PS 100 and/or PMX 60 spectrometers with tetramethylsilane as an internal reference. Mass spectra were recorded on a Hitachi RMU-7 spectrometer or a JEOL-D 300 spectrometer.

2-Oxabicyclo[3.2.1.]oct-3-one(9). (a) Using m-Chloroperbenzoic Acid. To an ice-cooled solution of (±)-norcamphor[6](8)(44.0 g, 0.40 mmol) in methylene chloride(1000 ml) was added m-chloroperbenzoic acid(85 % purity, 103.2 g, 0.51 mmol) and the mixture was stirred at room temperature for 20 h . After removal of the m-chlorobenzoic acid by filtration, the filtrate was washed with 2 % $Na_2S_2O_4$, saturated $NaHCO_3$ and saturated NaCl, and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded a pale yellow oil(60 g), which was distilled in vacuo to provide 9(44.25 g, 87.7 %) as a colorless semisolid: bp 132-135 °C(16 mm) [lit.[7], bp 77 °C(0.25 mm)]; IR(neat) 1718 cm^{-1}; NMR($CDCl_3$) δ 1.40-2.30(6H, m), 2.59 (3H, br.s), 4.82(1H, br.s).

(b) Using 30 % Hydrogen Peroxide. A mixture of (±)-norcamphor(8)(72 g,0.65 mol), and 30 % hydrogen peroxide(105 ml, 1.1 mol) in acetic acid(130 ml) was heated at 50 °C for 20 h with stirring. To a cooled reaction mixture was added $FeSO_4$

(152 g, 1 mol) and most of the acetic acid was removed in vacuo. The residue was extracted with methylene chloride and the extract was washed with saturated $NaHCO_3$, water and saturated NaCl, and dried over anhydrous Na_2SO_4. Removel of the solvent in vacuo afforded a yellow oil(89 g) which, upon distillation, gave 9(58.9 g, 72.0 %) as a colorless semisolid.

Endo-4-Ethyl-2-oxabicyclo[3.2.1.]oct-3-one(10). To a stirred solution of lithium diisopropylamide, prepared from diisopropylamine(98 ml, 0.69 mol) in anhydrous tetrahydrofuran(600 ml) and n-butyllithium in n-hexane(10(W/V) %, 440 ml, 0.69 mmol), under nitrogen at -78 °C was added the lactone(9)(58 g, 0.46 mol) in THF(400 ml). After stirring at -78 °C for 20 min, a solution of ethyl bromide (75 g, 0.69 mol) in anhydrous hexamethylphosphoramide(123 g, 0.69 mol) was added all at once. After the addition was complete, the temperature was allowed to rise to -35 °C and the mixture was stirred for 24 h at the same temperature. The reaction was quenched by the addition of saturated NH_4Cl and the organic layer was separated. The aqueous layer was extracted with benzene,and the combined organic layers were washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield a pale yellow oil, which was purified by distillation to give 4-ethyl-2-oxabicyclo[3.2.1]oct-3-one(10)(50.2 g, 71 %) as a clear oil: bp 139-142 °C(20 mmHg); IR(neat) 1720 cm^{-1}; NMR($CDCl_3$) δ 0.70(3H, t, J=7.0 Hz), 1.25-2.70 (10H, m), 4.85(1H, br.s). *Anal.* ($C_9H_{14}O_2$) C, H.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(3-hydroxycyclopentyl)butanamide(11). A mixture of 10(2.37 g, 15 mmol) and homoveratrylamine(4.00 g, 22 mmol) was heated at 180 °C for 6 h under nitrogen. The resulting deep red viscous oil was extracted with methylene cloride and the extract was washed with 5 % HCl, saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield a yellow viscous oil(4.80 g) which was crystallized from acetone to give 11(3.79 g, 75.8 %) as colorless needles: mp 131.5-132.5 °C; IR(Nujol) 3510, 3260, 1625 cm^{-1}; NMR($CDCl_3$) δ 0.84(3H, t, J=7.0 Hz), 2.26(1H, br.s, exchangeable), 2.77(2H, t, J=6.5 Hz), 3.53 (2H, q, J=6,5 Hz), 3.85(6H, s), 4.27(1H, m), 5.80(1H, br.t, J=6.5 Hz, exchangeable), 6.27(3H, s); MS(m/e) 335(M^+), 165, 164, 151. *Anal.* ($C_{19}H_{29}NO_4$) C, H, N.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(3-oxocyclopentyl)butanamide(12). To a stirred solution of 11(3.00 g, 9mmol) in acetone(75 ml) with cooling in an ice bath was added dropwise Jones reagent, prepared by mixing chromium trioxide (1.35 g, 13.5 mmol) in water(9.1 ml) with 98 % H_2SO_4(0.9 ml), keeping the reaction

mixture below 25 °C. After the addition was complete, the mixture was stirred at room tempetature for 5.5 h . The reaction was quenched by the addition of isopropyl alcohol(1.0 ml) and most of the acetone was removed in vacuo below 35 °C. The residue was diluted with water and extracted with methylene chloride. The extract was washed with water, 5 % NaOH, saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield a light viscous oil(3.30 g), which was crystallized from benzene to give 12(2.72 g, 90.6 %) as colorless prisms: mp 109-110 °C; IR(Nujol) 3260, 1735, 1630 cm^{-1}; NMR($CDCl_3$) δ 0.88(3H, t, J=7.0 Hz), 2.80 (2H, t, J=6.5 Hz), 3.60(2H, q, J=6.5 Hz), 3.87(6H, s), 5.93(1H, br.t, exchangeable), 6.80(3H, s); MS(m/e) 333(M^+), 208, 165, 164, 151. *Anal.* ($C_{19}H_{27}NO_4$) C, H, N.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-[3-oxo-4,4-(propane-1,3-dithio)cyclopentyl]butanamide(13). A mixture of 12(3.00 g, 9 mmol) and pyrrolidine(1.90 g, 27 mmol) in benzene(50 ml) was refluxed equipping with a Dean-Stark head until no more water was collected(6 h). The excess pyrrolidine and the solvent were removed in vacuo to give the enamine(3.50 g) as pale yellow crystals, which was used without further purification.

A mixture of the enamine(3.50 g), trimethylene dithiotosylate(3.74 g, 9 mmol), and triethylamine(4.5 ml) in anhydrous acetonitrile(75 ml) was refluxed under nitrogen for 4 h . The reaction mixture was concentrated in vacuo and the residue was extracted with benzene. The extract was washed with water, 5 % NaOH, saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to leave a brown crystalline mass(3.94 g), which was recrystallized from isopropyl alcohol to give 13(2.28 g, 58.1 %) as colorless needles : mp 155-156 °C; IR(Nujol) 3250, 1718, 1635 cm^{-1}; NMR($CDCl_3$) δ 0.87(3H, t, J=7.0 Hz), 3.60(2H, q, J=6.5 Hz), 6.00(1H, br.t, J=6.5 Hz , exchangeable), 6.80(3H, s); MS(m/e) 437(M^+), 347, 164, 151, 106. *Anal.* ($C_{22}H_{31}NO_4S_2 \frac{1}{2} H_2O$) C, H, N, S.

Cleavage of the α-Diketone Monothioketal(13). A suspension of 13(1.00 g, 2.33 mmol) and pulverized KOH(80 % purity, 0.49 g, 7.00 mmol) in tert-butyl alcohol(30 ml) was heated with stirring at 60 °C for 3 h . Most of the solvent was removed in vacuo and the residue was dissolved in water. The aqueous solution was washed with benzene and extracted with methylene chloride after acidification with 10 % HCl. The extract was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the acid(14)(1.15 g) as a pale yellow viscous oil, which was used without further purification: IR(neat) 3300-2400, 1710, 1620 cm^{-1}; NMR($CDCl_3$) δ 0.85(3H, t, J=7.0 Hz), 3.54(2H, br.q, J=6.0 Hz), 3.88(6H, s),

6.29(1H, br.t, J=6 Hz), 6.77(3H, s), 8.95(1H, br.s, exchangeable).

Cyclization of the Compound(14). (a) At Reflux Temperature. A mixture of crude 14(1.15 g, 2.3 mmol), methyl iodide(5.0 ml, 80 mmol) and water (4.0 ml, 22 mmol) in acetonitrile(30 ml) was refluxed under nitrogen for 24 h . The resulting mixture was concentrated in vacuo and the residue was extracted with methylene chloride. The extract was washed with water, 1 % $Na_2S_2O_3$, saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to leave a pale yellow crystalline mass(1.27 g), which was washed with acetone and recrystallized from chloroform-ethanol to give 22(510 mg, 63.9 % from 13) as colorless needles : mp 224-225.5 °C(lit.[14], mp 223-225 °C); IR(Nujol) 3400-2400, 1710, 1588 cm^{-1}; NMR ($CDCl_3$+CD_3OD) δ 0.94(3H, t, J=7.0 Hz), 3.87(6H, s), 6.74(1H, s), 6.83(1H, s); MS (m/e) 347(M^+), 332, 318, 316, 286, 260, 258, 205, 191, 176.

The mother liquor and the washing were concentrated in vacuo to leave a pale yellow crystalline mass. Preparative thin layer chromatography on silica gel developed with a mixture of chloroform, methanol, and acetic acid(v/v 95:4.5:0.5), followed by recrystallization from acetone gave 17(236 mg, 29.6 % from 13) as colorless needles : mp 187-188 °C; IR(Nujol) 3200-2300, 1720, 1590 cm^{-1}; NMR($CDCl_3$) δ 0.93(3H, t, J=7.0 Hz), 3.87(6H, s), 4.40-5.10(2H, m), 6.68(1H, s), 6.73(1H, s), 9.10(1H, br.s, exchangeable); the mass spectrum was similar to that of 20.

(b) At Room Temperature. A mixture of crude 14(190 mg, 0.42 mmol), methyl iodide(1 ml, 16 mmol), and water(0.8 ml, 4.4 mmol) in acetonitrile(6 ml) was stirred at room temperature under nitrogen for 63 h . The resulting mixture was treated as above to give 22(75 mg, 51.5 % from 13).

Methyl 3α-Ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxy-4-oxo-11bαH-benzo[a]-quinolizine-2β-acetate(18). To a solution of the lactam-acid(17)(100 mg, 0.29 mmol) in methanol(5.0 ml) was added 30 % methanolic HCl(2.5 ml) and the solution was refluxed for 3 h . Most of the methanol was removed in vacuo and the residue was extracted with methylene chloride. The extract was washed with water, saturated $NaHCO_3$, saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a colorless viscous oil(110 mg), which was crystallized from ether to give 18(85 mg, 81.2 %) as colorless prisms: mp 56-57 °C(lit.[14], mp 53-54 °C); IR(Nujol) 1725, 1638 cm^{-1}; NMR($CDCl_3$) δ 0.93(3H, t, J=7.0 Hz), 3.76(3H, s), 3.90(6H, s), 6.68 (1H, s), 6.71(1H, s); MS(m/e) 361(M^+), 346, 332, 330, 286, 205, 191.

The Amino-ester(19) from the Lactam(18). A mixture of 18(60 mg, 0.16 mmol) and phosphorus oxychloride(0.23 ml, 2.5 mmol) in dry benzene(3.0 ml) was refluxed

under nitrogen for 3.5 h . The excess phosphorous oxychloride and the solvent were removed in vacuo. To the residue dissolved in absolute methanol(2 ml) was added sodium borohydride(50 mg, 1.30 mmol) with stirring at 0 °C. After 1 h , the reaction mixture was concentrated in vacuo, and the residue was extracted with methylene chloride. The extract was washed with water, saturated NaCl, dried over anhydrous K_2CO_3, concentrated in vacuo to leave a yellow viscous oil(65 mg). Preparative thin-layer chromatography on silica gel developed with 5 % methanol-chloroform, followed by recrystallization from petroleum ether gave the amino-ester (19)(30 mg, 54.5 %) as colorless needles: mp 77-79 °C(lit.[17,23], mp 79.5-82 °C); IR(Nujol) 1730 cm^{-1}; NMR($CDCl_3$) δ 0.92(3H, unsym. t, J=7.0 Hz), 3.72(3H, s), 3.85 (6H, s), 6.63(1H, s), 6.72(1H, s); MS(m/e) 347(M^+), 332, 246, 205, 191. The spectral data of this material was identical with those of an authentic sample[17]. Its perchlorate, a pale yellow prisms(recrystallized from methanol), showed the same melting point as that reported: mp 193-194 °C(lit.[23], mp 192-193 °C).

(±)-Protoemetinol(3). To an ice-cooled solution of 17(100 mg, 0.29 mmol) in anhydrous tetrahydrofuran(10 ml) under nitrogen was added lithium aluminum hydride(110 mg, 2.9 mmol) and the suspension was refluxed for 3 h . The reaction was quenched by the addithion of 10% NH_4OH with cooling in an ice bath. The resulting sludge was removed by filtration and washed thoroughly with methylene chloride. The combined filtrates were washed with saturated NaCl, dried over anhydrous K_2CO_3, and concentrated in vacuo to leave a pale yellow viscous oil(98 mg). Preparative thin layer chromatography on silica gel developed with 10 % methanol-chloroform gave (±)-protoemetinol(3)(88 mg, 95.1 %) as a pale yellow viscous oil: IR($CHCl_3$) 3480, 2850-2750 cm^{-1}; NMR($CDCl_3$) δ 0.90(3H, unsym.t, J=6.0 Hz), 3.86(6H, s), 6.60 (1H, s), 6.71(1H, s); MS(m/e) 319(M^+), 318, 246, 205, 191. This material was identical with an authentic sample[17] prepared from the amino-ester(19). Its percholrate, colorless hygroscopic needles(recrystallized from ethanol-ether), showed the same melting point as that reported: mp 178-181 °C(lit.[14], mp 178-181 °C).

Methyl 3α-Ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxy-4-oxo-11bβH-benzo[a]-quinolizine-2β-acetate(23). The lactam acid(22)(400 mg, 1.15 mmol) was esterified in the same manner as (17). The work-up afforded a colorless viscous oil(430 mg), which was crystallized from methanol-ether to give 23(333 mg, 80.2 %) as colorless prisms:mp 139-141 °C; IR(Nujol) 1720, 1625 cm^{-1}; NMR($CDCl_3$) δ 0.95(3H,

t, J=7.0 Hz), 3.73(3H, s), 3.87(6H, s), 6.68(1H, s), 6.72(1H, s); the mass spectrum was similar to that of 18.

Reduction of the Lactam-ester(23). (a) Treatment of the lactam-ester(23) (120 mg, 0.33 mmol) with phosphorus oxychloride(0.46 ml, 5.00 mmol) in boiling benzene(5.0 ml), followed by reduction with sodium borohydride(100 mg, 2.60 mmol) in methanol(2.0 ml), in the manner as described for the lactam-ester(18), afforded a yellow viscous oil(120 mg). Preparetive thin layer chromatography on silica gel developed with 5 % methanol-chloroform gave the amino-ester(24)(60 mg, 52.6 %) as a pale yellow viscous oil: IR(neat) 1722 cm^{-1}; NMR($CDCl_3$) δ 0.90(3H, t, J=7.0 Hz), 3.73(3H, s), 3.86(3H, s), 3.89(3H, s), 6.63(1H, s), 6.78(1H, s); the mass spectrum was similar to that of 19. Its perchlorate, pale yellow hygroscopic prisms(recrystallized from methanol-ether), had mp 125-126 °C. *Anal.* ($C_{20}H_{30}NO_8Cl$) C, H, N, Cl. (b) A solution of the lactam-ester(23)(300 mg, 0.83 mmol) in phosphorus oxychloride(5.0 ml) was refluxed under nitrogen for 5 h . After removal of phosphrus oxychloride in vacuo, the residue was reduced with sodium borohydride (378 mg, 10.0 mmol) in methanol(10 ml) in the manner as described above. The work-up afforded a yellow viscous oil(330 mg). Preparative thin-layer chromatography on silica gel developed with 5 % methanol-chloroform gave the amino-ester(19)(90 mg, 31.3 %) and its 11b-epimer(24)(45 mg, 15.6 %) each as a pale yellow viscous oil.

Formation of The Amino-ester(19) from Its 11b-Epimer(24). A mixture of 24 (60 mg, 0.17 mmol) and mercuric acetate(112 mg, 0.35 mmol) in acetic acid(5.0 ml) was stirred under nitrogen at room temperature for 24 h . After evaporation of the solvent in vacuo, the residue was dissolved in methylene chloride and the inorganic precipitate was removed by filtration. The filtrate was concentrated in vacuo and the residue in methanol(5.0 ml) was reduced with sodium borohydride(50 mg, 1.30 mmol) at 0 °C for 1 h . After concentration in vacuo the residue was extracted with methylene chloride. The extract was washed with water, saturated NaCl, dried over anhydrous K_2CO_3, and concentrated in vacuo to leave a light yellow gum(63 mg). Preparative thin-layer chromatography on silica gel developed with 5 % methanol-chloroform gave the amino-esters, (19)(38 mg, 63.3 %) and (24)(7 mg, 11.7 %).

Reduction of the Lactam-acid(22) Using Lithium Aluminum Hydride. The lactam-acid(22)(247 mmg, 1.0 mmol) was reduced with lithium aluminum hydride(380 mg, 10 mmol) in anhydrous tetrahydrofuran(30 ml) in the manner as described for the preparation of (±)-protoemetinol(3). The work-up afforded a pale yellow viscous oil (350 mg), which was purified by preparative thin-layer chromatography on silica gel

developed with 10 % methanol-chloroform to give (±)-protoemetinol(3)(40 mg, 12.5 %) and (±)-11b-epiprotoemetinol(25)(265 mg, 83.1 %).

(±)-11b-Epiprotoemetinol(25) showed the following characteristics: IR($CHCl_3$) 3500 cm^{-1}; NMR($CDCl_3$) δ 0.88(3H, t, J=7.0 Hz), 3.15(1H, br.s, exchangeable), 3.80 (6H, s), 6.52(1H, s), 6.63(1H, s); the mass spectrum was similar to that of (±)-protoemetinol(3). Its perchlorate, colorless hygroscopic needles(recrystallized from ethanol-ether), melted at 95-98 °C. *Anal.* ($C_{19}H_{30}NO_7Cl\ H_2O$) C, H, N, Cl.

Formation of (±)-Protoemetinol(3) from Its 11b-Epimer(25). A mixture of the perchlorate of 25(50 mg, 0.12 mmol), acetic anhydride(0.1 ml, 1.00 mmol), and sodium acetate(21 mg, 0.25 mmol) in benzene(5.0 ml) was refluxed for 3 h . After cooling, the reaction mixture was washed with saturated $NaHCO_3$, water, saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the acetate of 25(50 mg) as a light green oil.

To a solution of the crude acetate(50 mg) in acetic acid(3.00 ml) under nitrogen was added mercuric acetate(80 mg, 0.25 mmol) and the mixture was stirred for 12 h at room temperature. After concentration, the residue was dissolved in methylene chloride and the inorganic precipitate was removed by filtration. The filtrate was concentrated in vacuo to afford the iminium salt(28)(60 mg) as a yellow gum.

To a stirred solution of the crude iminium salt(28)(60 mg) in methanol(5.0 ml) with cooling in an ice bath was added sodium borohydride(50 mg, 1.32 mmol). After stirring at 0 °C for 30 min, the solvent was removed in vacuo. The residue was treated with water and extracted with methylene chloride. The extract was washed with water, saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the acetate of 3(45 mg) as a yellow viscous oil.

A mixture of the crude acetate(45 mg) and KOH(56 mg, 1.0 mmol) in methanol(5.0 ml) was refluxed for 3 h , diluted with water, and extracted with methylene chloride. The extract was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to leave a yellow viscous oil(33 mg). Preparative thin layer chromatography on silica gel developed with 10 % methanol-chloroform gave (±)-protoemetinol(3)(23 mg, 60.5 %) and its 11b-epimer(25)(3 mg, 7.9 %).

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-ethyl-3-[2,2-(propane-1,3-dithio)ethyl]-glutarimide(32). Crude 14(560 mg, 1.23 mmol) was heated in vacuo(15 mm) at 200 °C for 7 h with removing water. After cooling, the reaction mixture was extracted with methylene chloride and the extract was washed with saturated $NaHCO_3$, saturated NaCl, dried over anhydrous Na_2SO_4 , concentrated in vacuo to give

practically pure 32(470 mg, 87.5 %) as a yellow viscous oil, which was used without further purification. Preparative thin layer-chromatography on silica gel developed with 10 % ethyl acetate-benzene gave an analytically pure 32: IR(neat) 1660 cm^{-1}; NMR($CDCl_3$) δ 3.87(3H, s), 3.90(3H, s), 4.03(1H, br.t, J=6.0 Hz), 6.80 (3H, s); MS(m/e) 437(M^+), 165, 164, 151, 150, 149, 119. *Anal.* ($C_{22}H_{29}NO_4S_2$) C, H, N.

Cyclization of the Glutarimide(32). (a) via the ω-Ethoxy Lactam(33). To a stirred solution of 32(270 mg, 0.6 mmol) in 90 % ethanol(5.0 ml) at 0 °C was added sodium borohydride(114 mg,3.0 mmol). After stirring at 0 °C for 15 min, few drops of 2N HCl were added at regular intervals(ca.15 min) such that acidity of the solution was maintained at pH 8-10. After this operation(ca.2 h), sodium borohydride(114 mg, 3.0 mmol) was added and the mixture was kept sitrring at 0 °C for 2 h . The mixture was made acidic(pH 3) by the addition of 2N HCl over a period of 20 min. The reaction mixture was diluted with water and extracted with chloroform. The extract was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford 33(250 mg) as a yellow gum which was used without further purification: IR(neat) 1620 cm^{-1}; NMR($CDCl_3$) δ 1.27(3H, t, J=7.0 Hz), 3.54(2H, br.q, J=7.0 Hz), 4.00(6H, s), 6.90(3H, s).

A solution of crude 33(250 mg) in benzene(60 ml) was refluxed in the presence of a catalytic amount of p-toluenesulfonic acid monohydrate(15 mg) under nitrogen for 9 h . The reaction mixture was washed with saturated $NaHCO_3$, saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a yellow viscous oil(230 mg). Praparative thin layer chromatography on silica gel developed with 1 % methanol-chloroform gave three lactams, 42(60 mg, 23.8 %), 43(50 mg, 19.8 %), and 44(60 mg, 23.8 %).

The lactam(42), pale yellow crystals, showed the following characteristics: mp 68-69 °C: IR(neat) 1620 cm^{-1}; NMR($CDCl_3$) δ 0.97(3H, collapsed t, J=5.0 Hz), 3.73(6H, s), 4.16(1H, t, J=7.0 Hz), 6.63(1H, s), 6.76(1H, s); MS(m/e) 421(M^+), 346, 286, 258, 192, 191, 119. *Anal.* ($C_{22}H_{31}NO_3S_2$) C, H, N.

The lactam(43), pale yellow crystals, exhibited the following chracteristics: mp 76-77 °C; IR(neat) 1620 cm^{-1}; NMR($CDCl_3$) δ 1.10(3H, unsym. t, J=6.0 Hz), 3.88 (6H, s), 4.10(1H, t, J=7.0 Hz), 6.70(1H, s), 6.87(1H, s); the mass spectrum was similar to that of 42. *Anal.* ($C_{22}H_{31}NO_3S_2$) C, H, N.

The lactam(44), colorless crystals from ethanol, showed the following charac-

teristics: mp 64.5-65 °C; IR(Nujol) 1625 cm^{-1}; NMR($CDCl_3$) δ 1.03(3H, unsym. t, J= 7.0 Hz), 3.93(6H, s), 6,66(1H, s), 6.73(1H, s); the mass spectrum was similar to that of 42. *Anal.* ($C_{22}H_{31}NO_3S_2$) C, H, N, S.

(b) via The ω-Hydroxy Lactam(36). To a stirred solution of 32(110 mg, 0.2 mmol) in dry toluene(10 ml) under nitrogen at -65 °C was added a solution of diisobutylaluminum hydride in dry benzene(2M, 0.28 ml, 0.56 mmol). After stirring at -65 °C for 5 h , the reaction was quenched by the addition of saturated NH_4Cl. The resulting sludge was removed by filtration and washed thoroughly with benzene. The filtrate was separated and the organic layer was dried over anhydrous Na_2SO_4. Removal of the slovent in vacuo gave the ω-hydroxy lactam(34)(110 mg) as a yellow oil, which was used without further purification: IR(neat)3330, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.88(3H, br.t), 3.87(6H, s), 6.77(3H, s).

A solution of crude 34(110 mg) in benzene(10 ml) was refluxed in the presence of a catalytic amount of p-toluenesulfonic acid monohydrate(60 mg) under nitrogen for 4 h . The work-up afforded a yellow viscous oil(90 mg). Preparative thin-layer chromatography on silica gel developed with 1 % methanol-chloroform gave the lactams, 42(30 mg, 35.7 %) and 44(5 mg, 6.0 %), each as pale yellow crystals.

3α-Ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxy-2β-[2,2-(propane-1,3-dithio)-ethyl]-11bαH-benzo[a]quinolizine(20). To a stirred solution of the lactam(42) (150 mg, 0.35 mmol) in anhydrous tetrahydrofuran(2 ml) with cooling in an ice bath under nitrogen was added a solution of lithium aluminum hydride in anhydrous tetrahydrofuran(2.2 M, 1.5 ml, 3.3 mmol) and the mixture was refluxed for 8.5 h . The reaction was quenched with 10 % NH_4OH with cooling in an ice bath. The resulting sludge was removed by filtration and washed thoroughly with methylene chloride. The combined filtrate was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to leave a yellow gum(140 mg). Praparative thin-layer chromatography on silica gel developed with 2 % methanol-chloroform gave 20(80 mg, 56.3 %) as a pale yellow viscous oil: IR(neat) 2800-2700 cm^{-1}; NMR($CDCl_3$) δ 0.97 (3H, collapsed t, J=5.0 Hz), 3.87(6H, s), 4.16(1H, t, J=7,0 Hz), 6.63(1H, s), 6.73 (1H, s); MS(m/e) 407(M^+), 364, 246, 205, 191.

(±)-Protoemetine(2). A mixture of the hydrochloride of 20(30 mg, 0.06 mmol) and methyl iodide(1 ml, 16 mmol) in 3.2 % aqueous acetonitrile(6.2 ml) was stirred at room temperature for 16 h . Most of the slovent was removed in vacuo and the residue was extracted with methylene chloride after basification with saturated $NaHCO_3$. The extract was washed with 1 % $Na_2S_2O_3$, water, saturated NaCl, dried

over anhydrous Na_2SO_4, and concentrated in vacuo to give practically pure (±)-protoemetine(2)(25 mg, 100 %) as a pale yellow gum, which was further purified by preparative thin layer chromatography on silica gel developed with 5 % methanol-chloroform: IR(neat) 1725 cm^{-1}; NMR($CDCl_3$) δ 0.96(3H, collapsed t), 3.86(6H, s), 6.63(1H, s), 6.68(1H, s), 9,95(1H, s). The spectral data of this material were identical with those of an authentic sample[22].

Conversion of (±)-Protoemetine(2) into (±)-Protoemetinol(3). (±)-Protoemetine(2)(25 mg, 0.075 mmol) obtained as above in methanol(5 ml) was reduced with sodium borohydride(30 mg) in the usual manner. After removal of the solvent in vacuo, the residue was treated with water and extracted with methylene chloride. The extract was washed with water, saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give (±)-protoemetinol(3)(20 mg, 79.4 %) which was identical in all respects with an authentic sample.

Conversion of the Lactams(42), (43), and (44) into the Corresponding Lactam-acids(17), (22), and (38). A mixture of the thioacetal-lactam(42)(80 mg, 0.19 mmol), methyl iodide(1 ml, 16 mmol) and Na_2CO_3(150 mg, 1.4 mmol) in 40 % aqueous acetonitrile(10 ml) was stirred at room temperature for 24 h . After removal of the solvent in vacuo below 40 °C, the residue was extracted with methylene chloride. The extract was washed with water, 1 % $Na_2S_2O_3$, saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the practically pure aldehyde(21)(75 mg) as a pale yellow viscous oil, which was used without further purification: IR(neat) 1720, 1630 cm^{-1}; NMR($CDCl_3$) δ 1.00(3H, t, J=7.0 Hz), 3.89(6H, s), 6.63(2H, s), 9.90 (1H, br.t); MS(m/e) 331(M^+), 286, 273, 258, 205, 191, 176. The spectral data of this material were identical with those of an authentic sample[22].

A solution of the crude aldehyde(21)(75 mg) in tetrahydrofuran(2 ml) was added to a stirred solution of Ag_2O in water, prepared by mixting 3 % aqueous $AgNO_3$(2 ml, 0.36 mmol) and 1.4 % aqueous NaOH(2 ml, 1.72 mmol). After stirring at room temperature for 30 min, the reaction mixture was filtered using Celite and the filter-cake was washed with water and the aqueous layer was washed with methylene chloride. The aqueous layer was acidified with cold 10 % HCl and extracted with methylene chloride. The extract was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield a yellow crystalline residue(60 mg). Recrystallization from acetone gave the lactam-acid(17)(40 mg, 60.6 % from 42) as colorless needles, which was completely identical with that obtained by the cyclization of 14.

Similary, the isomeric lactam(43) was converted to the lactam-acid(22) in 61.8 % overall yield *via* the aldehyde(26).

The aldehyde(26), a pale yellow viscous oil, showed the following characteristics: IR(neat) 1720, 1635 cm^{-1}; NMR($CDCl_3$) δ 1.13(3H, unsym. t, J=7.0 Hz), 3.90(3H, s), 4.00(3H, s), 6.70(2H, s), 9.86(1H, s); the mass spectrum was similar to that of 21. *Anal.* ($C_{19}H_{25}NO_4$) C, H, N.

The isomeric lactam(44) was also converted to the lactam-acid(38) in 34.2 % overall yeild *via* the aldehyde(37) in the same manner as described above.

The aldehyde(37), a pale yellow viscous oil, showed the following characteristics: IR(neat) 1710, 1620 cm^{-1}; NMR($CDCl_3$) δ 1.00(3H, t, J=7.0 Hz), 3.89(3H, s), 3.91(3H, s), 6.69(1H, s), 6.74(1H, s), 9.96(1H, s); the mass spectrum was similar to that of 21. *Anal.* ($C_{19}H_{25}NO_4$) C, H, N.

The lactam-acid(38), colorless needles(recrystallized from acetone), exhibited the following characteristics: mp 207-210 °C; IR(Nujol) 3200-2400, 1710, 1580 cm^{-1}; NMR($CDCl_3$) δ 1.03(3H, unsym. t, J=6.0 Hz), 3.89(6H, s), 6.70(1H, s), 6.76(1H, s), 8.70(1H, br.s, exchangeable); the mass spectrum was similar to that of 17. *Anal.* ($C_{19}H_{25}NO_5$ $\frac{1}{2}H_2O$) C, H, N.

Reduction of the Aldehyde(37) using Lithium Aluminum Hydride. To an ice-cooled solution of the aldehyde(37)(150 mg, 0.46 mmol) in anhydrous tetrahydrofuran (2 ml) under nitrogen was added a solution of lithium aluminum hydride in anhydrous tetrahydrofuran(1.3 M, 2 ml, 2.6 mmol) and the mixture was refluxed for 3 h . The reaction mixture was treated with 10 % NH_4OH with cooling in an ice bath. The resulting sludge was removed by filtration using Celite and the filter-cake was washed with methylene chloride. The combined filtrate was washed with saturated NaCl, dried over anhydrous K_2CO_3, and concentrated *in vacuo* to yield a pale yellow gum(150 mg). Praparative thin-layer chromatography on silica gel developed with 10 % methanol-chloroform gave (±)-protoemetinol(3)(50 mg, 34.0 %), its 11b-epimer(25)(70 mg, 47.6 %), and the isomeric amino-alcohol(39)(20 mg, 13.6 %). The compound(39), a pale yellow gum, showed the following characteristics: IR(neat) 3350 cm^{-1}; NMR($CDCl_3$) δ 0.95(3H, collapsed t, J=6.0 Hz), 3.88(6H, s), 6.63(1H, s), 6.72(1H, s); the mass spectrum was similar to that of (±)-protoemetinol(3). *Anal.* ($C_{19}H_{29}NO_3$) C, H, N.

Conversion of the Amino-alcohol(39) into (±)-3-Epiprotoemitinol(41). A mixture of the amino-alcohol(39)(10 mg, 0.03 mmol), acetic anhydride(0.1 ml, 1.00 mmol), and sodium acetate(5 mg, 0.06 mmol) in benzene(2.0 ml) was refluxed

for 3 h . After cooling the reaction mixture was washed with saturated $NaHCO_3$, water, saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was dissolved in acetic acid(3.0 ml) containing mercuric acetate (15 mg, 0.046 mmol), and was stirred at room temperature for 12 h under nitrogen. After removal of the solvent in vacuo, the residue was dissolved in methylene chloride and the inorganic precipitate was removed by filtration. The filtrate was concentrated in vacuo to leave the dehydro base(15 mg) as a yellow gum.

To a stirred solution of the crude dehydro base(15 ml) in methanol(3.0 ml) with cooling in an ice bath was added sodium borohydride(20 mg, 0.53 mmol). After stirring at 0 °C for 30 min, the mixture was concentrated in vacuo, treated with water, and extracted with methylene chloride. The extract was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to leave the acetate of 41. The crude acetate was dissolved in methanol containing KOH(10 mg, 0.18 mmol) and the solution was refluxed for 3 h . The reaction mixture was diluted with water and extracted with methylene chloride. The extract was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give (±)-3-epiprotoemetinol(44) ^{22}(4 mg, 40.0 %) as a pale yellow gum.

Isomerization of the Thioacetal Lactam(44) to the Thioacetal Lactam(42) Using Boron Trifluoride Etherate. A mixture of the lactam(44)(10 mg, 0.02 mmol) and boron trifluoride etherate(0.05 mg, 0.36 mmol) in dry benzene(1.0 ml) was stirred at room temperature for 2 h under nitrogen. The reaction mixture was treated with saturated $NaHCO_3$ and the organic layer was separated. The organic layer was washed with saturated $NaHCO_3$ saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the isomeric lactam(42)(10 mg, 100 %).

When aluminum chloride was used as a catalyst in place of boron trifluoride etherate, more prolonged reaction time(ca. 20 h) was required.

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