Studies on the Syntheses of Heterocyclic Compounds. Part 766.[1] A Total Stereoselective Synthesis of Emetine and (±)-Dihydroprotoemetine

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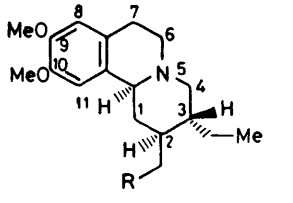
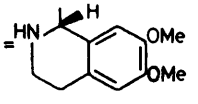
Reaction of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (3) with diethyl αγ-diethoxycarbonylglutaconate (2) in ethanol, followed by silica gel chromatography, formed 3-ethoxycarbonyl-6,7-dihydro-9,10-dimethoxybenzo[*a*]quinolizin-4-one (6). The same reaction of (3) with (2), followed by reduction with sodium borohydride, afforded 3-ethoxycarbonyl-2-diethoxycarbonylmethyl-1,2,3,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-4-one(10).

Condensation of (3) with dimethyl 3-methoxyallylidenemalonate (11) gave 2,3,6,7-tetrahydro-9,10-dimethoxy-3-methoxycarbonyl-2-(ββ-dimethoxyethyl)benzo[*a*]quinolizin-4-one (13), which was converted to (±)-emetine (1) in seven steps and (±)-dihydroprotoemetine (2) in six steps.

Decarboxylation of the enamide form (22) furnished mainly the *cis*-substituted compound (23).

THE benzo[*a*]quinolizine ring system appears in a wide variety of alkaloids such as emetine, cephaeline, and tubulosine. Although there are many methods for the synthesis of emetine (1), the development of facile synthetic procedures of the benzo[*a*]quinolizine derivatives still continues because some of the natural products and the synthetic compounds possess medicinal activity.[2-5] We have studied the one-step synthesis of benzo[*a*]quinolizines from 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (3) utilising its enamine character.[6] Further investigation led to a new synthesis of benzo[*a*]-quinolizines suitably substituted for the total synthesis of natural products. Here we wish to report a simple stereoselective synthesis of emetine (1) and (±)-dihydroprotoemetine (2).[7]



(1) R = 

(2) R = CH_2OH

RESULTS AND DISCUSSION

In a preliminary experiment, 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (3)[8] was stirred for 5 h with diethyl αγ-diethoxycarbonylglutaconate (4)[9] at room temperature in ethanol. Purification of the product by silica gel chromatography afforded 3-ethoxycarbonyl-6,7-dihydro-9,10-dimethoxybenzo[*a*]quinolizin-4-one (6), m.p. 189—190 °C, in 94% yield, along with diethyl malonate. The structure of the product (6) was supported by the spectral data and microanalysis (see Experimental section) and further confirmed by its conversion into the known compound (8).[10] Thus refluxing (6) with a mixture (1 : 1 v/v) of concentrated hydrochloric acid and acetic acid for 20 h gave, in 65% yield, a phenolic compound (7), m.p. 235—238 °C. 6,7-Dihydro-10-hydroxy-9-methoxybenzo[*a*]quinolizin-4-one (7) is expected to be the product of this reaction if demethylation accompanied by de-ethoxycarbonylation occurs preferentially at the 10- rather than the 9-methoxy-group because of electronic factors.[11] Methylation of the phenol (7) with diazomethane gave (8), the spectroscopic data of which were identical to those of an authentic sample.[10]

It was probable that the Michael addition of the enamine (3) to the unsaturated ester (4), followed by cyclisation, yielded an enamide (5), which then underwent retro-Michael reaction on silica gel to give (6) and diethyl malonate. In order to prevent the above retro-Michael reaction, the reaction product was immediately reduced with sodium borohydride. Thus, after a mixture of (3) and (4) had been treated in a similar manner to that described above, sodium borohydride was added in small portions to the stirred reaction mixture at room temperature. The usual work-up, followed by purification of the reaction product by silica gel chromatography, gave in 60% yield the triester (10) as a syrup. The molecular-ion peak was observed at *m/e* 491 in the mass spectrum, and carbonyl bands appeared at 1 725 and 1 640 cm^{-1} in the i.r. spectrum ($CHCl_3$). It was apparent from the n.m.r. spectrum [δ($CDCl_3$) 1.24 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.28 (6 H, t, *J* 7 Hz, 2 CH_2CH_3), 4.12 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.15 (4 H, q, *J* 7 Hz, 2 CH_2CH_3), 6.45 (1 H, s, 8-H), and 6.53 (1 H, s, 11-H)] and the chromatographic behaviour that the product (10) was a single stereoisomer though its stereochemistry was unclear.

Saponification of (10) with aqueous ethanolic potassium hydroxide at 50 °C for 6 h gave the monocarboxylic acid (9), which was identical with a sample prepared from (6) by hydrolysis under the similar condition. The carboxylic acid (9) would be formed from (10) by a retro-Michael reaction accompanied by dehydration.

It was thus expected that certain αβ-unsaturated αα-diesters would be suitable precursors for the synthesis of benzo[*a*]quinolizines by condensation with an enamine. In order to obtain a more appropriately substituted inter-

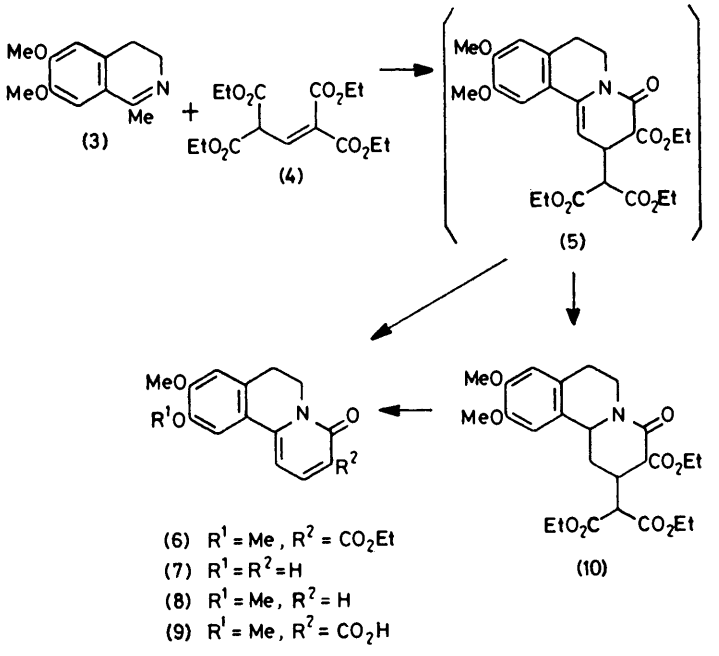
mediate for the synthesis of natural products, dimethyl 3-methoxyallylidenemalonate (11), which was easily available by the reaction of 1,1,3,3-tetramethoxypropane and dimethyl malonate,[12 13] was chosen. Treatment of (3) with (11) in methanol for 6 d at room temperature, followed by refluxing, afforded 2,3,6,7-tetrahydro-9,10-dimethoxy-3-methoxycarbonyl-2-(ββ-dimethoxyethyl)benzo[*a*]quinolizin-4-one (13) as a syrup in 88.5% yield. The mass spectrum of (13) showed a molecular-ion peak at *m/e* 405 and the i.r. spectrum ($CHCl_3$) exhibited ν(CO) at 1 740 and 1 660 cm^{-1}. Signals due to three different types of methoxy-groups were observed in the ^1H n.m.r. spectrum ($CDCl_3$) at δ 3.36 (6 H, s), 3.76 (3 H, s), and 3.90 (6 H, s), in addition to signals at 1.80 [2 H, t, *J* 6.0 Hz, $CH_2CH(OMe)_2$], 2.80 (2 H, t, *J* 6.5 Hz, 7-CH_2), 4.56 [1 H, t, *J* 6.0 Hz, $CH_2CH(OMe)_2$], 5.68 (1 H, d, *J* 5 Hz, 1-CH), 6.63 (1 H, s, 8-CH), and 7.02 (1 H, s, 11-CH).

With a shorter reaction time, an intermediate, the structure of which was determined to be the diester (12) by the n.m.r. spectrum {δ($CDCl_3$) 1.83 [2 H, br t, $CH_2CH(OMe)_2$], 3.20 (3 H, s, OMe), 3.26 (3 H, s, OMe), 3.77 (6 H, s, 2 OMe), 3.95 (3 H, s, OMe), 3.99 (3 H, s, OMe), 4.43 [1 H, t, *J* 5 Hz, $CH(OMe)_2$], 6.67 (1 H, s, 5-CH), and 7.33 (1 H, s, 8-CH)} was isolated as a syrup after purification by preparative t.l.c. on silica gel.

Treatment of the cyclised product (13) with ethyl iodide in the presence of sodium hydride in benzene–dimethylformamide, for 5 h at room temperature, gave quantitatively the 3-ethyl compound (14) as crystals, m.p. 132.5—133.5 °C. Reduction of (14) with Adams catalyst in methanol at atmospheric pressure and room temperature yielded the lactam (15) as a single product. The relative configuration at C-2 and C-3 of the compounds (13)—(15) was obscure but one stereoisomer was obtained in each reaction. It was considered that hydrogen selectively attacked the carbon at the C-11b position, from the opposite side to the bulky substituent at the C-2 position. Hydrolysis of (15) was carried out by heating with potassium hydroxide in aqueous methanol for 4 h to afford the carboxylic acid (16) as a crystalline compound, m.p. 132—132.5 °C (decomp.), in excellent yield.

Heating the acid (16) in dimethylformamide at 120—130 °C for 2 h furnished the decarboxylated product (17) as an oil in 88.8% yield. The homogeneity of the product (17) was verified from the spectral data and h.p.l.c. analysis. The stereochemistry was determined by its conversion into (±)-dihydroprotoemetine (2).

Stirring the acetal (17) in acetone containing dilute



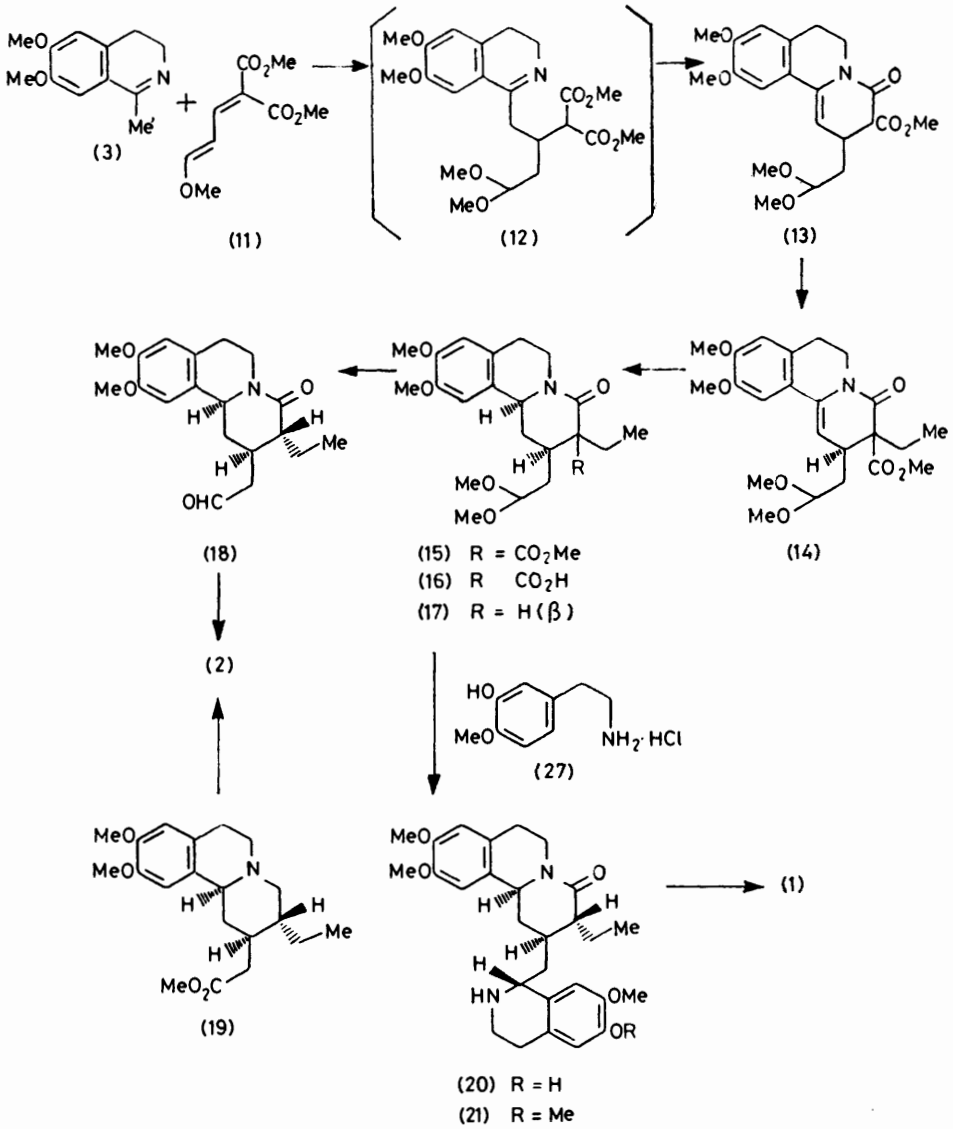
(6) R^1 = Me, R^2 = CO_2Et
(7) R^1 = R^2 = H
(8) R^1 = Me, R^2 = H
(9) R^1 = Me, R^2 = CO_2H

hydrochloric acid at room temperature for 1 h gave the aldehyde (18), which was refluxed with lithium aluminium hydride in dioxan–ether to give (±)-dihydroprotoemetine (2) in 59% yield. The spectral data and chromatographic behaviour were identical with those of an authentic sample prepared from the ester (19).[5]

A diastereoisomeric mixture of the aldehyde (18) has already been transformed to (±)-emetine (1) by Burgstahler and Bithos [14] but the sequence was not stereoselective. On the other hand, Szántay and his coworkers found that Pictet–Spengler condensation of protoemetine with 3-hydroxy-4-methoxyphenethylamine (27) produced cephaeline as the main product.[15] Therefore Pictet–Spengler reaction of the acetal (17) or the aldehyde (18) with the phenolic base (27) was examined under several conditions. Two products were formed but t.l.c. analysis showed that the ratio (*ca.* 7 : 3) between them was approximately constant. The main product (20), formed by the reaction of the acetal (17) with hydrochloride of the amine (27) in hot methanol–

dilute hydrochloric acid, was separated by chromatography and treated with diazomethane. The crude methylated product (21) was reduced with lithium aluminium hydride in hot ether–dioxan to yield (±)-emetine (1), the i.r. ($CHCl_3$) and n.m.r. spectra of which were superimposable on those of the natural product. Racemic emetine has already been resolved by Brossi and his co-workers.[16]

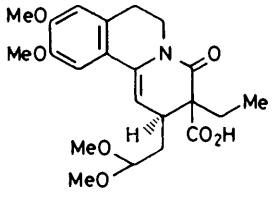
in 92.5% yield. Heating the acid (22) in dimethylformamide under the same condition as for (16) gave the decarboxylated product (23), the n.m.r. spectrum ($CDCl_3$) of which indicated that it was a mixture of two stereoisomers. Compound (23) was then hydrogenated in the presence of Adams catalyst in methanol at atmospheric pressure and room temperature. H.p.l.c. analysis revealed that the product, obtained in 61%



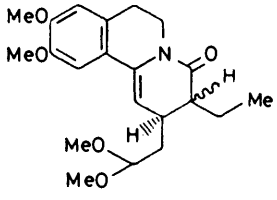
Thus total stereoselective synthesis was accomplished and the above method could be applied to the synthesis of several types of indole alkaloids as well as other *ipecac* alkaloids. For the synthesis of some indole alkaloids, the relative configuration between the C-2 and C-3 substituents is required to be *cis*. Stereoselective introduction of the substituent at C-3 *cis* to the one at C-2 was demonstrated as follows. The ester (14) was hydrolysed by refluxing with potassium hydroxide in aqueous methanol for 2 h to yield the corresponding carboxylic acid (22) as crystals, m.p. 147.5 °C (decomp.), yield based on the acid (22), was composed of two stereoisomers (17) and (24) in a ratio of 1 : 5. The minor component separated by the preparative h.p.l.c. was identical with the sample (17) prepared as above. The i.r. and n.m.r. spectra of the major product (24) were very similar to those of (17), and (24) was converted to (17) by refluxing with sodium hydride in dimethylformamide. Since only the ethyl group at the C-3 position of (24) would be epimerised under basic condition, the stereochemistry of (24) was determined to be as shown.

The mixture of (17) and (24), without separation, was stirred with dilute hydrochloric acid–acetone to give a mixture (18) and (25), which was reduced with lithium aluminium hydride to the amino-alcohols (2) and (26) (1 : 5). The mixture was separated into (±)-dihydroprotoemetine (2) and its stereoisomer (26) by h.p.l.c. Compound (26) showed Bohlmann bands in the i.r. spectrum and was characterised as the perchlorate, m.p. 202—203 °C.

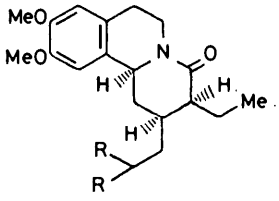
Application of the above method to the synthesis of the indole alkaloids is under investigation.



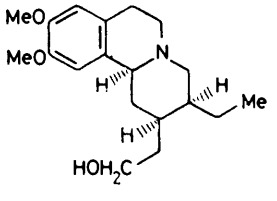
(22)



(23)



(24) R = OMe
(25) RR = O



(26)

EXPERIMENTAL

I.r. spectra were taken with a Hitachi 215 spectrophotometer, n.m.r. spectra with a JNM-PS-60 spectrometer (tetramethylsilane as internal reference), and mass spectra with a Hitachi RMU-7 spectrometer. H.p.l.c. was carried out with a Hitachi 635 instrument.

3-Ethoxycarbonyl-6,7-dihydro-9,10-dimethoxybenzo[a]*quinolizin-4-one* (6).—Diethyl αγ-diethoxycarbonylglutaconate (4) (730 mg) [9] was added to a solution of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (3) [8] (500 mg) in ethanol (10 ml) and the mixture was stirred for 5 h at room temperature under nitrogen. After evaporation of the solvent, the resulting yellow oil (1.2 g) was subjected to silica gel column chromatography. Elution with benzene gave diethyl malonate [identified by comparison of i.r. ($CHCl_3$) and n.m.r. ($CDCl_3$) spectra with those of an authentic sample]. Further elution with benzene–methanol (99 : 1 v/v) gave a yellowish powder (750 mg, 94%), which was recrystallised from ethanol to afford the amide (5) as *yellow needles*, m.p. 189—190 °C; $\nu_{max.}$ ($CHCl_3$) 1 720, 1 685, and 1 650 cm^{-1}; δ($CDCl_3$) 1.37 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.97 (6 H, s, 2 OMe), 4.35 (2 H, q, *J* 7 Hz, CH_2CH_3), 6.54 (1 H, d, *J* 8 Hz, 1-CH), 6.73 (1 H, s, 8-CH), 7.16 (1 H, s, 11-CH), and 8.08 (1 H, d, *J* 8 Hz, 2-CH); *m/e* 329 (M^+) (Found: C, 65.6; H, 5.7; N, 4.05. $C_{18}H_{19}NO_5$ requires C, 65.65; H, 5.8; N, 4.25%).

6,7-Dihydro-9,10-dimethoxybenzo[a]*quinolizin-4-one* (8).—A mixture of the above compound (5) (200 mg) in concentrated hydrochloric acid–acetic acid (1 : 1 v/v, 20 ml) was refluxed for 20 h and the solvent was evaporated off to give the phenol (7) (140 mg) as a hygroscopic mass, m.p. 235—238 °C; $\nu_{max.}$ (KBr) 1 640 cm^{-1}; δ(CF_3CO_2H) 3.20 (2 H, br t, *J* 7 Hz, 7-CH_2), 4.08 (3 H, s, OMe), 4.65 (2 H, br t, 6-CH_2), 7.00 (1 H, s, 8-CH), 7.27 (1 H, d, *J* 8 Hz, 1- or 3-CH), 7.57 (1 H, s, 11-CH), 7.63 (1 H, d, *J* 8 Hz, 1- or 3-CH), and 8.18 (1 H, t, *J* 8 Hz, 2-CH); *m/e* 243 (M^+). The phenol (7) (50 mg) was dissolved in methanol (50 ml), and an excess of diazomethane in ether was added. The mixture was set aside at 4 °C overnight, and the solvent was evaporated off to give a yellow powder (50 mg), which was recrystallised from ethanol to afford the compound (8) as yellowish scales, m.p. 173—174 °C (lit.,[10] m.p. 172—173 °C), the i.r. ($CHCl_3$) and n.m.r. ($CDCl_3$) spectra of which were superimposable on those of the authentic sample.[10]

3-Ethoxycarbonyl-2-diethoxycarbonylmethyl-1,2,3,6,7,11b-hexahydro-9,10-dimethoxybenzo[a]*quinolizin-4-one* (10).—A mixture of the enamine (3) (0.92 g) and the ester (4) (1.5 g) in ethanol (10 ml) was stirred for 5 h at room temperature under nitrogen. Sodium borohydride (0.15 g) was added in small portions to the resulting mixture with stirring at room temperature. After stirring for 3 h, the solvent was evaporated off to give a yellowish oil, which was taken up in chloroform. The chloroform layer was washed with water, dried (Na_2SO_4), and evaporated to dryness to give an oily residue. Chromatography on silica gel [benzene–methanol (99.8 : 0.2 v/v)] gave the triester (10) (1.32 g, 60%) as an oil; $\nu_{max.}$ ($CHCl_3$) 1 725 and 1 640 cm^{-1}; δ($CDCl_3$) 1.24 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.28 (6 H, t, *J* 7 Hz, 2 CH_2CH_3), 3.73 (6 H, s, 2 OMe), 4.12 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.15 (4 H, *J* 7 Hz, 2 CH_2CH_3), 6.45 (1 H, s, 8-CH), and 6.53 (1 H, s, 11-CH); *m/e* 491 (M^+); this was used in the next reaction without further purification.

6,7-Dihydro-9,10-dimethoxy-4-oxobenzo[a]*quinolizine-3-carboxylic Acid* (9).—(*a*) The above compound (10) (200 mg) was dissolved in a 10% ethanolic potassium hydroxide solution (20 ml) and the mixture was heated at 50—60 °C for 6 h. After evaporation of the solvent, water (10 ml) was added to the residue. The aqueous layer was washed with ether, then acidified by addition of hydrochloric acid and extracted with chloroform. The extract was washed with a brine, dried (Na_2SO_4), and evaporated to dryness to give the acid (9) (88 mg, 66%) as a yellow powder, which was recrystallised from methanol to afford *yellow needles*, m.p. >270 °C; $\nu_{max.}$ (KBr) 1 740 and 1 620 cm^{-1}; δ(CF_3CO_2H) 3.28 (2 H, t, *J* 7 Hz, 7-CH_2), 4.12 (6 H, s, 2 OMe), 4.73 (2 H, t, *J* 7 Hz, 6-CH_2), 7.06 (1 H, s, 8-CH), 7.57 (1 H, s, 11-CH), 7.80 (1 H, d, *J* 8.5 Hz, 1-CH), and 8.80 (1 H, d, *J* 8.5 Hz, 2-CH); *m/e* 301 (M^+) and 257 ($M^+ - 44$) (Found: C, 62.8; H, 4.9; N, 4.45. $C_{16}H_{15}NO_5$,0.25H_2O requires C, 62.9; H, 5.05; N, 4.6%).

(*b*) A mixture of the ester (6) (100 mg) in a 10% ethanolic potassium hydroxide solution (10 ml) was heated for 6 h at 50—60 °C and then evaporated to dryness. The residue was dissolved in water (10 ml), and washed with ether. The aqueous layer was acidified with hydrochloric acid and extracted with chloroform. The extract was washed with brine, dried (Na_2SO_4), and evaporated to dryness to give the acid (9) (80 mg, 88%) as a yellow powder, which was recrystallised from methanol to afford yellow needles, m.p. >270 °C, whose spectral data were identical with those of the sample prepared by method (*a*).

2,3,6,7-Tetrahydro-9,10-dimethoxy-3-methoxycarbonyl-2-(2,2-dimethoxyethyl)benzo[a]*quinolizin-4-one* (13).—A solution of the enamine (3) (246 mg) and dimethyl 3-methoxyallylidenemalonate (11) [13] (250 mg) in methanol (10 ml) was stirred for 6 d at room temperature and then refluxed for

12 h under nitrogen. After evaporation of the solvent, the residue was chromatographed on silica gel with benzene–ethyl acetate (4 : 1 v/v) to give the enamide (13) (439 mg, 88.5%) as a reddish oil; $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 660 cm^{-1}; δ($CDCl_3$) 1.80 [2 H, t, *J* 6 Hz, $CH_2CH(OMe)_2$], 2.80 (2 H, t, *J* 6.5 Hz, 7-CH_2), 3.36 [6 H, s, $CH(OMe)_2$], 3.76 (3 H, s, CO_2Me), 3.90 (6 H, s, 2 OMe), 4.56 [1 H, t, *J* 6 Hz, $CH(OMe)_2$], 5.68 (1 H, d, *J* 5 Hz), 6.63 (1 H, s, 8-CH), and 7.02 (1 H, s, 11-CH); *m/e* 405 (M^+); crystallisation of this failed and therefore it was used in the next reaction without further purification.

3-Ethyl-2,3,6,7-tetrahydro-9,10-dimethoxy-3-methoxycarbonyl-2-(2,2-dimethoxyethyl)benzo[a]*quinolizin-4-one* (14).—To a solution of the above compound (13) (180 mg) in dry benzene (10 ml)–dry dimethylformamide (5 ml), 50% sodium hydride (21 mg) was added with stirring under nitrogen at 0 °C. After stirring for 1 h at room temperature, ethyl iodide (300 mg) was added dropwise to the above mixture at room temperature and the resulting mixture was stirred for 5 h. Benzene (100 ml) was added to the reaction mixture, which was then washed with water. The organic layer was dried (Na_2SO_4) and evaporated to give an oily residue, which was recrystallised from di-isopropyl ether to afford the ethyl compound (15) (190 mg, 99%) as *prisms*, m.p. 132.5—133.5 °C; $\nu_{max.}$ ($CHCl_3$) 1 725 and 1 660 cm^{-1}; δ($CDCl_3$) 1.00 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.82 (2 H, t, *J* 6.5 Hz, 7-CH_2), 3.38 [6 H, s, $CH(OMe)_2$], 3.62 (3 H, s, CO_2Me), 3.90 (6 H, s, 2 OMe), 4.57 [1 H, t, *J* 5 Hz, $CH(OMe)_2$], 5.63 (1 H, d, *J* 3.5 Hz, 1-CH), 6.63 (1 H, s, 8-CH), and 7.02 (1 H, s, 11-CH); *m/e* 433 (M^+) (Found: C, 63.4; H, 7.2; N, 2.8. $C_{23}H_{31}NO_7$ requires C, 63.7; H, 7.2; N, 3.25%).

(±)-*3-Ethyl-1,2,3,6,7,11bα-hexahydro-9,10-dimethoxy-3-methoxycarbonyl-2β-(2,2-dimethoxyethyl)benzo*[a]*quinolizin-4-one* (15).—After a mixture of platinum oxide (20 mg) and methanol (5 ml) had been stirred for 15 min under hydrogen, a solution of the above compound (14) (150 mg) in methanol (10 ml) was added and the reaction stirred for 3 h at room temperature under hydrogen. The reaction mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in benzene, washed with water, dried (Na_2SO_4), and evaporated to give the *lactam* (15) (149 mg, 99%) as an oil; $\nu_{max.}$ ($CHCl_3$) 1 730 and 1 625 cm^{-1}; δ($CDCl_3$) 0.90 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.37 [6 H, s, $CH(OMe)_2$], 3.61 (3 H, s, CO_2Me), 3.86 (6 H, s, 2 OMe), and 6.60 and 6.62 (each 1 H, s, 8- and 11-CH); this was used in the next reaction without further purification.

(±)-*3-Ethyl-1,2,3,6,7,11bα-hexahydro-9,10-dimethoxy-2β-(2,2-dimethoxyethyl)-4-oxobenzo*[a]*quinolizine-3-carboxylic Acid* (16).—A solution of the above compound (15) (54 mg) in 10% methanolic potassium hydroxide solution (3 ml) was refluxed for 4 h and the resulting mixture was evaporated to dryness. The residue was taken up into water (20 ml) and washed with ether. The aqueous layer was acidified to pH 6 with acetic acid and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the *acid* (16) (47 mg, 91%) as a pale yellow oil, which was recrystallised from ethyl acetate to afford fine needles, m.p. 132—132.5 °C (decomp.); $\nu_{max.}$ ($CHCl_3$) 1 735 and 1 620 cm^{-1}; δ ($CDCl_3$) 0.88 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.33 [6 H, s, $CH(OMe)_2$], 3.70 (6 H, s, 2 OMe), and 6.58 and 6.64 (each 1 H, s, 8- and 11-CH); *m/e* 377 ($[M - CO_2]^+$) (Found: C, 62.85; H, 7.65; N, 3.35. $C_{22}H_{31}NO_7$ requires C, 62.7; H, 7.4; N, 3.3%).

(±)-*3α-Ethyl-1,2,3,6,7,11bα-hexahydro-9,10-dimethoxy-2β-(2,2-dimethoxyethyl)benzo*[a]*quinolizin-4-one* (17).—A solution of the acid (16) (34 mg) in dimethylformamide (2 ml) was heated at 120—130 °C under nitrogen and the resulting mixture was evaporated to dryness. The oily residue was taken up into benzene (20 ml), washed with a saturated aqueous sodium hydrogencarbonate solution, dried (Na_2SO_4), and evaporated to give the acetal (17) (27 mg, 88.8%) as a yellowish oil; $\nu_{max.}$ ($CHCl_3$) 1 620 cm^{-1}; δ($CDCl_3$) 0.91 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.33 [6 H, s, $CH(OMe)_2$], 3.84 (6 H, s, 2 OMe), and 6.60 and 6.65 (each 1 H, s, 8- and 11-CH); *m/e* 377 (M^+); this was used in the next reaction without further purification.

(±)-*Dihydroprotoemetine* (19).—To a solution of the above acetal (17) (50 mg) in acetone (3 ml) was added 3.6% hydrochloric acid (2 ml) and the mixture was stirred for 1 h at room temperature under nitrogen. After evaporation of acetone, the resulting aqueous residue was basified with a saturated aqueous sodium hydrogencarbonate solution and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the aldehyde (18) (38 mg, 86.6%) as a syrup; $\nu_{max.}$ ($CHCl_3$) 1 728 and 1 620 cm^{-1}; δ($CDCl_3$) 0.90 (3 H, t, *J* 6 Hz, CH_2CH_3), 3.85 (6 H, s, 2 OMe), 6.92 (2 H, s, 8- and 11-CH), and 9.80 (1 H, s, CHO); *m/e* 331 (M^+).

To lithium aluminium hydride (72 mg) in dry ether (10 ml), a solution of the above aldehyde (18) (52 mg) in dry dioxan (10 ml) was dropwise added with stirring under reflux. The mixture was stirred for 5 h under reflux and then cooled with ice. The excess of reagent was decomposed with addition of 15% aqueous sodium hydroxide solution and the organic layer was separated by decantation. The aqueous layer was extracted with chloroform and the combined organic extracts were evaporated. The residue was taken up into 5% hydrochloric acid, washed with ether, and basified with a saturated aqueous sodium hydrogencarbonate. After extraction with chloroform, the extract was washed with water, dried (Na_2SO_4), and evaporated to give (±)-dihydroprotoemetine (2) (34 mg, 67.9%) as a syrup, the i.r. ($CHCl_3$) and n.m.r. [δ($CDCl_3$) 3.84 (6 H, s, 2 OMe), and 6.56 and 6.69 (each 1 H, s, 8- and 11-CH)] spectra of which were identical with those of an authentic sample derived from the ester (19) supplied by Professor Takano.[5]

The free base was converted to its perchlorate and recrystallised from ethanol–ethyl acetate to give prisms, m.p. 178—181 °C (lit.,[14,17] m.p. 178—181 °C), mixed m.p. test of which with an authentic sample showed no depression.

(±)-*Emetine* (1).—To a stirred solution of (±)-3α-ethyl-1,2,3,6,7,11bα-hexahydro-9,10-dimethoxy-2β-(2,2-dimethoxyethyl)benzo[*a*]quinolizin-4-one (17) (139 mg) and 3-hydroxy-4-methoxy-β-phenethylamine hydrochloride (27) (75 mg) in methanol–water (2 : 3 v/v, 25 ml) was added 3 drops of 10% hydrochloric acid, and the mixture was heated under nitrogen at 60—70 °C for 2 weeks. The methanol was removed, the aqueous residue was basified with solid sodium hydrogencarbonate, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a gummy material. Silica gel column chromatography [chloroform–methanol (100 : 3, v/v)] gave (20) (95 mg, 53.7%) as a syrup; $\nu_{max.}$ ($CHCl_3$) 3 560 and 1 620 cm^{-1}; δ($CDCl_3$) 0.91 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.79 (3 H, s, OMe), 3.86 (6 H, s, 2 OMe), 6.43 (1 H, s, Ar-H), 6.61 (2 H, s, 2 Ar-H), and 6.73 (1 H, s,

Ar-H); *m/e* 480 (M^+). To a solution of the above syrup (95 mg) in methanol (20 ml) was added an excess of ethereal diazomethane, and the mixture was set aside for 6 h at room temperature. The solvents and the excess of diazomethane were removed by evaporation and the residue was taken up into chloroform. The chloroform layer was washed with 2N aqueous sodium hydroxide solution, dried (Na_2SO_4), and evaporated to give (21) (93 mg) as a brown syrup. A solution of the product (93 mg) in dry dioxan (10 ml) was added portionwise to a refluxing suspension of lithium aluminium hydride (100 mg) in dry ether (10 ml). The mixture was stirred under reflux for 3 h and then cooled with ice. The excess of lithium aluminium hydride was decomposed with addition of 15% aqueous sodium hydroxide solution. The organic layer was separated by decantation and the aqueous residue was extracted with chloroform. The combined organic extracts were evaporated, and the residue was dissolved in 5% hydrochloric acid, washed with ether, basified with a saturated aqueous sodium hydrogencarbonate solution, and extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4), and evaporated to give (±)-emetine (48 mg, 50.5%) as a syrup, the spectra of which were identical with those of natural emetine. The free base was converted to its oxalate, m.p. 158—160 °C (lit.,[14] m.p. 159—160 °C; lit.,[16] m.p. 180—182 °C), after recrystallisation from methanol–ether.

3-Ethyl-2,3,6,7-tetrahydro-9,10-dimethoxy-2-(2,2-dimethoxyethyl)-4-oxobenzo[a]*quinolizine-3-carboxylic Acid* (22).—A mixture of the ester (14) (280 mg) in 10% methanolic potassium hydroxide solution (10 ml) was refluxed for 4 h. After evaporation of the solvent, the residue was taken up into water (40 ml) and washed with ether. The aqueous layer was acidified to pH 6 with acetic acid and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a powder, recrystallisation of which from chloroform–methanol gave the acid (22) (250 mg, 92.5%) as *prisms*, m.p. 147.5 °C (decomp.); $\nu_{max.}$ (KBr) 1 740 cm^{-1}; δ($CDCl_3$) 0.93 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.26 [6 H, s, $CH(OMe)_2$], 3.93 (6 H, s, 2 OMe), 4.50 [1 H, t, *J* 6 Hz, $CH(OMe)_2$], 5.90 (1 H, d, *J* 7 Hz, 1-CH), 6.67 (1 H, s, 8-CH), and 7.06 (1 H, s, 11-CH); *m/e* 419 (M^+) (Found: C, 62.75; H, 6.95; N, 3.35. $C_{22}H_{29}NO_7$ requires C, 63.0; H, 6.95; N, 3.35%).

Stereoisomeric Mixture (17) *and* (24) *of 3-Ethyl-1,2,3,6,7,11b-hexahydro-9,10-dimethoxy-2-(2,2-dimethoxyethyl)benzo*[a]*quinolizin-4-one*.—A solution of the acid (22) (105 mg) in dimethylformamide (2 ml) was heated at 120—130 °C under nitrogen for 2 h. After evaporation of the solvent, the residue was taken up into benzene. The extract was washed with saturated aqueous sodium hydrogencarbonate solution, dried (Na_2SO_4), and evaporated to give a stereoisomeric mixture (23) (71 mg) as an orange syrup; $\nu_{max.}$ ($CHCl_3$) 1 660 cm^{-1}; δ($CDCl_3$) 0.98 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.33 [6 H, s, $CH(OMe)_2$], 3.92 (6 H, s, 2 OMe), and 6.60 and 7.03 (each 1 H, each s, 8- and 11-CH), *m/e* 375 (M^+).

To a suspension of Adams catalyst (20 mg) in methanol (5 ml) pre-saturated with hydrogen, a solution of the above compound (150 mg) in methanol (10 ml) was added. The mixture was stirred for 3 h at room temperature under hydrogen. After filtration, the filtrate was evaporated to give a syrup, which was extracted with benzene. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a mixture of (17) and (24) (121 mg) as a syrup, which was separated using h.p.l.c. (packing material: Hitachi gel 3011; mobile phase: methanol) to afford two compounds in a ratio of 1 : 5. The minor component was identical with a sample (17) prepared as above, on spectral and chromatographic comparison. Spectral data of the major compound (24) were similar to those of (17).

Epimerisation of (24) *into* (17). To a solution of the above main product (24) (80 mg) in dry dimethylformamide (15 ml) was added 50% sodium hydride (6 mg) and the mixture was refluxed for 1 h under nitrogen. After evaporation of the solvent, the residue was taken up into benzene, washed with water, dried (Na_2SO_4), and evaporated to give a syrup (50 mg), which was identified as (17) by spectral and h.p.l.c. analysis.

(±)-Dihydroprotoemetine (2) *and its Stereoisomer* (26).—The above crude mixture of (17) and (24) (46 mg) was treated with 3.6% hydrochloric acid in acetone and worked up as the case of (17) to give a mixture of (18) and (25) (30 mg) as a yellowish syrup; $\nu_{max.}$ ($CHCl_3$) 1 728 and 1 620 cm^{-1}; δ($CDCl_3$) 0.90 (3 H, t, *J* 6 Hz, CH_2CH_3), 3.85 (6 H, s, 2 OMe), 6.92 (2 H, s, 8- and 11-CH), 9.77 (0.83 H, s, CHO), and 9.80 (0.17 H, s, CHO); *m/e* 331 (M^+).

The above product [(18) + (25)] (75 mg) was reduced with lithium aluminium hydride (100 mg) in hot dry ether (10 ml)–dry dioxan (10 ml) and worked up in the same way as for pure (18) to give a mixture of (±)-dihydroprotoemetine (2) and its stereoisomer (26) as a syrup, which was separated by h.p.l.c. [packing material: μ-Bondapak C_{18}, mobile phase: methanol–0.5% aqueous ammonium carbonate (3 : 1 v/v)]. The faster eluate gave (±)-dihydroprotoemetine (2) (8.5 mg) as a syrup, the spectral data of which were identical with those of an authentic sample. The perchlorate was recrystallised from ethanol–ethyl acetate as prisms, m.p. 178—181 °C (lit.,[14,17] m.p. 178—181 °C). The slower eluate gave the isomer (26) (42.6 mg) as a syrup; $\nu_{max.}$ ($CHCl_3$) 2 950—2 750 cm^{-1} (*trans*-quinolizine bond); δ($CDCl_3$) 3.84 (3 H, s, 2 OMe) and 6.55 and 6.67 (each 1 H, s, 8- and 11-CH); *m/e* 319 (M^+). The perchlorate was recrystallised from methanol–ether to yield *needles*, m.p. 202—203 °C (Found: C, 54.2; H, 7.2; N, 2.9. $C_{19}H_{29}NO_3 \cdot HClO_4$ requires C, 54.35; H, 7.2; N, 3.35%).

We thank Professor S. Takano and Dr. K. Ogasawara for their kind gift of the authentic ester (19), and Mr. Kawamura, Mrs. C. Koyanagi, Miss K. Mushiake, Mrs. R. Kobayashi, Miss R. Suenaga, Miss E. Nagaoka, and Miss M. Tanno for microanalyses and spectral measurements.

[8/287 *Received*, 20*th February*, 1978]

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