Studies on the Syntheses of Heterocyclic Compounds. Part 673.† New Routes to Benzo[*a*]quinolizines

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Heating 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (1) with crotonic anhydride (2) gave 3,4,6,7-tetrahydro-9,10-dimethoxy-4-methylbenzo[*a*]quinolizin-2-one (5) along with 2-crotonoyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3) and *N*-(2-acetyl-4,5-dimethoxyphenethyl)crotonamide (4). Heating the isoquinoline (1) with glutaconic anhydride (17) in pyridine provided 1,6,7,11b-tetrahydro-9,10-dimethoxy-11b-methylbenzo[*a*]quinolizin-4-one (19).

In approaches to a synthesis of emetine,[1-8] which possesses important biological activity, numerous methods of synthesising benzo[*a*]quinolizines have been developed. Recently, the photocyclisation of *N*-aroyl-1,2,3,4-tetrahydro-1-methyleneisoquinolines was reported to be successful in the synthesis of dibenzo[*a*,*g*]quinolizine derivatives.[9,10] With the intention of studying the cyclisation of *N*-(α- or β-substituted acryloyl)-1,2,3,4-tetrahydro-1-methyleneisoquinolines to benzo[*a*]quinolizines, we heated 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (1) [11] with crotonic anhydride (2) in pyridine; the resulting crude material was purified by alumina column chromatography to afford three products. The main product (65% yield) was the desired enamide (3), identified by spectroscopic analysis. Irradiation of the enamide (3) in one of several solvents or treatment with any of several kinds of acid including a Lewis acid gave one of the minor products isolated originally, which was identified as *N*-(2-acetyl-4,5-dimethoxyphenethyl)crotonamide (4). Its mass spectrum showed a molecular ion peak at *m/e* 291 and its n.m.r. spectrum (deuteriochloroform) exhibited two *C*-methyl signals [δ 1.82 (dd, *J* 2 and 7 Hz) and 2.56 (s)] in addition to a signal for two *O*-methyl groups [δ 3.88 (s)]. Several attempts to cyclise the enamide (3) to a benzo[*a*]quinolizine (6) resulted in failure.

The other minor product, obtained in 17.5% yield from (1) showed a molecular ion peak at *m/e* 273, i.r. carbonyl absorption at 1 605 cm^{-1} (chloroform), and in the n.m.r. spectrum one *C*-methyl signal at δ 1.32 (d, *J* 6 Hz), two *O*-methyl signals at δ 3.85 and 3.89 (each s), and three olefinic proton signals at δ 5.55, 6.64, and 7.11. On the basis of the above spectral data, two possible structures, (5) and (6), were considered for the product. The compound was then hydrogenated over Adams catalyst and the resulting material was compared with the 2-methylbenzo[*a*]quinolizin-4-one (11), synthesised as follows. Heating 3,4-dimethoxyphenethylamine (7) with 3-methylglutaric acid (8) at 240 °C yielded the glutarimide (9) in 52% yield, which was reduced in ethanol with sodium borohydride in the presence of hydrochloric acid [12] to furnish the ethoxypiperidine (10) in 91% yield. Refluxing the amide (10) with toluene-*p*-sulphonic acid in benzene [12] provided a *ca.* 1 : 1 epimeric mixture of benzo[*a*]quinolizin-4-ones (11) in 94% yield. This sample of (11) was not identical with the foregoing reduction product (t.l.c. and spectral comparison), thus excluding structure (6). Reduction of (11) with lithium aluminium hydride followed by preparative t.l.c. gave two compounds (12) and (13) in 32 and 37% yield, respectively. Because both compounds showed Bohlmann-type i.r. absorptions at 2 800—2 700 cm^{-1} (chloroform) and no angular 11b-proton signal below δ 3.8 in their n.m.r. spectra (deuteriochloroform) [13,14] they are considered to exist in the *trans*-form. Compound (12) showed the *C*-methyl signal at δ 1.10 as a doublet, *J* 6 Hz, whereas compound (13) showed the corresponding signal at δ 1.02 as a doublet, *J* 5 Hz.

Compound (5) was dehydrogenated by refluxing with palladium oxide in xylene to give the dienone (15), M^+ 271, δ ($CDCl_3$) 2.39 (s, Me) and 6.24, 6.72, 6.73, and 7.17 (each 1H, s, olefinic), identical with material synthesised from 1,6,7,11b-tetrahydro-9,10-dimethoxy-4-methylbenzo[*a*]quinolizin-2-one (14)[15] by oxidation with potassium permanganate or palladium oxide. It was considered that compound (5) was formed *via* the enamine

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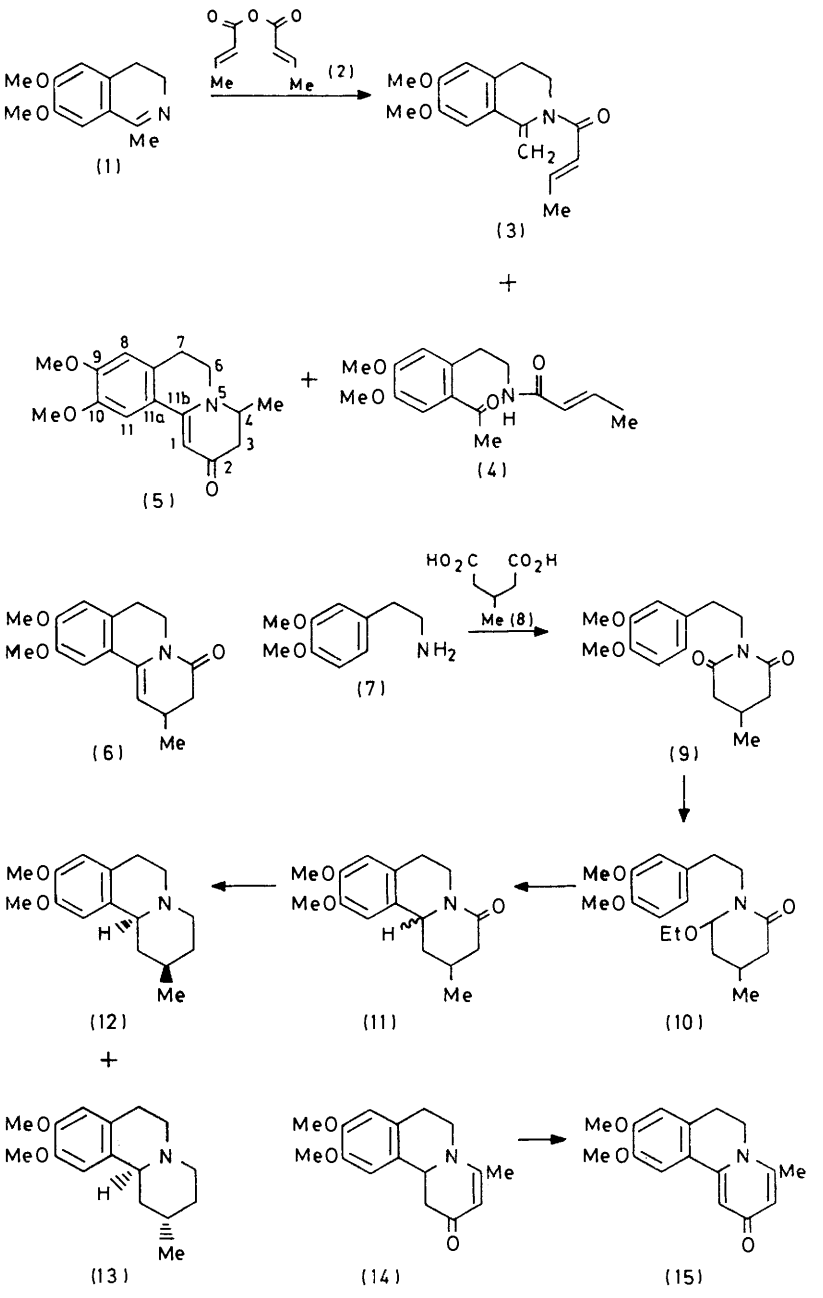
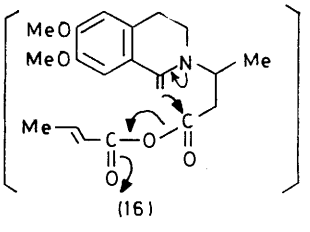


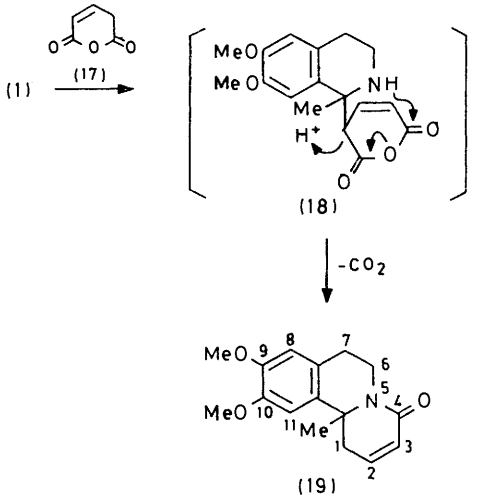
(16) produced by Michael addition of the 3,4-dihydro-1-methylisoquinoline (1) to crotonic anhydride (2).



(16)

Heating the 3,4-dihydro-1-methylisoquinoline (1) at 100 °C with glutaconic anhydride in pyridine followed by chromatography on alumina afforded, in 56% yield as the sole product, 1,6,7,11b-tetrahydro-9,10-dimethoxy-11b-methylbenzo[*a*]quinolizin-4-one (19). The mass spectrum showed the molecular ion peak at *m/e* 273 and the i.r. spectrum (chloroform) exhibited carbonyl absorption at 1 625 cm^{-1}. In the n.m.r. spectrum one *C*-methyl signal was observed at δ ($CDCl_3$) 1.69 (s), two *O*-methyl signals at 3.84 and 3.87, two aromatic proton signals at 6.57 and 6.72 (singlets), and resonances for two olefinic protons at 5.75 (dt, *J* 3.4 and 10 Hz) and 6.18 (d, *J* 10 Hz). Structure (19) was further supported by the ^{13}C n.m.r. spectrum (deuteriochloroform), which showed signals for sixteen carbon atoms, assigned by comparisons with models [14,16,17] and on the basis of splitting patterns in the off-resonance-decoupled spectrum: 11b-Me at δ

30.9, C(1) at 30.3 and/or 34.9, C(2) at 131.4, C(3) at 119.4, C(4) at 165.9, C(6) at 30.3 and/or 34.9, C(7) at 27.8, C(7a) at 125.8, C(8) at 110.8, C(9) and C(10) at 146.8, C(11) at 107.9, C(11a) at 131.4, C(11b) at 59.6, and two *O*-Me at 55.4 and 55.0. Compound (19) was presumably formed by nucleophilic attack of the methylene carbon of glutaconic anhydride at C-1 of the dihydroisoquinoline (1),[15] followed by cyclisation of the resulting anhydride (18) accompanied by decarboxylation.



EXPERIMENTAL

I.r. spectra were taken with a Hitachi EPI-3 recording spectrometer, n.m.r. spectra with a JEOL JNM-PMX-60 spectrometer, ^{13}C n.m.r. spectra with a JEOL JNM-PFT-100 system equipped with a JNM-PS-100 spectrometer, and mass spectra with a Hitachi RMU-7 spectrometer.

2-Crotonoyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3), *N-(2-Acetyl-4,5-dimethoxyphenethyl)crotonamide* (4), *and 3,4,6,7-Tetrahydro-9,10-dimethoxy-4-methylbenzo*[a]*quinolizin-2-one* (5).—To a solution of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (1) [11] (1.5 g) in pyridine (2 ml), crotonic anhydride (2) (1.2 g) was added, and the resulting mixture was heated on a water-bath for 2 h under nitrogen. After cooling, water (20 ml) was added and the solution was extracted with benzene. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a red syrup (2.2 g), which was chromatographed on neutral alumina (grade III). Elution with benzene afforded the *enamide* (3), which was recrystallised from n-hexane to give needles, m.p. 125°, $\nu_{max.}$ ($CHCl_3$) 1 655 and 1 605 cm^{-1}; δ ($CDCl_3$) 1.85 (3 H, d, *J* 6 Hz, Me), 2.83 (2 H, t, *J* 6.5 Hz, $ArCH_2$), 3.86 (3 H, s, OMe), 3.90 (3 H, s, OMe), 4.03 (2 H, t, *J* 6.5 Hz, $CH_2{\cdot}N$), 4.87 and 5.57 (each 1 H, each s, $=CH_2$), 6.25—7.20 (2 H, m, 2 × olefinic H), 6.56 (1 H, s, 5-H), and 7.09 (1 H, s, 8-H); *m/e* 273 (M^+) (Found: C, 70.1; H, 6.95; N, 5.0. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.15%). Further elution with benzene–methanol (99 : 1 v/v) gave the *amide* (4) (150 mg, 7%), which was recrystallised from benzene to afford needles, m.p. 146°, $\nu_{max.}$ ($CHCl_3$) 1 655, 1 625, and 1600 cm^{-1}; δ($CDCl_3$) 1.82 (3 H, dd, *J* 2 and 7 Hz, Me), 2.56 (3 H. s, Ac), 2.99 (2 H, t, *J* 6.5 Hz, $ArCH_2$), 3.50 (2 H, t, *J* 6.5 Hz, $CH_2{\cdot}N$), 3.88 (6 H, s, 2 × OMe), 5.75 (1 H, d, *J* 15 Hz, COCH=), 6.41 ~ 7.25 (1 H, m, COCH=C*H*), 6.73 (1 H, s, 5-H), and 7.14 (1 H, s, 8-H); *m/e* 291 (M^+) (Found: C, 65.7; H, 7.15; N, 4.7. $C_{16}H_{21}NO_4$ requires C, 65.95; H, 7.25; N, 4.8%). Further elution with benzene–methanol (98 : 2 v/v) gave the *benzo*[a]*quinolizine* (5) (350 mg, 17.5%), which was recrystallised from benzene to afford pale yellow needles, m.p. 156—157°, $\nu_{max.}$ ($CHCl_3$) 1 605 and 1 580 cm^{-1}; δ($CDCl_3$) 1.32 (3 H, d, *J* 6 Hz, Me), 2.05—3.80 (7 H, m), 3.85 (3 H, s, OMe), 3.89 (3 H, s, OMe), 5.55 (1 H, s, 1-H), 6.64 (1 H, s, 5-H), and 7.11 (1 H, s, 8-H); *m/e* 273 (M^+) (Found: C, 70.2; H, 6.9; N, 5.05. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.15%).

N-(3,4-Dimethoxyphenethyl)-3-methylglutarimide (9).—A mixture of 3,4-dimethoxyphenethylamine (7) (1.8 g) and 3-methylglutaric anhydride (8) (1.5 g) was heated at 240 °C until the formation of water had ceased. After cooling, the mixture was dissolved in chloroform, which was then washed with aqueous 5% sodium hydroxide and saturated aqueous sodium chloride solution, dried (Na_2SO_4), and evaporated. The resulting solid, after trituration with cold benzene, was crystallised from benzene–n-hexane to afford the glutarimide (9) (1.5 g, 52%) as scales, m.p. 123° (lit.,[18] 116.5—118°), $\nu_{max.}$ ($CHCl_3$) 1 715 and 1665 cm^{-1}; δ ($CDCl_3$) 1.05 (3 H, d, *J* 6 Hz, Me), 3.83 (3 H, s, OMe), 3.86 (3 H, s, OMe), and 6.73 (3 H, s, 3 × ArH).

N-(3,4-Dimethoxyphenethyl)-6-ethoxy-4-methyl-2-piperidone (10).—Sodium borohydride (250 mg) was added in small portions to a stirred solution of the glutarimide (9) (250 mg) in ethanol (25 ml) at —10 °C. At regular intervals (*ca.* 15 min), 2—3 drops of 4N-hydrochloric acid were added during 4 h, with stirring. The excess of sodium borohydride was decomposed by slow addition of hydrochloric acid to the cooled solution, until pH 3 was reached. The mixture was then stirred for an additional 45—60 min at 50 °C, neutralised with ethanolic 1% potassium hydroxide and evaporated. Extraction of the residue with chloroform, followed by evaporation, afforded the amide (10) (200 mg, 91%) as an oil, $\nu_{max.}$ ($CHCl_3$) 1 630 cm^{-1}; δ ($CDCl_3$) 0.83 (3 H, d, *J* 6 Hz, Me), 1.07 (3 H, t, *J* 7 Hz, CH_2Me), 4.13 (1 H, t, *J* 3 Hz, EtO·C*H*·N), and 6.62 (3 H, s, 3 × ArH), which was used without further purification.

1,2,3,6,7,11b-Hexahydro-9,10-dimethoxy-2-methylbenzo[a]*quinolizin-4-one*(11). —A solution of the amide (10) (200 mg) in benzene (50 ml) containing toluene-*p*-sulphonic acid (70 mg) was refluxed for 3 h. After cooling, the benzene layer was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to leave the product (11) as an oily mixture of epimers (160 mg, 94%) $\nu_{max.}$ ($CHCl_3$) 1 620 cm^{-1}; δ ($CDCl_3$) 1.11 (3 H, m, Me), 3.83 (6 H, s, 2 × OMe), 4.40—5.15 (2 H, m, 6- and 11b-H), 6.58 (1 H, s, ArH), and 6.63 (1 H, s, ArH), which was used without further purification.

1,3,4,6,7,11bα-Hexahydro-9,10-dimethoxy-2β-methyl-2H-benzo[a]*quinolizine* [*Racemate of* (12)] *and its 2α-Methyl Isomer* [*Racemate of* (13)].—To a suspension of lithium aluminium hydride (15 mg) in dry tetrahydrofuran (20 ml), a solution of compound (11) (100 mg) in dry tetrahydrofuran

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(10 ml) was added dropwise with stirring at room temperature. After stirring for further 0.5 h, the solution was refluxed for 3 h and the excess of lithium aluminium hydride was then decomposed by slow addition of aqueous 40% sodium hydroxide. The solution was evaporated to give an oil which was extracted with ether. The extract was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to leave an orange oil (80 mg), which was purified by a preparative t.l.c. on silica gel [benzene–ethyl acetate–methanol (5 : 5 : 2 v/v)] to afford the products (12) (30 mg, 32%), as an oil, $\nu_{max.}$ ($CHCl_3$) 2 800—2 700 and 1 600 cm^{-1}; δ($CDCl_3$) 1.10 (3 H, d, *J* 6 Hz, Me), 3.80 (6 H, s, 2 × OMe), 6.53 (1 H, s, ArH), and 6.62 (1 H, s, ArH); *m/e* 261 (M^+) [the *hydrochloride formed needles*, m.p. 215—216° (from ethanol–ether) (Found: C, 64.05; H, 8.15; N, 4.6. $C_{16}H_{24}ClNO_2$ requires C, 64.5; H, 8.1; N, 4.7%)], and (13) (35 mg, 37%), as an oil, $\nu_{max.}$ ($CHCl_3$) 2 800—2 700 and 1 600 cm^{-1}; δ ($CDCl_3$) 1.02 (3 H, d, *J* 5 Hz, Me), 3.82 (6 H, s, 2 × OMe), 6.55 (1 H, s, ArH), and 6.68 (1 H, s, ArH); *m/e* 261 (M^+) [the *hydrochloride* formed needles, m.p. 195—198° (from ethanol–ether) (Found: C, 63.45; H, 8.35; N, 4.45. $C_{16}H_{24}ClNO_2,0.25H_2O$ requires C, 63.55; H, 8.15; N, 4.65%)].

5,6-*Dihydro*-9,10-*dimethoxy*-4-*methylbenzo*[a]*quinolizin*-2-*one* (15).—(a) *Oxidation of compound* (14). (i) *With potassium permanganate*. A mixture of compound (14) (50 mg), potassium permanganate (29 mg), and acetone (10 ml) was stirred for 5 h at room temperature. Manganese dioxide was precipitated out and the solution became colourless. The mixture was filtered through Celite and evaporated to afford a powder (45 mg), which was recrystallised from acetone to give the *dienone* (15) (40 mg, 80%) as needles, m.p. 262°, $\nu_{max.}$ ($CHCl_3$) 1 630 and 1 610 cm^{-1}; δ ($CDCl_3$) 2.39 (3 H, s, Me), 2.98 (2 H, t, *J* 7 Hz, $ArCH_2$), 3.89 (3 H, s, OMe), 3.91 (3 H, s, OMe), 4.02 (2 H, t, *J* 7, CH_2·N), 6.24 (1 H, d, *J* 2.5 Hz, 1- or 3-H), 6.72 (1 H, s, 8-H), 6.73 (1 H, d, *J* 2.5 Hz, 1- or 3-H), and 7.17 (1 H, s, 11-H); *m/e* 271 (M^+) (Found: C, 70.45; H, 6.35; N, 5.1. $C_{16}H_{17}NO_3$ requires C, 70.85; H, 6.3; N, 5.15%).

(ii) *With palladium oxide*. A suspension of compound (14) (100 mg) and palladium oxide (100 mg) in xylene (10 ml) was refluxed for 20 h. After cooling, the mixture was filtered through Celite and evaporated to afford a powder (80 mg), which was recrystallised from acetone to give (15) (70 mg, 70%) as needles, m.p. 262°, the spectral data of which were identical with those of the above compound.

(b) *Dehydrogenation of compound* (5) *with palladium oxide*. A suspension of compound (5) (60 mg) and palladium oxide (80 mg) in xylene (5 ml) was refluxed for 24 h. After cooling, the mixture was filtered through Celite and evaporated to give a black oil (50 mg), which was purified by preparative t.l.c. on silica gel [benzene–ethyl acetate–methanol (5 : 5 : 2 v/v)]. A fraction of R_F 0.2 gave compound (15) (15 mg, 30%) as needles, m.p. 262°, with spectral data identical with those of the foregoing product.

1,6,7,11b-*Tetrahydro*-9,10-*dimethoxy*-11b-*methylbenzo*[a]-*quinolizin*-4-*one* (19).—A solution of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (1) (200 mg) and glutaconic anhydride (17) [19] (110 mg) in pyridine (2 ml) was heated on a water-bath for 3 h. After cooling, water (5 ml) was added to the resulting red solution, which was then extracted with ether. The extract was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give an orange oil (190 mg), which was chromatographed on neutral alumina (grade III). Elution with benzene afforded a solid which was recrystallised from n-hexane to give the product (19) (150 mg, 56%) as *needles*, m.p. 115°, $\nu_{max.}$ ($CHCl_3$) 1 625 cm^{-1}; δ ($CDCl_3$) 1.69 (3 H, s, Me), 2.36—3.43 (5 H, m, 1-H_2, 6-H, and 7-H_2), 3.84 (3 H, s, OMe), 3.87 (3 H, s, OMe), 4.93—5.25 (1 H, m, 6-H), 5.75 (1 H, dt, *J* 3.4 and 10 Hz, 2-H), 6.18 (1 H, d, *J* 10 Hz, 3-H), 6.57 (1 H, s, ArH), and 6.72 (1 H, s, ArH); *m/e* 273 (M^+) (Found: C, 70.1; H, 6.85; N, 4.9. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.15%).

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