Quinoline Alkaloids. Part 19.[1,2] Synthesis of *O*-Methylptelefolonium Iodide and (±)-Dubinidine

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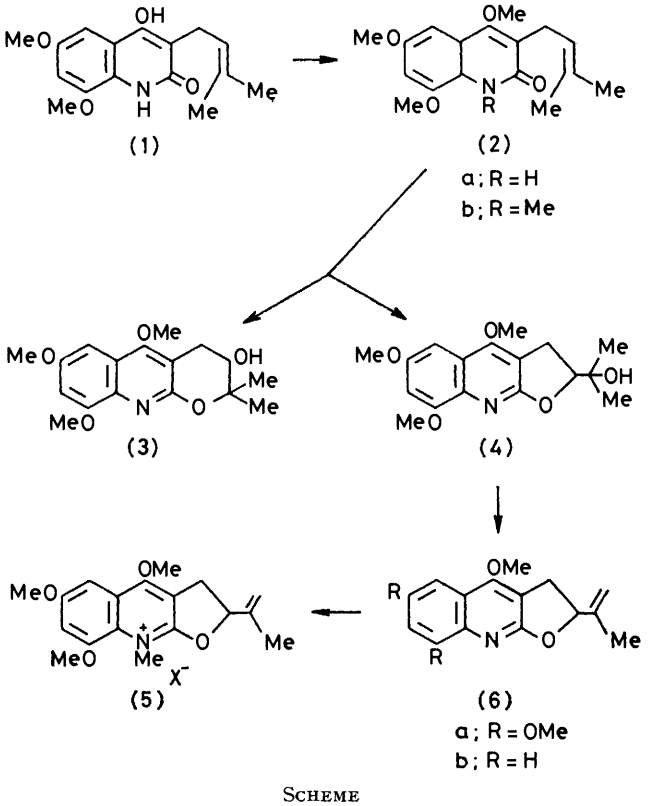
The terminal olefin, *O*-methylptelefolonium iodide (5; X = I), was synthesised from the hydroxyisopropyldihydrofuroquinoline (4) by successive dehydration and methylation. Dehydration of the tertiary alcohol (9a) with triphenyl phosphite dibromide and then hydroxylation furnished (±)-dubinidine (8).

OUR interest in the cyclisation of aromatic hemiterpenoids containing terminal epoxide groups required the synthesis of olefins from which the epoxides were derived.[3] Terminal olefins of this type are occasionally found as natural products, and we have now turned our attention to the synthesis of hemiterpenoid quinoline alkaloids of related structure.

An intensive study of the minor constituents of *Ptelea trifoliata*, mainly by Reisch and co-workers, resulted in the isolation of ten quinoline alkaloids with terminal double bonds in the prenyl side-chains,[4] *e.g.* *O*-methylptelefolonium cation (5) and ptelefolone (7). The structures of these alkaloids were established by spectroscopy, ^{1}H n.m.r. and mass spectroscopy proving to be particularly useful. Although little is known about the biosynthesis of terminal olefins in the aromatic hemiterpenoid group, plausible precursors are the corresponding tertiary alcohols. In preparation for future biosynthetic studies we were interested in exploring the synthesis of furoquinoline alkaloids by this probable biomimetic pathway and in this paper we describe the formation of *O*-methylptelefolonium iodide (5; X = I) from the hydroxyisopropyldihydrofuroquinoline (4) (Scheme).



SCHEME

RESULTS AND DISCUSSION

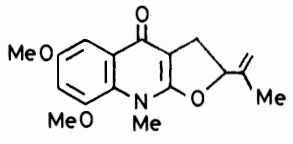
Reaction of 2,4-dimethoxyaniline with diethyl (3-methylbut-2-enyl)malonate in boiling diphenyl ether[5] and isolation of the acidic product gave the 4-hydroxy-2-quinolone (1) (20%). The structure was confirmed by i.r. and ^{1}H n.m.r. spectroscopy (see Experimental section). Brief treatment of the 4-hydroxy-2-quinolone in methanol with an ethereal solution of diazomethane, and chromatography of the non-acidic fraction, gave a monomethyl (37%) and a dimethyl derivative (23%). The monomethylation product showed $\nu_{max.}$ at 1 645 cm^{-1} (2-quinolone carbonyl) and was clearly the required 4-methoxy-2-quinolone (2a). The n.m.r. spectrum of the product of dimethylation showed that the prenyl group had been retained; the absence of carbonyl absorption in the i.r. spectrum indicated that the compound was 2,4,6,8-tetramethoxy-3-(3-methylbut-2-enyl)quinoline rather than the isomeric *N*-methyltrimethoxy-2-quinolone (2b). The starting 4-hydroxy-2-quinolone (1) (24%) was recovered from the alkaline solution.

Oxidation of the 4-methoxy-2-quinolone with *m*-chloroperoxybenzoic acid in chloroform at 0 °C and preparative t.l.c. of the resultant mixture gave two isomeric products in a ratio of *ca.* 7 : 5. By analogy with similar oxidations[5] the two compounds were the pyranoquinolone (3) and the furoquinoline (4) formed by spontaneous cyclisation of an intermediate epoxide. The isomers were distinguished by n.m.r. spectroscopy, the methine proton resonating at higher field in the pyrano-derivative, and *C*-methyl groups furnishing a singlet in the pyranoquinoline and separate signals in the furoquinoline. The major product was the pyranoquinoline (3) representing a reversal of the product ratios observed in earlier examples of the reaction.

Dehydration of the hydroxyisopropyldihydrofuroquinoline (4) was accomplished by reaction with thionyl chloride in pyridine at 0 °C; a single product was isolated as an oil, and although not fully characterised it was shown by its n.m.r. spectrum (see Experimental section) to be the terminal olefin (6a). Reaction with methyl iodide afforded crystalline (±)-*O*-methylptelefolonium iodide (5; X = I); the n.m.r. spectrum of the synthetic

compound corresponds to that reported for the alkaloid, isolated from *P. trifoliata* as the racemic chloride (5; X = Cl). In each case the mass spectrum accords with that expected for the dihydrofuroquinolone (7) formed from the quaternary salts by loss of methyl halide.

The optically active quinoline alkaloid, dubinidine, is a constituent of *Haplophyllum dubium*.[6] Several structures have been advanced for dubinidine, the latest and most likely [7] being the dihydroxyisopropyldihydrofuroquinoline (8) of unspecified stereochemistry. On this basis the alkaloid can be regarded as a derivative of the terminal olefin (6b) and we decided to study the preparation and hydroxylation of this compound in order to investigate the structure of dubinidine.



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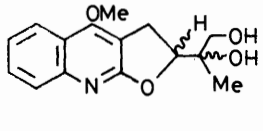

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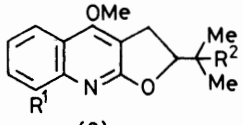

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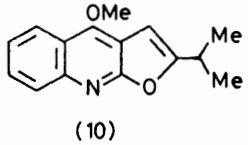

(10)

a ; R^1 = H, R^2 = OH
b ; R^1 = OMe, R^2 = OH
c ; R^1 = H, R^2 = Br

(±)-Platydesmine (9a) was the starting point of the synthesis. Terminal olefins have been prepared previously from tertiary alcohols related to platydesmine by a number of low-yield procedures,[8] but these methods were unsuccessful when applied to the hydroxyisopropyldihydrofuroquinoline (9b).[9] Alcohols are readily converted into bromides with triphenyl phosphite dibromide [10] and in an attempt to prepare the tertiary bromide (9c), platydesmine was refluxed with the reagent in the presence of potassium carbonate. Two products were isolated by chromatography. The minor component (23%) was shown by its n.m.r. spectrum (see Experimental section), and by comparison with a sample prepared by reaction of platydesmine with concentrated sulphuric acid, to be the isopropylfuroquinoline (10).[11] The second compound was the terminal olefin (6b) (48%); its structure was established by $\nu_{max.}$ at 908 cm^{-1} ($>C=CH_2$) and by the n.m.r. spectrum (see Experimental section) which was similar to that of compound (6a). Dehydration of alcohols by triphenyl phosphite dibromide apparently has not been observed previously; in this case the reaction occurs presumably by rapid dehydrobromination of the intermediate bromide (9c).

Reaction of the terminal olefin (6b) with osmium tetraoxide in dioxan afforded the diol (±)-dubinidine (8) (86% yield), with n.m.r. and mass spectra in agreement with the data recorded for the (−)-alkaloid; it appears from t.l.c. data that only a single diastereoisomer was obtained.

EXPERIMENTAL

N.m.r. spectra were determined with Perkin-Elmer R12 (60 MHz) or R32 (90 MHz) spectrometers using tetramethylsilane as an internal standard.

4-Hydroxy-6,8-dimethoxy-3-(3-methylbut-2-enyl)-2-quinolone (1).—2,3-Dimethoxyaniline (4.2 g) in diphenyl ether (40 ml) was added during 1 h to a refluxing solution of diethyl (3-methylbut-2-enyl)malonate (11.5 g) in diphenyl ether (90 ml) under nitrogen. After 4 h, the solution was filtered, the solvent was evaporated, and the chloroform-soluble residue was extracted with 2M-sodium carbonate. Acidification of the alkaline solution gave a precipitate of the *2-quinolone* (3.0 g, 20%) separating from aqueous ethanol in needles, m.p. 210—212 °C; $\nu_{max.}$ (KBr) 3 360 (OH); τ [$(CD_3)_2SO$] 2.85 (1 H, d, 5-H), 3.29 (1 H, d, 7-H), 4.8 (1 H, t, C*H*=CMe_2), 6.1 (3 H, s, OMe), 6.2 (3 H, s, OMe), 6.7 (2 H, d, CH_2–CH=), 8.25 (3 H, s), and 8.35 (3 H, s, 2 × Me); *m/e* 288 (M^+) (Found: C, 65.8; H, 7.1; N, 4.4. $C_{16}H_{19}NO_4$ requires C, 66.4; H, 6.6; N, 4.8%).

4,6,8-Trimethoxy-3-(3-methylbut-2-enyl)-2-quinolone (2a).—An excess of diazomethane in ether was added to a solution of the 4-hydroxy-2-quinolone (1) (5 g) in methanol (90 ml). After 5 min, the excess of diazomethane was destroyed with acetic acid, the solvent was evaporated, and the residue was treated with 2M-sodium carbonate and ether. The ether solution was evaporated and the residue was chromatographed on alumina. Elution with ether–chloroform (3 : 1) gave *2,4,6,8-tetramethoxy-3-(3-methylbut-2-enyl)-quinoline* as an oil (1.1 g, 23%); τ ($CDCl_3$) 3.14 (1 H, d) and 3.32 (1 H, d) (2 × Ar-H), 4.75 (1 H, t, C*H*=CMe_2), 5.9 (3 H, s), 6.0 (3 H, s), 6.09 (3 H, s), and 6.1 (3 H, s) (4 × OMe), 6.55 (2 H, d, CH_2–CH=), and 8.05 (3 H, s) and 8.15 (3 H, s) (2 × Me); *m/e* 317 (M^+). Further elution with the same solvent gave *4,6,8-trimethoxy-3-(3-methylbut-2-enyl)-2-quinolone* (1.7 g, 37%), separating from ethyl acetate in prisms, m.p. 132—133 °C; $\nu_{max.}$ 1 645 cm^{-1} (2-quinolone CO); τ ($CDCl_3$) 3.32 (1 H, d) and 3.5 (1 H, d) (2 × Ar-H), 4.72 (1 H, t, C*H*=CMe_2), 6.13 (6 H, s, 2 × OMe), 6.2 (3 H, s, OMe), 6.63 (2 H, CH_2=CH), and 8.21 (3 H, s) and 8.31 (3 H, s) (2 × Me); *m/e* 303 (M^+) (Found: C, 67.3; H, 7.4; N, 4.8. $C_{17}H_{21}NO_4$ requires C, 67.3; H, 7.0; N, 4.6%).

Acidification of the sodium carbonate solution with dilute hydrochloric acid gave the starting 4-hydroxy-2-quinolone (1) (1.2 g, 24%).

Oxidation of 4,6,8-Trimethoxy-3-(3-methylbut-2-enyl)-2-quinolone.—A solution of the 2-quinolone (2a) (100 mg) and *m*-chloroperoxybenzoic acid (120 mg) in ethanol-free chloroform (20 ml) was kept at 0 °C for 4 days, extracted with 2M-sodium hydroxide, and then evaporated. Preparative t.l.c. on silica with ether–chloroform (4 : 1) gave *3,4-dihydro-3-hydroxy-5,7,9-trimethoxy-2,2-dimethyl-2H-pyrano[2,3-b]-quinoline* (3) (prisms from ethanol–di-isopropyl ether) (35 mg), m.p. 180—183 °C, R_F 0.2; τ ($CDCl_3$) 3.26 (1 H, d) and 3.30 (1 H, d) (2 × Ar-H), 6.03 (7 H, m, 2 × OMe and C*H*), 6.12 (3 H, s, OMe), 6.91 (2 H, m, CH_2), and 8.58 (6 H, s, 2 × Me); *m/e* 319 (M^+) (Found: C, 64.2; H, 7.1. $C_{17}H_{22}NO_5$ requires C, 63.7; H, 6.9%): then *2,3-dihydro-2-(1-hydroxyisopropyl)-4,6,8-trimethoxyfuro[2,3-b]quinoline* (4) as an oil (24 mg), R_F 0.1; τ ($CDCl_3$) 3.1 (1 H, d) and 3.37 (1 H, d) (2 × Ar-H), 5.41 (1 H, t, $CH_2CH<$), 5.8 (3 H, s), 6.05 (3 H, s), and 6.14 (3 H, s) (3 × OMe), 6.45 (2 H, d, CH_2–CH), and 8.65 and 8.75 (6 H, 2 × Me).

O-Methylptelefolonium Iodide (5; X = I).—Thionyl chloride (0.13 ml) was added to a solution of the furoquinoline (4) (90 mg) in pyridine (0.2 ml) at 0 °C. After 1 h,

water was added and the product was obtained by addition of chloroform. Preparative t.l.c. on silica with ether–chloroform (4 : 1) gave the terminal olefin (6a) as an oil (20 mg), R_F 0.6; τ ($CDCl_3$) 3.07 (1 H, d) and 3.35 (1 H, d) (2 × Ar-H), 4.85 (1 H, t, CH_2–C*H*<), 4.85 (1 H, s) and 5.08 (1 H, s) (=CH_2), 5.82 (3 H, s), 6.05 (3 H, s), and 6.13 (3 H, s) (3 × OMe), 6.30 (1 H, d) and 6.55 (1 H, d) (*C*H_2–CH<), and 8.2 (3 H, s, Me).

A solution of the olefin (6a) in methyl iodide was kept for 12 h and evaporated. Crystallisation of the residue from methanol–ether gave the *iodide* (5; X = I) as prisms, m.p. 120—121 °C; τ ($CDCl_3$) (90 MHz) 2.8 (1 H, d) and 3.13 (1 H, d) (2 × Ar-H), 4.0 (1 H, t, CH_2–C*H*<), 4.76 (1 H, s) and 4.90 (1 H, s) (=CH_2), 5.44 (3 H, s, $^+$NMe), 5.72 (3 H, s), 6.03 (3 H, s), and 6.10 (3 H, s) (3 × OMe) and 8.12 (3 H, s, Me); *m/e* 301 (87, M^+ − MeI) and 286 (100) (Found: C, 48.5; H, 5.1; N, 3.6. $C_{18}H_{22}INO_4$ requires C, 48.7; H, 5.0; N, 3.2%).

Dehydration of (±)-*Platydesmine* (9a).—Triphenyl phosphite dibromide was prepared from triphenyl phosphite (1.10 ml) and bromine (0.20 ml) in di-isopropyl ether (40 ml).[10] Potassium carbonate (3 g) was added and then (±)-platydesmine (0.5 g) with vigorous stirring. After the mixture had been refluxed for 30 min, water was added and the product was obtained by addition of ether as an oil, which was chromatographed on alumina. Elution with pentane–ether (4 : 1) gave the isopropylfuroquinoline (10) (107 mg, 23%), R_F 0.67, as needles [from ether–light petroleum (b.p. 40—60 °C)], m.p. 106 °C, identical with a sample, m.p. 106—108 °C (lit.,[11] m.p. 107—108 °C) prepared by reaction of (±)-platydesmine with concentrated sulphuric acid. Elution with pentane–ether (3 : 1) gave the *olefin* (6b) (223 mg, 48%), R_F 0.56, crystallising from pentane–ether as prisms, m.p. 76—77 °C; $\nu_{max.}$ (liquid) 908 cm^{-1} (>C=CH_2); τ ($CDCl_3$) 1.9—2.9 (4 H, m, Ar-H), 4.82 (1 H, t, *J* 8.5 Hz, >C*H*–CH_2), 4.85 (1 H, s) and 5.06 (1 H, s) (=CH_2, H_{cisoid} and $H_{transoid}$, respectively), 5.88 (3 H, s, OMe), 6.40 (1 H, d) and 6.58 (1 H, d) [½(J_{AX} + J_{BX}) 8.5 Hz, >CH–C*H*$_2$], and 8.25 [3 H, s, =C(*Me*)–]; *m/e* Found: M^+ = 241.110 2, $C_{12}H_{15}NO_2$ requires *M*, 241.110 3.

(±)-*Dubinidine* (8)—Osmium tetraoxide (80 mg) in dioxan (3 ml) was added to the terminal olefin (6b) (54 mg) in dioxan (5 ml), and after 3.5 days hydrogen sulphide was bubbled through the mixture. The product, obtained by filtration and evaporation of the filtrate, was chromatographed on alumina. Elution with ether gave unchanged olefin (21 mg) and elution with ethyl acetate gave (±)-dubinidine (30 mg), R_F 0.14, separating from chloroform–ether in needles, m.p. 214—216 °C; $\nu_{max.}$ (KBr) 3 500 (OH); τ ($CDCl_3$) 1.88—3.03 (4 H, m, Ar-H), 5.21 (1 H, m, $ArCH_2$–C*H*–O–), 5.80 (3 H, s, OMe), 6.30 (2 H, m, $ArCH_2$C*H*<), and 8.79 (3 H, s, *Me*–C(OH)–) (Found: M^+, 275.115 74; $C_{15}H_{17}NO_4$ requires *M*, 275.115 74; $M - C_3H_7O_2$ 200.071 14; $C_{12}H_{10}NO_2$ requires *M*, 200.071 14.

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