Quinoline Alkaloids. Part 22.[1] Synthesis of the Monoterpenoid Quinoline Alkaloid, Bucharaine

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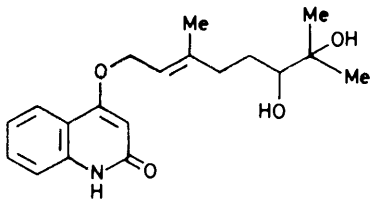
Reaction of 4-hydroxy-2-quinolone with geranyl chloride gave the geranyl ether (5a), the *C*-geranyl derivatives (6) and (7), and the vinylhexenyl derivative (8). The geranyl ether was converted into bucharaine (1) by selective hydroxylation and *via* mono-epoxidation.

THE *Haplophyllum* species growing in Central Asia have been shown by Yunusov and his co-workers to contain a variety of hemiterpenoid quinoline alkaloids typical of other rutaceous plants.[2] *Haplophyllum bucharicum*, however, is unique in producing the first examples of monoterpenoid quinoline alkaloids; three compounds were isolated, bucharaine, bucharidine, and bucharamine, for which structures (1), (2), and (3), respectively, were proposed.[2] We decided to establish the structures by synthesis and to study the reactions of the alkaloids; the synthesis of bucharaine is described here.

Bucharaine was first isolated in 1968 and after identification of functional groups, catalytic hydrogenation was shown to give 4-hydroxy-2-quinolone and a saturated diol, $C_{10}H_{22}O_2$. An earlier structure (4) for bucharaine was assigned on the basis of ozonolysis to a carboxylic acid and acetaldehyde and the observation in the ^{1}H n.m.r. spectrum of a doublet at τ 5.4 and a quartet at 6.41 attributed to the group $ArOCH_2CH(OH)$.[3] The revised structure (1) was suggested, mainly as a result of cleavage of the alkaloid with periodate and of mass spectral studies, which indicated that Claisen and abnormal Claisen rearrangement products were formed under electron impact.[4] Structure (1) is more acceptable for a number of reasons. Thus, the hydrogenation of the alkaloid can be reasonably interpreted as proceeding through allylic hydrogenolysis and subsequent reduction of the C_{10} fragment and, in contrast to earlier structures, a logical biosynthetic pathway from 4-hydroxy-2-quinolone and geranyl pyrophosphate can be perceived. On the other hand, the formation of acetaldehyde in the ozonolysis of bucharaine is difficult to explain. Although it contains a chiral centre, the alkaloid was apparently isolated as a racemate.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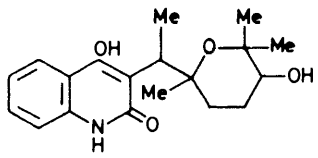
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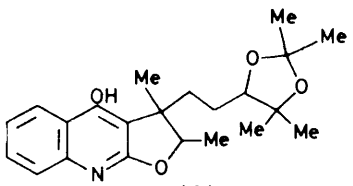
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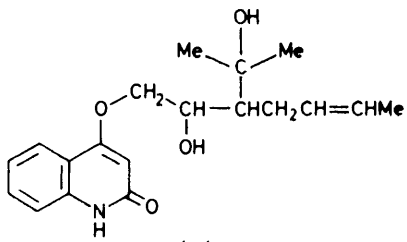
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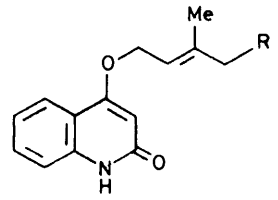
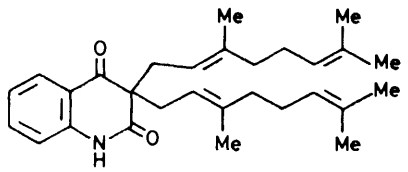
RESULTS AND DISCUSSION

We decided to synthesise the diol (1) from the geranyl ether (5a). The latter compound was prepared from 4-hydroxy-2-quinolone and geranyl chloride by prolonged reflux of the reactants in acetone with potassium carbonate. A complex mixture of products was obtained, but the geranyl ether was conveniently isolated from the non-acidic fraction (12% yield) by means of its sparing solubility in light petroleum. The structure of the compound was established by i.r. absorption at 1 645 cm^{-1} (2-quinolone carbonyl) and by the n.m.r. spectrum; the latter showed a one-proton singlet at τ 3.95 (H-3), a two-proton doublet at 5.30 ($ArO-CH_2-CH=$), and olefinic resonances at 4.40 and 4.85 characteristic of groups $ArOCH_2CH=$ and $-CH_2CH=CMe_2$, respectively. A second non-acidic product was shown to be the 3,3-bisgeranyl keto-lactam (6) (7% yield). Thus, the presence of two carbonyl groups was indicated by i.r. absorption at 1 710 (ketone carbonyl)

and 1 660 cm^{-1} (2-carbonyl), and in the n.m.r. spectrum the doublet at τ 7.25 ($-CH_2-CH=$) showed that the two geranyl groups were attached to an sp^3 carbon atom. A molecular-ion peak at *m/e* 433 was observed in the mass spectrum, and major fragmentation peaks at 296 and 228



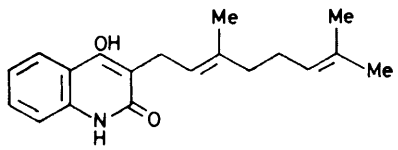
(5) a; R = $CH_2CH=CMe_2$
b; R = $CH_2CH(O)CMe_2$
c; R = $CH_2CHC(OH)Me_2$, O_2CH



(6)

indicated that loss of one geranyl group was followed by allylic cleavage of the other.

Several acidic products were formed in the reaction of 2,4-dihydroxyquinoline with geranyl chloride, and two have been identified as 4-hydroxy-2-quinolones. One is the 3-geranyl derivative (7); the structure of the side-chain is apparent from the n.m.r. spectrum (see Experimental section) and in the mass-spectral fragmentation peaks at $M^+ - C_5H_9$ and $M^+ - C_9H_{15}$ arise from expected allylic and benzylic fission, respectively. A second 4-hydroxy-2-quinolone was shown by n.m.r. spectroscopy to have a side-chain containing four olefinic protons and no methylene or methine group at C-3; resonances at τ 3.30 (1H) and at 4.45 (2 H) indicated that a mono-substituted vinyl group was present and a triplet at τ 4.95 was attributed to the group $-CH_2CH=CMe_2$. Structure (8) was supported by the mass spectrum in which the base peak at *m/e* 214 is apparently due to loss of a C_6H_{11} fragment through benzylic fission. The product appears to originate either by *C*-allylic substitution at the requisite tertiary centre of geranyl chloride, or by Claisen rearrangement of the geranyl ether (5a).



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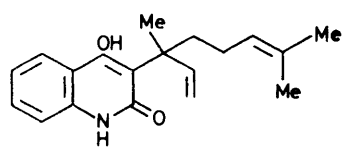

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Reaction of the geranyl ether (5a) with *m*-chloroperbenzoic acid in chloroform resulted in selective epoxidation of the more nucleophilic double bond to give epoxide (5b). The retention of the allylic ether function in this compound was indicated by n.m.r. resonances at τ 5.30 and 4.35; a one-proton triplet at τ 7.25 was attributed to the CH group of the oxiran ring. Treatment of epoxide (5b) with formic acid gave the formate ester (5c), which was hydrolysed by methanolic potassium hydroxide to the diol, bucharaine (1); the three-stage synthesis of the alkaloid from the geranyl ether (5a) occurred in an overall yield of 60%. Bucharaine was also obtained, although less efficiently, by reaction of the geranyl ether (5a) with osmium tetraoxide in pyridine–ether. The m.p. of the synthetic compound is almost the same as that reported for the alkaloid.[3] The structure was confirmed by the n.m.r. spectrum [and its comparison with those of compounds (5a), (5b), and (5c)] (see Experimental section) and by the mass spectrum, which corresponds with that recorded for the alkaloid.

EXPERIMENTAL

N.m.r. spectra were determined with a Perkin-Elmer R32 (90 MHz) spectrometer (tetramethylsilane as an internal standard), mass spectra with an AEI MS9 instrument, and i.r. spectra with a Perkin-Elmer 457 spectrometer.

Reaction of 4-Hydroxy-2-quinolone with Geranyl Chloride.—4-Hydroxy-2-quinolone (22 g) and anhydrous potassium carbonate (35 g) in dry acetone (500 ml) were stirred under reflux for 1 h. Geranyl chloride (25 g) in acetone (100 ml) was added, refluxing was continued for 10 days, and 4-hydroxy-2-quinolone (6.0 g) was obtained from the precipitate. The acetone solution was evaporated and the residue in ether (1.5 l) was extracted with 2N-sodium hydroxide and evaporated. Trituration with light petroleum (b.p. 40—60 °C) gave 4-(3,7-*dimethylocta*-2,6-*dienyloxy*)-2-*quinolone* (5a) (3.4 g), m.p. 94 °C [needles from ether–light petroleum (b.p. 40—60 °C)]; $\nu_{max.}$ (Nujol) 1 645 cm^{-1}; τ($CDCl_3$) −2.25 (1 H, s, NH), 2.13 (1 H, d, 5-H), 2.40—3.00 (3 H, Ar-H), 3.95 (1 H, s, 3-H), 4.40 (1 H, t, $-OCH_2CH=$), 4.85 (1 H, t, $CH_2CH_2CH=$), 5.30 (2 H, d, $-OCH_2CH=$), and 7.70—8.45 (13 H, m) (Found: C, 76.5; H, 7.5; N, 4.6. C_{19}-

$H_{23}NO_3$ requires C, 76.8; H, 7.7; N, 4.7%). Chromatography of the fraction soluble in light petroleum on silica and elution with chloroform gave the *3,3-bisgeranyl-2-quinolone* (6) as a gum (3.0 g); $\nu_{max.}$ ($CHCl_3$) 3 380, 1 710, and 1 660 cm^{-1}; τ($CDCl_3$) −0.18 (1 H, s, NH), 2.18 (1 H, d, 5-H), 2.40—3.18 (3 H, m, Ar-H), 5.05 (4 H, br t, $-CH_2CH=$), 7.25 (4 H, d, $-CH_2CH=$), and 8.0—8.6 (26 H, m); *m/e* 433.296 3 (M^+, 8%. $C_{29}H_{39}NO_2$ requires *M*, 433.298 1), 296 (93), 228 (86), and 174 (84).

Acidification of the alkaline solution, extraction with chloroform, and preparative t.l.c. of the chloroform extract on silica with chloroform–methanol (96 : 4) gave *3-(3,7-dimethylocta-2,6-dienyl)-4-hydroxy-2-quinolone* (7) as a gum (0.3 g), R_F 0.30; $\nu_{max.}$ 3 380, and 1 640 cm^{-1}; τ($CDCl_3$), 2.10 (1 H, d, 5-H), 2.40—2.95 (3 H, m, ArH), 4.60 (1 H, t, $ArCH_2CH=$), 4.95 (1 H, t, $-CH_2CH_2CH=$), 6.45 (2 H, d, $ArCH_2CH=$), and 7.90—8.65 (13 H, m); *m/e* 297.172 1 (M^+, 12%. $C_{19}H_{23}NO_2$ requires *M*, 297.172 9), 228 (48), 212 (70), 174 (42), and 149 (100); *3-(1,5-dimethyl-1-vinylhex-4$_F$-enyl)-4-hydroxy-2-quinolone* (8) as a gum (0.08 g), R_F 0.55; $\nu_{max.}$ 3 380 and 1 640 cm^{-1}; τ($CDCl_3$) −2.60 (1 H, s, NH), −1.55 (1 H, s, OH), 2.10 (1 H, d, 5-H), 2.40—3.00 (3 H, m, Ar-H), 3.30 (1 H, q, $MeCCH=CH_2$), 4.45 (2 H, t, $-CH=CH_2$), 4.95 (1 H, t, $-CH_2CH=$), and 7.80—8.00 (13 H, m); *m/e* 297.173 1 (M^+, 37%. $C_{19}H_{23}NO_2$ requires *M*, 297.172 9), 282 (M − Me, 5), 228 (M − C_5H_9, 45), and 214 (M − C_6H_{11}, 100).

Epoxide (5b).—The geranyl ether (5a) (1.2 g) and *m*-chloroperbenzoic acid (1 g) in chloroform (100 ml) were stirred at ambient temperature for 5 days. After washing with aqueous sodium hydrogencarbonate, the chloroform solution was evaporated. Trituration of the residue with pentane and crystallisation from ether–light petroleum (b.p. 40—60 °C) gave *epoxide* (5b) as prisms (1.2 g), m.p. 106 °C; $\nu_{max.}$ 1 650 cm^{-1}; τ($CDCl_3$) −2.20 (1 H, s, NH), 2.10 (1 H, d, 5-H), 2.45—3.05 (3 H, m, Ar-H), 3.95 (1 H, s, 3-H), 4.35 (1 H, t, $-OCH_2CH=$), 5.30 (2 H, d, $-OCH_2CH=$), 7.25 (1 H, t, CH of oxiran ring), 7.85 (2 H, m, $-CH_2CH_2$-oxiran), 8.27 (5 H, m, $-CH=CMeCH_2$), and 8.70 (3 H, s) and 8.73 (3 H, s Me_2 of oxiran ring) (Found: C, 73.0; H, 7.2; N, 4.1. $C_{19}H_{23}NO_3$ requires C, 72.8; H, 7.4; N, 4.5%).

Formate (5c).—Epoxide (5b) (1.2 g) in formic acid (30 ml) was kept at ambient temperature for 24 h and diluted with chloroform. The solution was washed with aqueous sodium hydrogencarbonate and evaporated. Crystallisation of the residue from ether–light petroleum (b.p. 40—60 °C) gave the *formate* as needles (1.0 g), m.p. 157—158 °C; $\nu_{max.}$ (Nujol) 3 330 (OH), 1 715 (OCHO), and 1 635 cm^{-1} (2-quinolone); τ($CDCl_3$) −2.40 (1 H, s, NH), 1.90 (1 H, s, CHO), 2.05 (1 H, d, 5-H), 2.35—3.00 (3 H, m, Ar-H), 3.95 (1 H, s, 3-H), 4.40 (1 H, t, $-OCH_2CH=$), 5.12 (1 H, t, $-CH_2CH-OCO-$), 5.28 (2 H, d, $-OCH_2CH=$), 7.70—8.50 (7 H, m, Me and 2 × CH_2), and 8.78 [6 H, s, $-C(OH)Me_2$] (Found: C, 67.1; H, 7.1; N, 4.1. $C_{20}H_{25}NO_5$ requires C, 66.9; H, 7.0; N, 3.9%).

Bucharaine (1).—(*a*) 5% Aqueous potassium hydroxide (40 ml) was added to the formate (5c) (1 g) in methanol and the mixture was stirred at ambient temperature for 6 h. Evaporation of methanol, neutralisation of the solution with hydrochloric acid, extraction with ethyl acetate, and crystallisation of the product from methanol–ether gave bucharaine as prisms (0.8 g), m.p. 150 °C (lit.,[3] m.p. 151—152 °C); $\nu_{max.}$ (Nujol) 3 290 (OH) and 1 640 cm^{-1} (2-quinolone); τ(CD_3OD) 2.05 (1 H, d, 5-H), 2.30—2.95 (3 H, m, Ar-H), 4.05 (1 H, s, 3-H), 4.35 (1 H, t, $-OCH_2CH=$), 5.25 (2 H, d, $-OCH_2CH=$), 6.25 (2 H, br s, 2 × OH), 6.68 [1 H, t, $-CH_2CH(OH)-$], 7.80 [2 H, t, $-CH_2CH(OH)-$], 8.20 (2 H, t, $-CH_2CH_2CMe=$), 8.20 (3 H, s, $CH_2CMe=$), and 8.80 [6 H, s, $-C(OH)Me_2$]; *m/e* 331.178 7 (M^+, 13%. $C_{19}H_{25}O_4N$ requires *M* 331.178 3), 316 (M^+ − Me, 23), 314 (M^+ − OH, 5), 313 (M^+ − H_2O, 16), 272 (M^+ − C_3H_7O, 59), 242 (M^+ − $C_4H_9O_2$, 13), 214 (M^+ − $C_6H_{13}O_2$, 69), 215 (31), 189 (55), 188 (37), 162 (27), 161 (14), and 143 (100) (lit.,[4] *m/e* 331, 316, 272, 215, 214, 189, 162, 161, and 143) (Found: C, 68.6; H, 7.6; N, 4.7. Calc. for $C_{19}H_{25}NO_4$: C, 68.9; H, 7.6; N, 4.2%).

(*b*) Osmium tetraoxide (1 g) in dry ether (25 ml) was added to a solution of the geranyl ether (5a) (1.2 g) in pyridine (3.2 g) and ether (25 ml), the mixture was stirred for 24 h, sodium hydrogensulphite (2.5 g) in water (50 ml) and pyridine (50 ml) was added, and stirring was continued for 5 min. The product was recovered with ethyl acetate, and crystallisation from methanol–ether gave bucharaine (0.60 g), m.p. and mixed m.p. 150 °C.

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