SYNTHESIS OF QUINOLINE ALKALOIDS AND RELATED COMPOUNDS†. SYNTHESIS OF ZANTHOPHYLLINE AND A NEW SYNTHESIS OF 3,3-BIS(γ,γ-DIMETHYLALLYL)-N-METHYL-2,4-DIOXO-1,2,3,4-TETRAHYDROQUINOLINE

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Abstract - The alkaloid zanthophylline (I) was synthesized from the 8-methoxyflindersine (III) by N-alkylation with chloromethyl-acetate. The 3,3-bis(γ,γ-dimethylallyl)-N-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (II) was also synthesized by direct methylation of (V).

In connection of our synthetic study on the quinoline alkaloids occurring in plants of Rutaceae family, we wish to report the synthesis of zanthophylline (I) and a new synthesis of 3,3-bis-(γ,γ-dimethylallyl)-N-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (II). The alkaloid zanthophylline isolated from Zanthophyllum monophyllum and shown to have the structure of 1-acethoxymethyl-8-methoxyflindersine (I) by Stermitz and Shariji[1] contains the rare N-CH_2OCOCH_3 grupping; it is the second time that this functionality has been discovered in a natural product[2].

As no synthetic work was mentioned, we now report a one-step synthesis of (I) by alkylation with chloromethyl acetate at the nitrogen atom of 8-methoxyflindersine (III), a new alkaloid which occurs in Myrtopsis macrocarpa[3].

The starting 8-methoxyflindersine (III), m.p. 176-177°, was readly prepared in high yield by cyclodehydrogenation of the (3-γ,γ-dimethylallyl)-4-hydroxy-8-methoxy-2-quinolone[4] (IV) with DDQ, following the synthesis of flindersine[5] and haplamine[6] to give the compound (III) identical (UV, IR, NMR) to the natural[3] product previously obtained[7].

A solution of 8-methoxyflindersine (III) (200 mg) in dry THF (30 ml) was treated with sodium hydride (500 mg) and refluxed for 2 hr under nitrogen. The flask was cooled into ice-water and then redistilled chloromethyl acetate[8] (3 ml) in THF (5 ml) was added. Stirring was continued for another 12 hr and then the mixture was poured into water, and extracted with ether. The organic layer was washed with water, dried over sodium sulphate and evaporated to give a raw

product, which was isolated by preparative TLC using cyclohexane-ethyl acetate (3:7) as a solvent, into 1-acethoxymethyl-8-methoxyflindersine (zanthophylline) (I) and unreacted 8-methoxyflindersine (III).

The product (I) was obtained as crystals, m.p. 128-130° (from AcOEt) (lit. 126-127°[1]) m/z 329 (M^+), UV (EtOH)λ_{max} 220, 245, 251 (sh), 322, 337, 348, 368; NMR (FT 80 Varian, $CDCl_3$): δ 1.51 (6H, s, $2xCH_3$); 2.08 (3H, s, $-O-COCH_3$); 3.94 (3H, s, $-OCH_3$); 5.30 and 6.80 (2H, d, J=10.0 Hz, H-3 and H-4); 6.70 (2H, s, $-N-CH_2-O-$); 6.97-7.50 (3H, m, aromatic).

This synthesis confirms the proposed structure of natural zanthophylline. Recently the 3,3-bis-(γ,γ-dimethylallyl)-N-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (II) has been isolated as an alkaloid from Esembeckia flava[9] but one multistep synthesis was described[10]. We now report a new and simple synthesis by direct methylation of 3,3-bis(γ,γ-dimethylallyl)-2,4-dioxo-1,2,3,4-tetrahydroquinoline (V) obtained by prenylation at C-3 of 3-(γ,γ-dimethylallyl)-4-hydroxy-2-quinolone[11].

The product (V) (150 mg) was dissolved in acetone (50 ml) with methyl iodide (4 ml) and anhydrous potassium carbonate (6 g) and refluxed 20 hr (monitored TLC). The mixture was filtered and the filtrate evaporated; the residue was dissolved *in ethyl ether and washed with water.* Evaporation gave 140 mg of (II), as an oil; m/z 311 (M^+), UV (EtOH)λ_{max} 235, 260 (sh), 340 nm; NMR (FT 80 Varian, $CDCl_3$): δ 1.48 and 1.55 (12H, 2s, $4xCH_3$); 2.72 (4H, d, J=8.0 Hz, $2xCH_2-CH=$); 3.46 (3H, s, $-NCH_3$); 4.88 (2H, t, J=8.0 Hz, $2xCH_2-CH=$); 6.90-8.20 (4H, m, aromatic). The above data were identical with those reported[9,10] for (II). To our knowledge, the alkaloid (II) is the first example occurring in nature.

We have then extended our investigation to the synthesis of (II) analogues by bis-prenylation at C-3 of 4-hydroxy-6-methoxy-2-quinolone[6] (VI), 4-hydroxy-8-methoxy-2-quinolone[12] (VII) and 4-hydroxy-6,8-dimethoxy-2-quinolone[13] (VIII), followed by methylation.

The 3,3-bis-(γ,γ-dimethylallyl)-6-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinoline (IX) was previously[6] prepared. As for (II), it gave the compound (X) by N-methylation.

The compound (X) is an oil, m/z 341 (M^+), UV (EtOH)λ_{max} 220, 268 (sh), 372, 383 (sh) nm; NMR (FT 80 Varian, $CDCl_3$): δ 1.50 and 1.56 (12H, s, $4xCH_3$); 2.70 (4H, d, J=7.0 Hz, $2xCH_2-CH=$); 3.42 (3H, s, $-NCH_3$); 3.84 (3H, s, $-OCH_3$); 4.86 (2H, t, J=7.0 Hz, $2xCH_2-CH=$); 7.10 (1H, d, J=9.0 Hz, J=3.0 Hz, H-7); 7.26 (1H, d, J=9.0 Hz, H-8); 7.50 (1H, d, J=3.0 Hz, H-5).

The reaction of 4-hydroxy-8-methoxy-2-quinolone (VII) in dry acetone was performed as reported[6] for (VI). The crude mixture was chromatographed on dry silica gel column using as solvents: *cyclohexane-ethyl acetate (3:1) and (1:3),*

and ethyl-acetate-methanol (99:1); yielding the following four products in order of elution.

The first product has the structure of 3,3-bis(γ,γ-dimethylallyl)-8-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinoline (XI) (Rf = 0.80, silica gel Merck, F_{254}, cyclohexane-ethyl-acetate (3:7), yield 35%. m/z 327 (M^+) for $C_{20}H_{25}NO_3$, m.p. 118-120° (from ethyl ether); UV (EtOH)λ_{max} 236, 281, 358 nm; NMR (FT 80 Varian, $CDCl_3$): δ 1.50 and 1.58 (12H, 2s, 4xCH_3); 2.72 (4H, d, J=7.5 Hz, 2xCH_2-CH=); 3.92 (3H, s, -OCH_3); 4.93 (2H, t, J=7.5 Hz, 2xCH_2-CH=); 6.90 and 7.80 (3H, m, aromatic); 8.41 (NH).

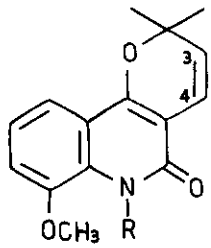
Treatment of (XI) in dry acetone with potassium carbonate and methyl iodide as described above for (II), gave (XII) as an oil (yield 85%). m/z 341 (M^+) for $C_{21}H_{27}NO_3$; UV (EtOH)λ_{max} 236, 281, 358 nm; NMR (FT 80 Varian, $CDCl_3$): δ 1.53 and 1.56 (2H, 2s, 4xCH_3); 2.65 (4H, d, J=7.0 Hz, 2xCH_2-CH=); 3.90 (3H,s, -OCH_3); 3.52 (3H, s, NCH_3); 4.92 (2H, t, J=7.0 Hz, 2xCH_2-CH=); 7.0 - 7.75 (3H,m, aromatic).

The second product was identified with the known 3-(γ,γ-dimethylallyl)-4-hydroxy-8-methoxy-2-quinolone[4] (IV).

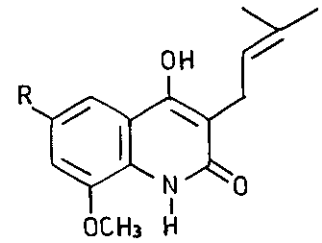
The third product, $C_{20}H_{25}NO_3$ is an oil which has the structure of 3-(γ,γ-dimethylallyl)-4-(γ,γ-dimethylallyloxy)-8-methoxy-2-quinolone (XIII). Rf = 0.60 (silica gel Merck, F_{254}, eluent cyclohexane-ethyl acetate 3:7); yield 20%. m/z 327 (M^+); UV (EtOH)λ_{max} 236, 245 (sh), 283, 292 (sh), 328, 342 (sh) nm; NMR (FT 80 Varian, $CDCl_3$): δ 1.68 and 1.79 (12H, 2s, 3xCH_3); 3.35 (2H, d, J=6.5 Hz, -CH_2-CH=); 3.95 (3H, s, -OCH_3); 4.52 (2H, d, J=7.0 Hz, -OCH_2-CH=); 5.27 (1H, t, J=6.5 Hz, CH_2-CH=); 5.60 (1H, t, J=7.0 Hz, -OCH_2-CH=); 6.80-7.40 (3H, m, aromatic); 9.30 (NH). The compound (XIII) is an analogue of the alkaloid isolated from Haplophyllum tuberculatum[11].

The fourth product has the structure of 4-(γ,γ-dimethylallyloxy)-8-methoxy-2-quinolone (XIV), Rf=0.25, silica gel F_{254}, cyclohexane-ethyl acetate (3:7), m.p. 137-138° (from MeOH). m/z 259 (M^+); UV (EtOH)λ_{max} 222, 248, 270 (sh), 282, 320, 335 (sh) nm; NMR (FT 80 Varian, $CDCl_3$): δ 1.77 and 1.82 (6H, 2s, 2xCH_3); 3.92 (3H, s, -OCH_3); 4.65 (2H, d, J=7.0 Hz, -OCH_2-CH=); 5.55 (1H, t, J=7.0 Hz, -OCH_2-CH=); 5.98 (1H, s, H-3); 6.80-7.60 (3H, m, aromatic); 9.25 (NH). Alkylation of the 4-hydroxy-6,8-dimethoxy-2-quinolone[13] (VIII) with γ,γ-dimethylallyl bromide as previously described, gave a mixture of three products which were chromatographed on silica gel.

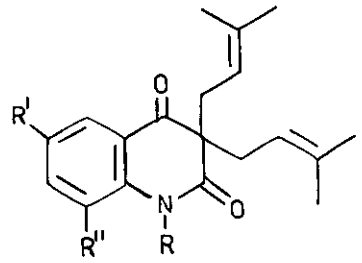
Elution with cyclohexane-ethylacetate (1:3) yielded the 3,3-bis-(γ,γ-dimethylallyl)-6,8-dimethoxy-2,4-dioxo-1,2,3,4-tetrahydroquinoline (XV) (yield 35%), m.p. 162-164° (from AcOEt). m/z 357 (M^+); UV (EtOH)λ_{max} 245, 288, 385 nm; NMR (FT 80 Varian, $CDCl_3$): δ 1.52 and 1.58 (12H, 2s, 4xCH_3); 2.70 (4H, d, J=7.5 Hz, 2xCH_2-CH=); 3.82 and 3.89 (6H, 2s, 2xOCH_3); 4.89 (2H, t, J=7.5 Hz, 2xCH_2-CH=);



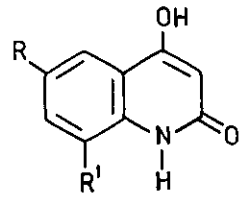
(I) R=CH_2-O-$COCH_3$;(III) R=H



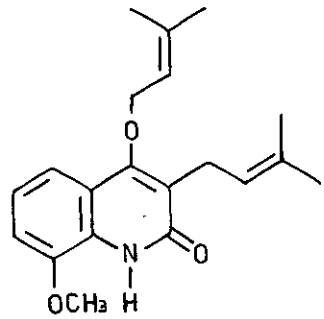
(IV) R=H; (XVII) R=OCH_3



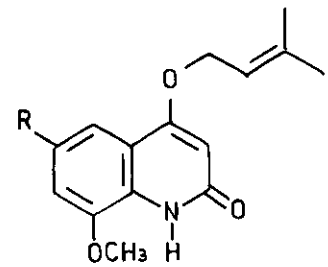
(II) R=CH_3,R'=R"=H; (V) R=R'=R"=H; (IX)R=R"=H;R'=OCH_3; (X) R=CH_3;R'=OCH_3;R"=H
(XI) R=R'=H;R"=OCH_3; (XII)R=CH_3;R'=H;R"=OCH_3; (XV)R=H;R'=R"=OCH_3;(XVI)R=CH_3;
R'=R"=OCH_3.



(VI)R=OCH_3,R'=H;(VII) R=H,R'=OCH_3; (VIII) R=R'=OCH_3



(XIII)



(XIV) R=H (XVIII) R=OCH_3

6.68 and 6.96 (2H, d, J_{meta}=2.5 Hz, H-7 and H-5); 8.03 (NH).

By methylation, as described above for (II), it gave (XVI) as an oil, Rf=0.9 (cyclohexane-ethyl acetate 3:7); MS m/z 371 (M^+); UV (EtOH)λ_{max} 246, 292 (sh), 385 nm; NMR (FT 80 Varian, $CDCl_3$): δ 1.53 and 1.58 (12H, 2s, 4xCH_3); 2.65 (4H, d, J=7.0 Hz, 2x$\underline{CH}_2$-CH=); 3.52 (3H, s, NCH_3); 3.85 and 3.88 (6H, 2s, 2xOCH_3); 4.93 (2H, t, J=7.0 Hz, 2xCH_2-$\underline{CH}$=); 6.78 and 7.05 (2H, d, J_{meta}=3.0 Hz, H-7 and H-5).

Elution with cyclohexane-ethyl-acetate (5:95) gave the known 3-(γ,γ-dimethyl-allyl)-6,8-dimethoxy-2-quinolone[14] (XVII), m.p. 196-198°, Rf=0.65, yield 5%.

Elution with ethyl acetate-methanol (95:5) gave the third product which was elucidated as 4-(γ,γ-dimethylallyloxy)-6,8-dimethoxy-2-quinolone (XVIII), Rf=0.30, yield 35%, m.p. 178° (from EtOH). MS m/z 289 (M^+): UV (EtOH)λ_{max} 225 (sh), 248, 282, 338, 352 (sh) nm; NMR (FT 80 Varian, $CDCl_3$): δ 1.77 and 1.82 (6H, 2s, 2xCH_3); 3.84 and 3.92 (6H, 2s, 2xOCH_3); 4.65 (2H, d, J=7.0 Hz, -$O\underline{CH}_2$-CH=); 5.52 (1H, t, J=7.0 Hz, -OCH_2-$\underline{CH}$=); 5.95 (1H, s, H-3); 6.62 and 6.87 (2H, d, J_{meta} = 2.5 Hz, H-7 and H-5); 8.80 (NH).

The compounds (XIV) and (XVIII) are analogues of the alkaloid ravenine[15] from Ravenia Spectabilis.

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