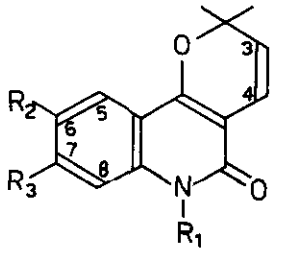
SYNTHESIS OF HAPLAMINE

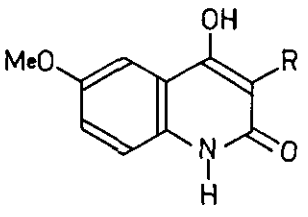
Pietro Venturella, Aurora Bellino and Franco Piozzi*

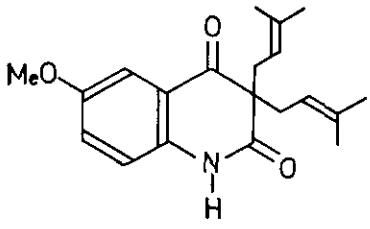
Institute of Organic Chemistry, University of Palermo
20, via Archirafi - 90123 Palermo (Italy)

The alkaloid haplamine was synthesized by isoprenylation at C-3 of 4-hydroxy-6-methoxy-2-quinolone and cyclodehydrogenation with DDQ.

The alkaloid haplamine was recently extracted from Haplophyllum perforatum (Rutaceae) and attributed[1] the structure [I] of 6-methoxyflindersine on the basis of spectroscopic and degradative evidence. The above product is the third representative, after flindersine[2] [II] and oricine[3] [III], of this class of chromeno-2-quinolone alkaloids. As no synthetic work was mentioned, we report here a two-steps synthesis of 6-methoxyflindersine, resting on isoprenylation[4] at C-3 and cyclodehydrogenation[5] with DDQ, that confirms the structure proposed for haplamine.







[I] R_1=R_3=H, R_2=OMe

[II] R_1=R_2=R_3=H

[III] R_1=Me, R_2=R_3=OMe

[IV] R = H

[V] R = $CH_2CH=CMe_2$

[VI]

A solution of 4-hydroxy-6-methoxy-2-quinolone[6] [IV] (1 g) in dry acetone (250 ml) is treated with anhydrous K_2CO_3 (1 g) and refluxed for 30 min: then γ,γ-dimethylallyl bromide (1.5 ml) in acetone (5 ml) is dropped into, and the solution is refluxed for 60 hr. After filtration, the solution is concentrated under reduced pressure, digested with 2N NaOH solution and extracted with $CHCl_3$. Acidification of the alkaline solution yields a solid precipitate, that is resolved by preparative tlc (silica gel, eluent benzene-AcOEt 3:7) into 3-γ,γ-dimethylallyl-4-hydroxy-6-methoxy-2-quinolone [V] (R_f 0.45, 68 mg, yield 5%) and unreacted 4-hydroxy-6-methoxy-2-quinolone [IV] (R_f 0.20, 300 mg).

Product [V] has mp 158°-160° (from AcOEt); ir (nujol mull) 1653 cm^{-1}; uv (EtOH) λ_{max} 345, 334, 275, 266, 230 nm; nmr (60 MHz, $CDCl_3$) 1.77 and 1.81 δ (broad s, allylic Me), 3.83 (s, OMe), 4.63 (d, J 6.7 Hz, CH_2), 5.55 (t, J 6.7 Hz, $C=\underline{CH}-CH_2$), 7.10 (dd, $J_{5,7}$ 3 Hz, $J_{7,8}$ 9 Hz, H-7), 7.30 (d, $J_{5,7}$ 3 Hz, H-5), 7.39 (d, $J_{7,8}$ 9 Hz, H-8), 12.40 (broad, NH). The lack of H-3 signal rules out the isomeric structure of O-γ,γ-dimethylallyl ether: such a product of O-alkylation was not observed either in the acidic or in the neutral fraction ($CHCl_3$ extract).

The $CHCl_3$ extract is evaporated and the residue is purified by preparative tlc: the product (R_f 0.90, 500 mg, 30%) has mp 134°-135° (from cyclohexane) and the structure [VI] of 3,3-bis-(γ,γ-dimethylallyl)-6-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinoline; ir 3175, 1695, 1667 cm^{-1}; uv λ_{max} 378, 259, 238 nm; nmr ($CDCl_3$) 1.49 and 1.58 δ (broad s, 2 allylic Me each), 2.72 (d, J 7.5 Hz, 2 CH_2), 3.81 (s, OMe), 4.87 (t, J 7.5 Hz, 2 $C=\underline{CH}-CH_2$), 6.90 (d, $J_{7,8}$ 8.3 Hz, H-8), 7.14 (dd, $J_{5,7}$ 2.5 Hz, $J_{7,8}$ 8.3 Hz, H-7), 7.30 (d, $J_{5,7}$ 2.5 Hz, H-5), 10.0 (broad, NH).

A solution of [V] (20 mg) and dichlorodicyanobenzoquinone

(DDQ, 20 mg) in dry benzene (30 ml) is refluxed for 2 hr, cooled, filtered and then evaporated. The residue is taken up with Et_2O; the solution is washed with aqueous Na_2CO_3 and evaporated, giving 6-methoxyflindersine [I] (19 mg), mp 199°-200° (from EtOH and then by sublimation in vacuum); ir 3100, 1650 cm^{-1}; uv λ_{max} 375, 356, 332, 234; nmr (100 MHz, $CDCl_3$) 1.27 and 1.56 δ (s, t.Me), 3.89 (s, OMe), 5.54 (d, J 10 Hz, H-3), 6.68 (d, J 10 Hz, H-4), 7.0-7.4 (unresolved pattern, H-5, H-7, H-8); ms 257 (M^+), 242, 227, 149, 121, 57, 43 m/e. An alternative structure of linear chromeno-4--quinolone can be ruled out easily, because the angular isomers only are formed by DDQ cyclodehydrogenation[7,8]. The angular structure [I] is also consistent with the ir maximum at 1650 cm^{-1}, suitable for a 2-quinolone system[9].

The data for synthetic 6-methoxyflindersine are in rather good agreement with those reported[1] for natural haplamine, thus confirming the structure [I] proposed for the alkaloid.

The present work was supported by National Research Council (C.N.R.), Rome.

REFERENCES

1 V.I.Akhmedzhanova, I.A.Bessonova, and S.Yu.Yunusov, Khim.Prirod.Soedinenii, 1974, 10, 109 (Chem.Abstr., 1974, 80, 121153n).

2 R.F.C.Brown et al., Austral.J.Chem., 1955, 8, 348; 1956, 9, 277.

3 M.O.Abe and D.A.H.Taylor, Phytochemistry, 1971, 10, 1167; M.O. Abe, Phytochemistry, 1971, 10, 3328.

4 T.Kappe and E.Ziegler, Monatsh., 1968, 99, 1943; T.Kappe, H. Sterk, and E.Ziegler, Monatsh., 1968, 99, 1950; P.Venturella, A.Bellino, and F.Piozzi, Chim. and Ind.(Milano), 1969, 51, 62; T.R.Chamberlain and M.F.Grundon, J.Chem.Soc.(C), 1971, 910; D. Boulanger, B.K.Bailey, and W.Steck, Phytochemistry, 1973, 12,

2399.

5 F.Piozzi, P.Venturella, and A.Bellino, Gazzetta, 1969, 99, 711.

6 G.H.Patel and C.M.Mehta, J.Sci.Ind.Res.,India, 1960, 19 B, 436 (Chem.Abstr., 1961, 55, 9401).

7 R.M.Bowman, M.F.Grundon, and K.J.James, J.C.S.Chem.Communications, 1970, 666.

8 L.Maat, A.W.Buijen Van Weelderen, and H.C.Beyerman, Rec.Trav. Chim., 1973, 92, 1399.

9 E.A.Clarke and M.F.Grundon, J.Chem.Soc., 1964, 4190.

Received, 12th February, 1975