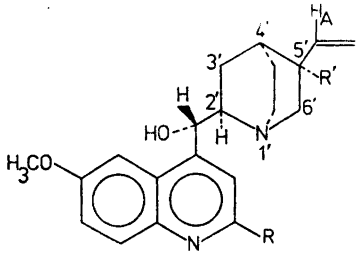
The Metabolism of Quinidine in Man: Structure of a Main Metabolite

BJÖRN BEERMANN,[a] KURT LEANDER[b] and BJÖRN LINDSTRÖM[c]*

[a]Department of Medicine, Serafimerlasarettet, S-112 21 Stockholm, Sweden, [b]Department of Toxicology, Swedish Medical Research Council, Karolinska Institute, S-104 01 Stockholm 60, Sweden and [c]National Board of Health and Welfare, Department of Drugs, Division of Clinical Drug Trials, S-106 30 Stockholm, Sweden

The chinchona alkaloid quinidine (*1*) is used as a drug for the treatment of cardiac arrythmia. Several metabolites of quinidine (*1*) in man have previously been isolated and characterised but the structure of only one of them (*2*) has been established.[1,2] One of the main metabolites, previously considered to be 6′-hydroxyquinidine (earlier denoted 2′-hydroxyquinidine),[1] is now demonstrated to have structure *3*.



1, R = R′ = H
2, R = OH; R′ = H
3, R = H; R′ = OH

Mass spectrometry shows that the metabolite *3* has a molecular weight of 340, which corresponds to quinidine (*1*) with an additional oxygen atom. The ^{1}H NMR spectrum of quinidine (*1*) exhibits a complex multiplet (1 H) at δ 5.9 – 6.4 attributed to H_A in formula *1*. The corresponding hydrogen atom in the metabolite appears as two doublets at δ 6.41, which establishes that the additional oxygen atom is situated at C-5′, and hence that the metabolite is 5′-hydroxyquinidine (*3*). The dissociation constants for *3* (in ethanol-water, 1:2) were found to be 7.3 and 4.0. The former value is in good agreement with that calculated for 5′-hydroxyquinidine.[3]

The absolute configuration at C-5′ is not at present known but, since enzymatic hydroxylation generally takes place with retention of the configuration,[4] the absolute configuration depicted in formula *3* is proposed for the metabolite.

Brodie *et al.*[1] have also studied the metabolism of quinine in man, and they reported that 6′-hydroxyquinine is one of the main metabolites. The assignment of structure was based on UV and pK_a measurements. The dissociation constants were found to be 7.24 and 4.12 (in 27 % ethanol), which are of the same magnitude as those here found for 5′-hydroxyquinidine (*3*). It thus seems probable that the metabolite formulated as 6′-hydroxyquinine in fact is 5′-hydroxyquinine.

Experimental. Melting points are corrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter, NMR spectra on a Varian XL-100 spectrometer, UV spectra on a Bausch and Lomb spectronic UVd instrument and the mass spectra on an LKB 2091 mass spectrometer. Solvents were evaporated under reduced pressure at bath temperatures not exceeding 25 °C. Plates pre-coated with silica gel F_{254} (2 mm, Merck) were used for preparative TLC.

Isolation of 3. Urine (4 l) from human subjects chronically treated with quinidine (0.8 – 1.2 g/day) was made alkaline (pH 9) with aqueous ammonia and extracted with ethyl acetate (3 × 1.6 l). The organic phase was washed twice with a saturated solution of sodium chloride, dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on preparative silica gel plates (methanol) giving *3* (30 mg). Metabolite *3* had R_F 0.6 (R_F for quinidine 0.5). Needles (water-ethanol), m.p. 209 – 212 °C. (Lit. 1 m.p. 210 – 212 °C). UV, indistinguishable from that previously reported.[1] $[\alpha]_D^{22}$ + 16° (*c* 1.0, methanol). pK_a (ethanol-water, 1:2) 7.3 and 4.0.

^{1}H NMR (CD_3OD): δ 1.0 – 1.3 (m, 2 H), 1.7 – 2.3 (m, 3 H), 2.64 (d, 1 H, *J* 14 Hz), 2.8 – 3.2 (m, 3 H), 3.94 (d, 1 H, *J* 14 Hz), 4.01 (s, 3 H), 5.21 (dd, 1 H, J_1 10.8 Hz, J_2 1.6 Hz), 5.45 (dd, 1 H, J_1 17.6 Hz, J_2 1.6 Hz), 5.66 (d, 1 H, *J* 2.6 Hz), 6.41 (dd, 1 H, J_1 17.6 Hz, J_2 10.8 Hz), 7.32 – 7.50 (m, 2 H), 7.70 (dd, 1 H, J_1 4.5 Hz, J_2 1 Hz), 7.99 (ddd, 1 H, J_1 10.0 Hz, J_2 1.6 Hz, J_3 1 Hz), 8.68 (d, 1 H, *J* 4.5 Hz). MS, *m/e* (rel. intensity): M^+ 340 (11), 189 (15), 152 (100).

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* To whom correspondence should be addressed.