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SYNTHESIS AND STEREOCHEMISTRY OF A METABOLITE RESULTING FROM THE BIOTRANSFORMATION OF QUINIDINE IN MAN

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Quinidine (1a), a member of the cinchona alkaloid family, is used in the treatment of cardiac arrhythmias.[1] The major biotransformation products of 1a have been isolated from the urine of man,[2,3] and their structures were shown to be 3-hydroxyquinidine (2a, metabolite-4)[4] and 2'-quinidinone (3, metabolite-5)[4] by an analysis of their ^{13}C-NMR, IR, UV, and mass spectral properties.[5] In the present paper we present the synthesis of 2a and describe a ^{13}C-NMR study for the assignment of stereochemistry.

Pure 1a[6] was converted to a mixture of α- and α'-10-bromodihydroquinidine (5)[7] by dissolving 1 in concentrated hydrobromic acid and passing HBr into the solution at 0° for six hours. Crude 5 was subjected to reaction with 1,5-diazabicyclo[5·4·0]undec-5-ene (DBU)[8] in dimethylsulfoxide at 90° for two hours to form apoquinidine methyl ether (4a)[7,9] which was directly converted into the acetate 4b by acetylation with pyridine-acetic anhydride. The acetate 4b obtained in 65% overall yield from quinidine had m.p. 110-112° (from Et_2O-hexane); $[\alpha]_D^{24}$ +61.09° (c 0.568, EtOH).[10] Ozonization of $\Delta^{3(10)}$-cinchona alkaloids similar to 4 are reported to proceed abnormally and give the corresponding 3-acetyl derivatives.[11] We found that the olefin acetate 4b was smoothly oxidized with osmium tetroxide-sodium periodate[12,13] in 80% acetic acid at 4° to give (8R,9S)-6-methoxy-3-oxo-9-rubanol acetate (6) in 75% yield; m.p. 162-163° [from $(CH_3)_2CO$-Et_2O]; $[\alpha]_D^{24}$ +58.46 (c 0.40, EtOH).[10] Treatment of 6 with vinyl magnesium bromide in dry THF gave two products which were separable by chromatography on Florisil using $CHCl_3 \rightarrow CHCl_3$:$(CH_3)_2CO$ (4:6) as the eluent. The first component 2c had m.p. 188-190° (from EtOAc); $[\alpha]_D^{25}$ +132.42° (c 0.91, EtOH).[10] The mass spectrum of 2c was essentially identical to the spectrum of metabolite-4, however, the TLC R_f values, as well as the IR, ^{1}H- and ^{13}C-NMR spectral properties of 2c, although similar, were different from those of metabolite-4. It is clear from the method of synthesis as well as the elemental analysis and spectral data that 2c is the 3-hydroxy epimer of metabolite-4. The second compound eluted from the column possessed m.p., TLC R_f values, gas chromatographic retention time, IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectral properties identical to metabolite-4. When the addition of vinyl magnesium bromide to 6 was carried out at 25°, the total yield of 2a and 2c was 80%, and the ratio of 2a/2c was 60/40. If the addition was conducted at reflux, the yield dropped to 40%, however, metabolite-4 was the predominant product and only trace amounts of 2c were obtained.

At the time of our earlier publication,[5] we were unable to establish the stereochemistry at C-3 of metabolite-4. However, since most biological hydroxylations proceed with retention of configuration,[14] metabolite-4 was tentatively assigned the structure 2a. A study of the ^{13}C-NMR

chemical shifts of the C-5 and C-7 methylenes of 1a, 1b,[15] 2a, 2b,[15] 2c and the model compounds 7a-d listed in Table 1 show that the original assignment is correct. The chemical shift assignment for the compounds listed in Table 1 are based on standard ^{13}C-NMR chemical shift theory[16] and arguments made for other cinchona alkaloids.[17] As expected, the chemical shift of C-7 of 1b is shifted downfield relative to 1a, whereas the chemical shift of C-5 in 1a and 1b are essentially identical.[16,17] The observation that the C-5 and C-7 resonances of 2b show similar differences in chemical shift relative to 2a confirm that the C-5 and C-7 assignments for 2a are correct. In addition, the data for the model compounds 7a-d show that the γ-effect of the 3-hydroxy group is larger than that of a 3-vinyl group in this series and show that the γ-effect of both the 3-hydroxy and the 3-vinyl is slightly reduced on going from the 3-monosubstituted derivatives 7b and 7c to the disubstituted derivative 7d.[18] (3S)-3-Hydroxyquinidine (2a) which has the 3-hydroxyl syn to C-5 shows a 5.68 ppm upfield and 0.83 ppm downfield shift for C-5 and C-7 respectively when compared to 1a. In comparison the 3-hydroxy-3-vinyl model 7d shows a 5.36 ppm upfield and 1.86 ppm downfield shift for C-5 and C-7 when compared to the 3-vinyl model 7c. (3R)-3-Hydroxyquinidine (2c) which contains the 3-hydroxyl group syn to C-7 might be expected to show a slightly larger γ-effect at C-7 compared to 1a and 2a, which have a 3-vinyl group syn to C-7, and a smaller γ-effect at C-5 compared to 2a, which has the 3-hydroxyl group syn to C-5. However, since the C-5 and C-7 resonances are so close together, it is not possible to make definite assignments in this case.

In summary, we have reported the first synthesis of (8R,9S)-6-methoxy-3-oxo-9-rubanol acetate (6) and described its use to prepare 2a, an important biotransformation product of quinidine. The use of ^{13}C-NMR was used to establish the stereochemistry of 2a as (3S)-3-hydroxyquinidine.

Table 1. Carbon-13 Chemical Shifts in DMSO-d_6[a]

Carbon Atom	1a[b]	1b	2a[c]	2b	2c	7a	7b[c]	7c[d]	7d[e]
5	26.37	26.10	20.69	20.34	23.86	26.39	18.97	26.53	21.17
7	23.28	24.49	24.11	26.15	22.39	26.39	24.70	21.17	23.03

a) Chemical shifts are in parts per million relative to tetramethylsilane.

b) Values taken from ref. 17.

c) Values taken from ref. 5.

d) 3-Vinylquinuclidine (7c) was prepared according to the procedure reported by L. N. Yakhontov, L. I. Mostafanova, S. L. Portnova and M. V. Rubtsov, Dokl. Akad. Nauk. SSSR, 162, 1075 (1965).

e) 3-Hydroxy-3-vinylquinuclidine (7d) was prepared according to the procedure reported by M. V. Rubtsov, L. N. Yakhontov and L. I. Mostafanova, Zh. Obshch. Khim., 33, 1180 (1963).

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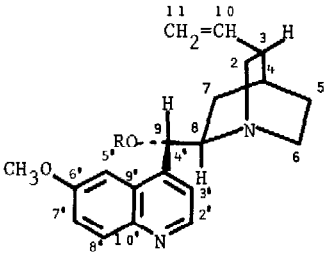
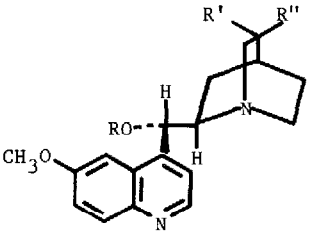
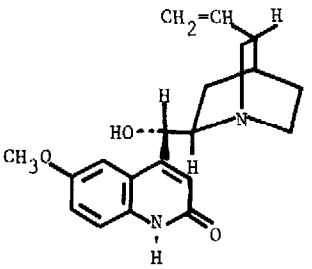


1a, R = H
b, R = C_6H_5CO



2a, R = H, R' = CH_2=CH, R'' = OH
b, R = C_6H_5CO, R' = CH_2=CH_2, R'' = OH
c, R = H, R' = HO, R'' = CH=CH_2



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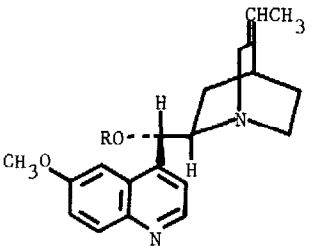
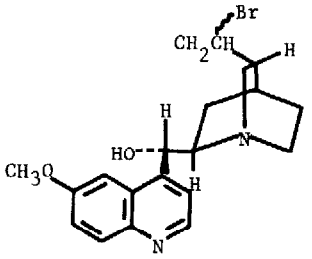


4a, R = H
b, R = CH_3CO



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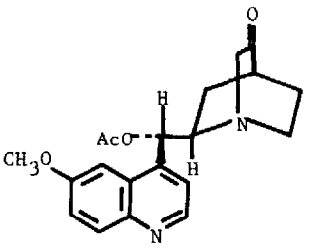

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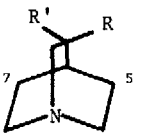

7a, R = R' = H
b, R = OH, R' = H
c, R = H, R' = CH=CH_2
d, R = OH, R' = CH=CH_2

References and Notes

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10. Satisfactory (a) IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra and (b) analytical data have been obtained for 2a, 2b·1/2 H_2O, 2c, 3, 4a, 4b, 6 and 8.

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15. The benzoates 1b and 2b, m.p. 188-189°, were prepared by treating 1a and 2a with benzoic anhydride in pyridine. The ^{1}H-NMRs of these compounds are in agreement with the assigned structures.

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17. C. G. Moreland, A. Philip and F. I. Carroll, J. Org. Chem., 39, 2413 (1974).

18. Similar type shifts were noted by Lippma and co-workers for some substituted norboranes. See E. Lippma, T. Pehk, J. Passivirta, N. Belikova and A. Plate, Org. Magn. Reson., 2, 581 (1970).