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PHOTOREACTIONS OF QUININE IN AQUEOUS CITRIC ACID SOLUTION. PART 3. PRODUCTS FORMED IN AQUEOUS 2-HYDROXY-2-METHYLPROPIONIC ACID

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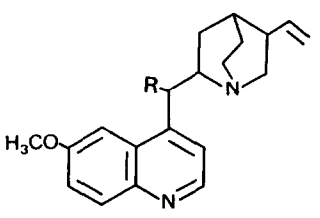
Abstract - 7'-(2-Hydroxyprop-2-yl)-7',8'-dihydroquinine and the corresponding 7',8'-dihydrodeoxyquinine derivative have been identified together with deoxyquinine as products of the irradiation of quinine in aqueous 2-hydroxy-2-methylpropionic acid. A cyclised product of 4'-(2-hydroxyprop-2-yl)-1',4'-dihydroquinine was also isolated from the reaction mixture.

INTRODUCTION

A complex mixture of photoproducts is generated when a solution of quinine (1) in aqueous citric acid solution is exposed to light.[1,2] The amphoteric nature of many of the photoproducts has complicated their recovery from the aqueous reaction mixture and hindered the study of the mechanisms involved in their formation. Since loss of the carboxy group from the β-carbon atom of citric acid is necessary for the formation of certain photoproducts, it was of interest to study the behaviour of structurally related acids in the photolysis. 2-Hydroxy-2-methylpropionic acid (2) was selected for study because it was expected to yield photoproducts lacking a carboxylic acid function and directly recoverable from the irradiated solution by solvent partition.



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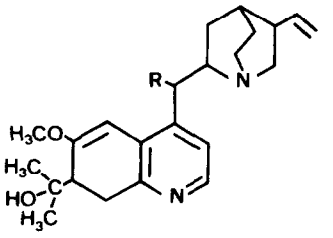
3 : R = H



4 : R = OH
5 : R = H

$(CH_3)_2C(OH)CO_2H$

2

RESULTS AND DISCUSSION

An aqueous solution of quinine (3.16 mM) and 2-hydroxy-2-methylpropionic acid (0.038 M) was irradiated with a medium pressure mercury lamp using a Pyrex filter. The course of the reaction was monitored by HPLC using UV detection at 250 nm and as the irradiation proceeded five peaks,

later eluting than quinine, developed. After five hours the irradiation was stopped and the solution was basified and extracted with chloroform. The extract, which gave a chromatogram similar to that of the irradiated solution, was fractionated by column chromatography on silica gel. The photoproducts isolated in this manner were purified by preparative TLC. In addition to deoxyquinine (3), an early formed photoproduct when quinine is irradiated in aqueous citric acid solution,[1] three photoproducts were isolated.

One of the isolated photoproducts co-eluted with quinine under the HPLC conditions used. The highest ion observed in the mass spectrum of this photoproduct occurred at m/z 369. CIMS indicated that this was not the molecular ion but $(M-15)^+$; mass measurement gave an accurate mass consistent with the molecular formula $C_{23}H_{32}N_2O_3$. The occurrence of the base peak at m/z 136 established that the compound had retained the vinyl quinuclidine ring system of quinine. A pseudomolecular ion at m/z 529 in the CIMS of the product from trimethylsilylation implied that two hydroxy groups were present.

In contrast to quinine, the ^1H NMR spectrum contained signals for only two aromatic protons, δ 8.09 and 7.41 attributable to H-2' and H-3', respectively. These signals are consistent with aromaticity being restricted to the nitrogen containing ring. The UV absorption spectrum in methanol (λ_{max} 286) suggested that there was a double bond in conjugation with the aromatic ring. The presence of a one proton singlet in the olefinic region at δ 5.81, assignable to H-5', supported this view. A three proton singlet at δ 3.82 and two three proton singlets at δ 1.15 and 0.90 established that the photoproduct contained a methoxyl and two methyl groups. These results are best accommodated by structure 4.

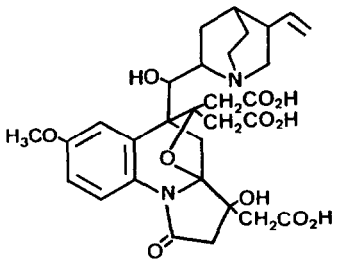
A photoproduct, which had a similar HPLC retention time to deoxyquinine, was identified on the basis of the spectral data as 5, the deoxyquinine derivative corresponding to 4. Examination of the ^1H NMR and ^{13}C NMR spectra revealed that many of the signals showed fine splitting which was solvent dependent. It was concluded that this was due to the presence of an equal mixture of the epimers resulting from the generation of the new chiral centre at C-7'.

A minor photoproduct, which eluted later than deoxyquinine in the HPLC system and was less polar by TLC, gave a mass spectrum with a weak ion at m/z 384. CIMS confirmed that this was the molecular ion and that the photoproduct was isomeric with 4. The occurrence of the base peak at m/z 136 indicated that the compound had retained the vinyl quinuclidine ring system of quinine.

The ^1H NMR spectrum confirmed the presence of the methoxy group (δ 3.73) and showed a six proton singlet at δ 1.40 attributable to two equivalent methyl groups and indicative that one molecule of 2 was involved in the formation of the photoproduct. In contrast to quinine, the spectrum contained signals for only three aromatic protons, δ 8.08, 6.67 and 6.46. The assignment of these signals to H-5', H-7' and H-8', respectively, was consistent with aromaticity being restricted to the methoxyl-bearing ring. The chemical shifts are best explained on the basis of a reduced carbon-nitrogen bond in the quinoline ring.

The ^{13}C NMR spectrum showed twenty resonances of which two were probably pairs of overlaying signals. The seven signals at lowest field arose from the eight unsaturated carbons of the methoxyl-bearing ring and the vinyl group. A resonance (δ 71.7) attributable to a quaternary carbon linked to oxygen was consistent with the presence of a 2-hydroxyprop-2-yl grouping derived from 2. The high field region of the spectrum contained three signals additional to those present in that of quinine. Two of these signals (δ 27.6, 29.0) were appropriate for the methyl carbons of the hydroxypropyl group. The signal for C-9 occurred at much lower field (δ 88.9) than in quinine but the trimethyl ester of the previously identified photoproduct 6 also showed such a shift.[2]

These data are best accommodated by structure 7. Of particular relevance is the nature of C-2', a carbon linked directly to an oxygen and a nitrogen. The signal in the ^{13}C NMR spectrum at δ 82.8 is appropriate for such a carbon. The proton attached to this carbon is probably responsible for the additional signals close to δ 5 in the ^{1}H NMR spectrum. The resonance absent from the ^{13}C NMR spectrum is that for C-4'; the low intensity signal from such a quaternary carbon may well be obscured by an overlaying resonance.



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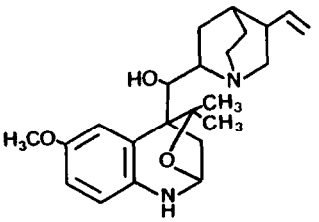

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It is apparent from these results that the course of the photo-induced reactions of quinine in aqueous 2-hydroxy-2-methylpropionic acid differs in many respects from that in aqueous citric acid. Although reduction to deoxyquinine is common to both systems and the acids lose the carboxy group from the hydroxyl-bearing carbon, the substitution reactions occur predominantly at different positions on the quinoline ring, at C-2' in aqueous citric acid and at C-7' in the presence of 2-hydroxy-2-methylpropionic acid. The carboxy groups of the radical from citric acid may play a role in directing substitution to C-2' through ionic association with the imino-nitrogen adjacent to C-2' in the radical from quinine. The reduced state of the methoxyl-bearing ring of the 7'-substituted photoproducts identified in the present work may reflect the mild conditions used to isolate these compounds rather than a difference in the course of the photoreactions.

EXPERIMENTAL

Irradiations were carried out in a Hanovia 10 litre photochemical reactor equipped with a 500 watt medium pressure mercury lamp immersed inside a water-cooled Pyrex thimble.

^{1}H and ^{13}C NMR spectra were recorded on a Jeol FX 90 Q spectrometer using tetramethylsilane as internal standard (δ = 0).

Mass spectra (probe analysis) were obtained on a VG 70/70F mass spectrometer equipped with a VG 2250 data system. Accurate mass measurements were carried out by peak matching. Chemical ionisation mass spectra were obtained using ammonia as reagent gas.

UV absorption spectra were recorded on a Perkin-Elmer Lambda 3 UV/VIS spectrometer in 1 cm path length cuvettes. Samples were measured in methanol.

IR spectra were recorded as thin films on a Perkin-Elmer 175G spectrometer.

Analytical high performance liquid chromatography (HPLC) was as described previously.[1] Analytical TLC used Merck Silica gel F254 (0.25 mm) plates developed with hexane-acetone-diethylamine (5:3:2, v/v/v) (HAD1), (10:3:2, v/v/v) (HAD2). Photoproducts were detected by the quenching of 254 nm UV light and by fluorescence in 366 nm UV light. Visualisation with potassium iodoplatinate was also used; alkaloid photoproducts gave a violet colour with the reagent.

A solution of quinine (1.0 g) and 2-hydroxy-2-methylpropionic acid (4.0 g) in water (1 L) was irradiated with stirring for 5 hours by which time HPLC analysis showed five peaks in addition to that for quinine. The irradiated solution was basified to pH 12 by the addition of sodium hydroxide solution (16 mL, 5 M) and extracted with chloroform (3 x 500 mL). The combined extracts were dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure. The resulting amber residue (0.99 g) was shown by TLC (HAD1) to contain deoxyquinine (R_f = 0.55), quinine (R_f = 0.45), 5 (R_f = 0.36) and 4 (R_f = 0.29). Preparative TLC (HAD1) gave 4 and 5. A minor component 7 that migrated in front of deoxyquinine was isolated using HAD2 as mobile phase.

Compound 4 (R_f = 0.29)

MS: m/z (rel. int.) $(M-15)^+$ 369(2), 326(55), 325(40), 136(100), 81(18), 59(19), 55(10). Accurate mass $(M-15)^+$ 369.2165 (calc. 369.2178) for $C_{22}H_{29}N_2O_3$ CIMS: m/z (rel. int.) $(M+1)^+$

385(100), 327(90), 325(60), 311(10), 248(10), 220(18), 160(33), 136(12). CIMS (TMS derivative): m/z (rel. int.) $(M+1)^+$ 529(100), 398(36), 397(14), 278(15), 199(38), 165(20). IR: $\nu_{max}(cm^{-1})$ 3200 (OH), 2950, 1635, 1580, 1415, 1300, 1240, 1195, 1000. UV: λ_{max}(nm) ε(L mole^{-1} cm^{-1}) 286 (12,000). ^{1}H NMR (CD_3OD): δ 0.90 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.30-3.50 (m, 13H, aliphatic protons, 3.82 (s, 3H, OCH_3), 4.85-5.25 (m, 2H, 2 x H-11), 5.40 (broad s, 1H, H-9), 5.60-6.00 (m, 1H, H-10), 5.81 (s, 1H, H-5'), 7.41 (d, 1H, J = 4.5 Hz, H-3'), 8.09 (d, 1H, J = 4.5 Hz, H-2').

Compound 5 (R_f = 0.36)

MS: m/z (rel. int.) $M^{+\cdot}$ 368(0.2), 353(5), 309(48), 136(100), 81(10), 59(24), 55(10). CIMS: m/z (rel. int.) $(M+1)^+$ 369(100), 309(20). Accurate mass $M^{+\cdot}$ 368.2477 (calc. 368.2464) for $C_{23}H_{32}N_2O_3$. CIMS (TMS derivative): m/z (rel. int.) $(M+1)^+$ 441(100), 309(20), 141(50), 90(17), 69(40). IR: $\nu_{max}(cm^{-1})$ 3250 (OH), 2940, 1635, 1580, 1415, 1380, 1200, 1075, 1000, 910. UV: λ_{max}(nm) ε(L mole^{-1} cm^{-1}) 286 (11,900). ^{1}H NMR ($CDCl_3$): δ 1.04 and 1.07 (s, 3H, CH_3), 1.15 and 1.18 (s, 3H, CH_3), 1.25-3.60 (m, 13H, aliphatic protons), 3.80 (s, 3H, OCH_3), 4.85-5.16 (m, 2H, 2 x H-11), 5.55-6.10 (m, 1H, H-10), 5.86 (s, 1H, H-5'), 6.83 and 6.88 (d, 1H, J = 4.5 Hz, H-3'), 8.06 (d, 1H, J = 4.5 Hz, H-2').

Compound 7

MS: m/z (rel. int.) $M^{+\cdot}$ 384(11), 369(20), 326(7), 218(13), 202(13), 189(5), 166(21), 160(36), 136(100). CIMS: m/z (rel. int.) $(M+1)^+$ 385(100). UV: λ_{max}(nm) ε(L mole^{-1} cm^{-1}) 240 (7,300), 310 (2,500). ^{1}H NMR ($CDCl_3$): δ 1.00-3.10 (m, aliphatic protons), 1.40 (s, 6H, 2 x CH_3), 3.73 (s, 3H, OCH_3), 4.42 (d, 1H, J = 9.0 Hz, H-9), 4.65-5.10 (complex, 3H, 2 x H-11 + one other), 5.58 (m, 1H, H-10), 6.46 (d, 1H, J = 8.8 Hz, H-5'), 6.67 (dd, 1H, J = 8.8, 2.8 Hz, H-7'), 8.08 (d, 1H, J = 2.8 Hz, H-5'). ^{13}C NMR: δ 25.8 (C-7), 27.3 (C-5), 27.6 (C-13, C-4), 29.0 (C-14), 38.1 (C-3), 39.7 (C-3'), 41.6 (C-6), 53.9 (C-2), 55.4 (C-8), 56.0 (OCH_3), 71.7 (C-12), 82.8 (C-2'), 88.9 (C-9), 114.4 (C-5', C-11), 116.2 (C-7'), 117.1 (C-8'), 129.0 (C-9'), 136.4 (C-10'), 141.4 (C-10), 152.9 (C-6').

ACKNOWLEDGEMENT

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