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PHOTOREACTIONS OF QUININE IN AQUEOUS CITRIC ACID SOLUTION. PART 2. SOME END-PRODUCTS

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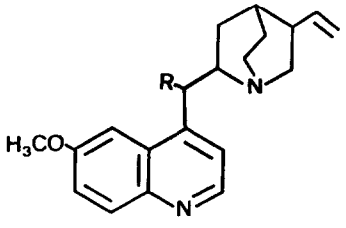
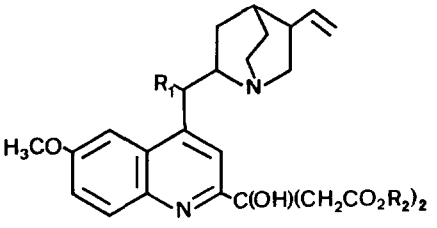
Abstract - A novel spiro-compound derived from 2',4'-bis-(1,3-dicarboxy-2-hydroxyprop-2-yl)-1',4'-dihydroquinine has been identified as a major end-product of the irradiation of quinine in aqueous citric acid solution. 7'-(1,3-Dicarboxy-2-hydroxyprop-2-yl)deoxyquinine and products arising from the cleavage of quinine at C-9 were also detected in the reaction mixture.

INTRODUCTION

The photolability of quinine (1) in aqueous citric acid solution has been recognised for many years[1] but it is only recently that any of the photoproducts have been identified. In Part 1, Laurie and co-workers[2] reported that 2'-(1,3-dicarboxy-2-hydroxyprop-2-yl)quinine (2) and the corresponding deoxyquinine derivative (3) were formed together with deoxyquinine (4) when quinine hydrochloride was irradiated in aqueous citric acid solution. It was noted that these three photoproducts were also photolabile and their individual concentration in the photolysed solution reached a maximum and then decreased on continued irradiation. In the present work the nature of the end-products of the photoreactions is discussed.



1 : R = OH
4 : R = H



2 : R_1 = OH R_2 = H
3 : R_1 = H R_2 = H
8 : R_1 = H R_2 = CH_3

RESULTS AND DISCUSSION

A solution of quinine hydrochloride (0.54 mM) in aqueous citric acid (0.02 M) was irradiated with a medium pressure mercury lamp using a Pyrex filter. The course of the reaction was monitored by UV spectrometry and the irradiation was continued until the characteristic three absorption bands of quinine at 250, 317 and 345 nm had been replaced by a single absorption at 270 nm (110 hours).

While only trace amounts of product were directly recoverable from the irradiated solution by solvent partition, preparative HPLC enabled the product to be isolated free from citric acid. Analytical reversed-phase gradient HPLC using UV detection at 270 nm showed the product to be a complex mixture of components of different polarity (Fig. 1). Base-line resolution was not achieved but the UV absorption spectra of the compounds associated with the main peaks were recorded as they eluted from the column in the acidic mobile phase. None showed the characteristic absorption spectrum of quinine and in all cases λ_{max} occurred from 5 to 30 nm higher than the wave-length of the main absorption of quinine (250 nm).

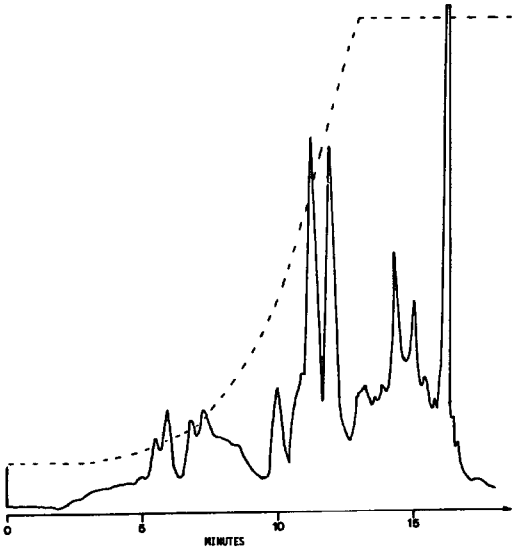


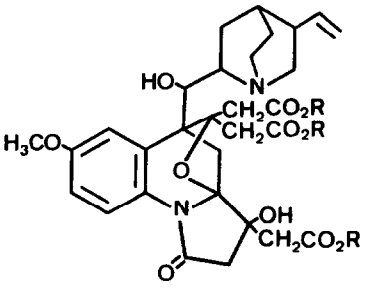
Fig. 1. HPLC separation of the isolated photoproduct mixture on LiChrosorb RP8.

As established in the earlier work[2] the separation of the photoproducts by TLC was facilitated by prior methylation of any carboxy groups present. The TLC pattern of the esterified reaction mixture was complex but showed a major component migrating close to the solvent front. This component and a second more polar component were isolated by preparative TLC.

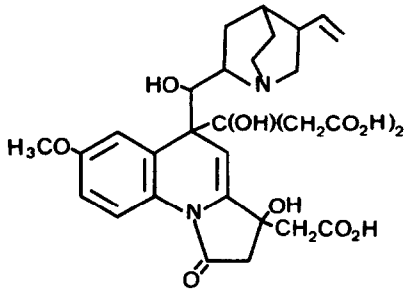
The mass spectrum of the less polar component showed a weak ion at m/z 642. CIMS confirmed that this was the molecular ion and mass measurement gave an accurate mass consistent with the formula $C_{33}H_{42}N_2O_{11}$. The occurrence of the base peak at m/z 136 suggested that the compound had retained the vinyl quinuclidine ring system of quinine. The IR spectrum contained bands indicative of carbonyl groups (ν_{max} 1740, 1700 cm^{-1}) and at least one hydroxy group (ν_{max} 3400 cm^{-1}); a pseudomolecular ion at m/z 787 in the CIMS of the product from trimethylsilylation with trimethylsilylimidazole implied that two hydroxy groups were present.

In contrast to quinine the ^1H NMR spectrum of the esterified photoproduct contained signals for only three aromatic protons, δ 8.63, 8.21 and 6.84 attributable to H-8', H-5' and H-7', respectively. These signals are consistent with aromaticity being restricted to the methoxyl-bearing ring as indicated by the UV absorption spectrum (λ_{max} 260 nm). The presence of a six proton singlet at δ 3.78 and two three proton singlets at δ 3.73 and 3.63 established that the photoproduct contained four methoxy groups. The high field region of the spectrum was complex but signals attributable to the eight protons of two equivalent and two non-equivalent methylene groups were discernible. These data implied that two molecules of citric acid were involved in the formation of the photoproduct and, if the aromatic methoxy group was retained, that one of the carboxy groups originating from the citric acid residues had not generated a methyl ester.

The ^{13}C NMR spectrum showed thirty-two reasonances of which one was undoubtedly due to two overlaying signals. Resonances attributable to four carbonyl carbons and two quaternary carbons linked to oxygen provided confirmatory evidence of the involvement of two molecules of citric acid. Nine signals indicative of unsaturated carbons were apparent. Of these, eight corresponded to the carbons of the methoxyl-bearing ring and the vinyl group. The ninth signal had the characteristic low intensity of a quaternary carbon and as the chemical shift (δ 100.0) did not fit any such types present in quinine or citric acid, it represented a site of chemical change. These results are best accommodated by structure 5 for the esterified photoproduct. Of particular relevance is the nature of C-2', a quaternary carbon linked directly to an oxygen and a nitrogen. The signal in the ^{13}C NMR spectrum at δ 100.0 is appropriate for such a carbon.[3]



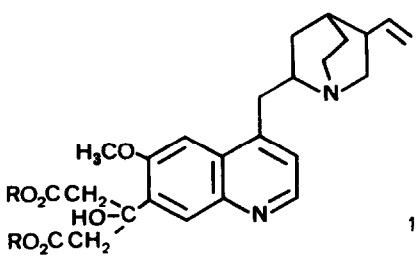
5 : R = CH_3; 6 : R = H



7

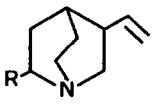
When the original photoproduct mixture was examined by FAB-MS the detection of a significant ion at m/z 601 provided evidence that the lactam ring was already present and was not formed during the esterification procedure. It is not possible to conclude from the available data whether the oxygen ring is present in the photoproduct or is generated under the acid conditions of the esterification. Thus, the alternative structures 6 and 7 are possible for the photoproduct. Both proposed structures contain chiral centres additional to those present in quinine. The stereochemistry of these centres has not been investigated nor has it been established that the relative configuration of the centres at C-8 and C-9 remains unchanged during the course of the photoreactions. In the absence of confirmation by unambiguous synthesis the proposed structures must remain tentative.

The more polar component isolated from the esterified reaction mixture was shown by CIMS to have the same molecular weight as 8. A comparison of the ^{1}H NMR spectrum with that of 8 suggested that the two compounds were isomers differing in the location of the citric acid derived substituent. In contrast to 8, the aromatic region of the spectrum resembled that of deoxyquinine in respect of the signals for H-2' and H-3'. The remaining two aromatic signals were singlets, indicating that substitution had occurred at C-7' and that the compound was 7'-(1,3-dimethoxycarbonyl-2-hydroxy-prop-2-yl)deoxyquinine (9). No evidence was obtained to confirm that the free acid (10) was present in the photoproduct mixture prior to esterification. It is possible that the irradiation yielded a photoproduct with a partially reduced aromatic ring system and that this was oxidised to 10 during the isolation procedure.

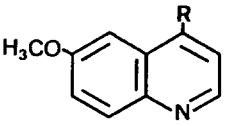


9 : R = CH_3
10 : R = H

The esterified mixture of photoproducts showed four closely grouped main peaks and several minor peaks by GC. MS established that the methyl acetals of two isomers of 5-vinylquinuclidine-2-carboxaldehyde (11), and the methyl esters of two isomers of 5-vinylquinuclidine-2-carboxylic acid (12) were responsible for the main peaks. The acetal formation was a consequence of the esterification conditions used. Compounds associated with the minor peaks included 11, 6-methoxyquinoline-4-carboxaldehyde (13) and the methyl ester of 6-methoxy quinoline-4-carboxylic acid (14). Only 12 has been reported previously to be a product of the photolysis of quinine,[4] although there is a recent report[5] that 6-methoxy-4-methylquinoline, a possible photoreduction product of 13, is formed when quinine in aqueous citric acid is exposed to sunlight. The present results would suggest that cleavage of the C-4'-C-9 bond is more favoured than cleavage of the C-8-C-9 bond and that the reaction is accompanied by epimerisation at C-8.



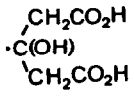
11 : R = CHO
12 : R = CO_2H



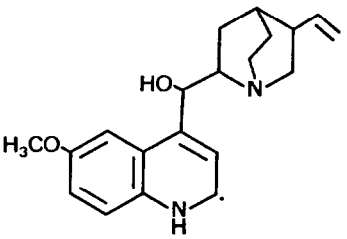
13 : R = CHO
14 : R = CO_2H

It would appear that several pathways are involved in the formation of the complex mixture of photoproducts observed. While not all the components of the mixture have been identified, a plausible reaction scheme leading to those for which evidence of occurrence has been obtained is given in Fig. 2.

It was suggested previously[2] that the formation of 2 could involve generation of a radical of the type a by UV light activation of a quinine-citric acid complex. The mechanism is not clear but radical b may be a key intermediate. The coupling of a and b would yield a dihydro-derivative capable of oxidation to 2. The observation that a higher maximum concentration of 2 was achieved when the irradiation was carried out in the presence of oxygen is in accord with such a view.



a



b

No detailed kinetic studies were undertaken but it was evident that the concentration of photoproducts estimated by HPLC to be present in the initial stages of the irradiation did not account for the loss of quinine observed. This suggested that other photoproducts were formed which were not detectable by the analytical procedure because they lacked the appropriate UV absorption at 250 nm. In view of the reducing conditions generated in the course of the irradiation it was concluded that photoreduction of the aromatic ring system occurred from the outset. Reduction or disproportionation of radical b would be expected to give a mixture of 1',2'- and 1',4'-dihydroquinine. Dehydration of the latter offers a plausible route to 4. The

failure to recover any significant quantity of product in the later stages of the irradiation by solvent extraction of the basified solution indicated that neither dihydroquinine was present as an end-product.

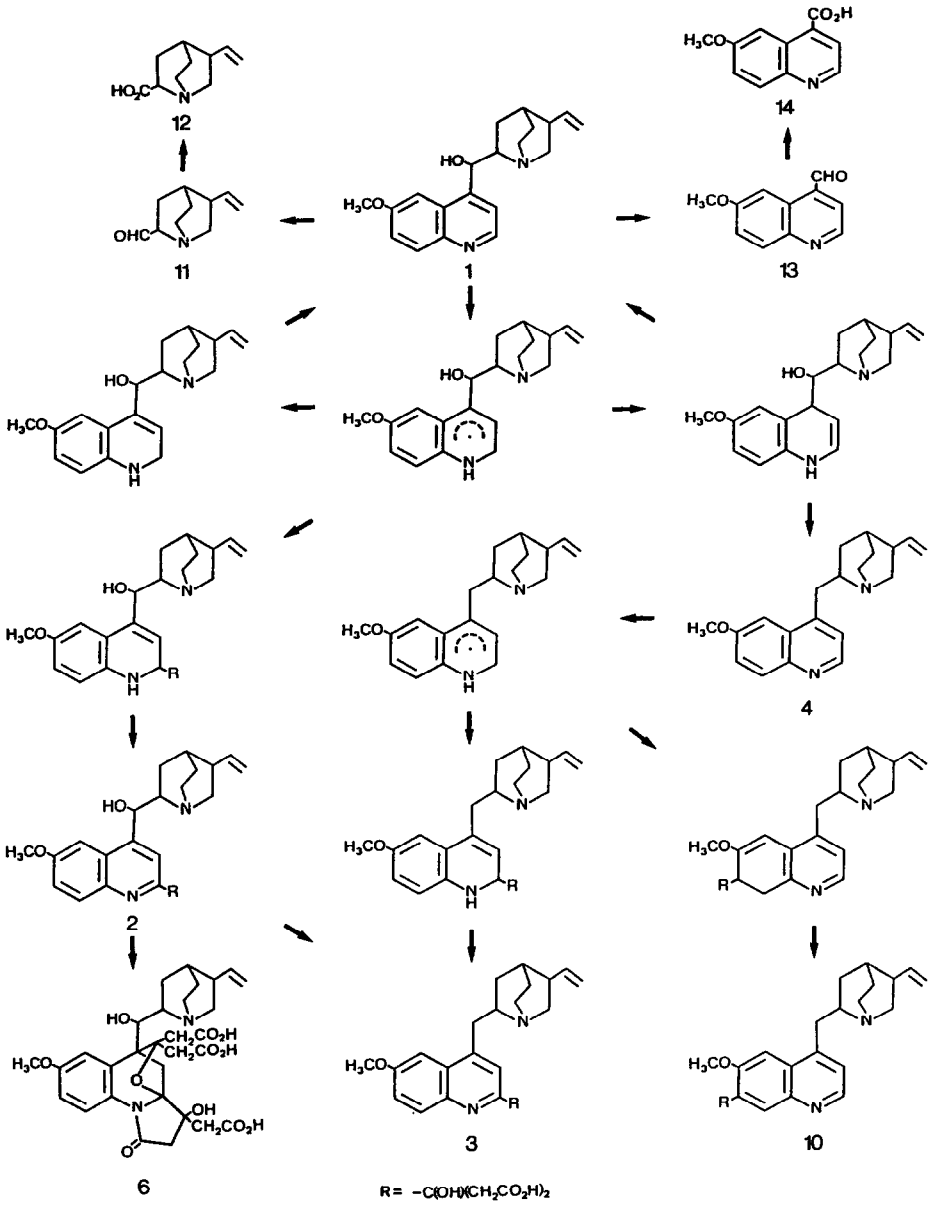


Fig. 2. Reaction scheme for formation of quinine photoproducts.

EXPERIMENTAL

Irradiations of quinine 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). Samples were prepared in deuterated chloroform.

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. GCMS was from a 25 m OV-1 capillary column. FAB mass spectra were generated on a VG ZAB-HF mass spectrometer. Samples were bombarded with a zenon atom beam from a Ion-Tech saddle field gun operating at 8 kv, 1 mA.

UV absorption spectra were measured in methanolic HCl and IR spectra were recorded as thin films.

The analytical and the preparative HPLC were carried out as described previously.[2] Analytical TLC used Merck Silica gel F254 (0.25 mm) plates developed with chloroform (saturated with ammonia)-ethanol (9:1, v/v). 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 this reagent.

A solution of quinine hydrochloride dihydrate (2.0 g) and citric acid monohydrate (40.0 g) in water (10 L) was irradiated with stirring for 110 hours by which time the characteristic three absorption bands of quinine at 250, 317 and 345 nm were replaced by a single absorption at 270 nm. The irradiated solution was pumped at a flow rate of 50 mL min^{-1} through a Prep. C_{18} cartridge that had been wetted with methanol (1 L) followed by water (2 L). The cartridge was washed with water (5 L) until the aqueous eluate was free from acid. The photoproducts were eluted with methanol (2 L) and the resulting solution was evaporated to dryness under vacuum to yield a brown residue (1.76 g) which gave a complex pattern of peaks by HPLC (Fig. 1). A solution of the residue in dry methanolic HCl (50 mL, 0.8 M) was refluxed for 1.5 hours and then evaporated to dryness under vacuum. A solution of the product in water was basified with Na_2CO_3 and extracted with chloroform. Evaporation of the extract gave a mixture which showed at least five spots by TLC. Two major components 5 and 9 with R_f = 0.85 and 0.63, respectively, were isolated and purified by TLC.

Compound 5

MS: m/z (rel. int.) $M^{+\cdot}$ 642(1), 569(12), 537(3), 468(4), 325(10), 136(100), 43(19). CIMS: m/z (rel. int.) $(M+1)^+$ 643(43), 537(7), 497(10), 477(27), 460(15), 325(20), 166(12), 136(100). Accurate mass $M^{+\cdot}$ 642.2757 (calc. 642.2788) for $C_{33}H_{42}N_2O_{11}$. CIMS (TMS derivative): m/z (rel. int.) $(M+1)^+$ 787(70), 715(31), 641(19), 550(20), 391(18), 203(15). IR: ν_{max} cm^{-1} 3400 (OH), 1740 (ester C=O), 1700 (lactam C=O). UV: λ_{max} 260 nm. ^1H NMR (90 MHz): δ 1.0-3.40 (m, aliphatic protons), 2.15 and 2.53 (ABq, 2H, J = 12.3 Hz, ring CH_2), 2.75 (d, 4H, 2 x CH_2), 3.15 (d, 2H, CH_2), 3.63 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.78 (s, 6H, 2 x OCH_3), 4.39 (d, 1H, J = 10 Hz, H-9), 4.60-4.95 (m, 2H, 2 x H-11), 5.30-5.70 (m, 1H, H-10), 6.84 (dd, 1H, J = 9.2, 2.9 Hz, H-7'), 8.21 (d, 1H, J = 2.9 Hz, H-5'), 8.63 (d, 1H, J = 9.2 Hz, H-8'). ^{13}C NMR: δ 25.5 (C-7), 27.0 (C-5), 27.5 (C-4), 37.5 (C-3), 39.4 (2 x $CH_2CO_2CH_3$), 41.0 (C-3'), 41.6 ($CH_2CO_2CH_3$), 42.6 (C-6), 45.9 (CH_2CON), 51.4, 51.7 and 52.1 (3 x OCH_3), 53.8 (C-2), 54.9 (C-8), 55.6 (aromatic OCH_3), 58.9 (C-4'), 73.4 and 73.7 (2 x COR), 88.2 (C-9), 100.0 (C-2'), 114.4 (C-5'), 114.8 (C-11), 115.1 (C-7'), 120.6 (C-8'), 128.9 (C-10'), 130.0 (C-9'), 140.6 (C-10), 155.6 (C-6'), 168.2, 171.3, 171.6 and 173.3 (4 x C=O).

Compound 9

MS: m/z (rel. int.) $M^{+\cdot}$ 482(0.2), 451(3), 148(19), 136(100), 81(16), 69(10), 57(18), 43(20). CIMS: m/z (rel. int.) $(M+1)^+$ 483(100), 136(35). CIMS (TMS derivative): m/z (rel. int.) $(M+1)^+$ 555(100), 466(26). ^1H NMR (90 MHz): δ 1.00-3.40 (m, 11H, quinuclidine ring protons), 3.62 (s, 6H, 2 x OCH_3), 3.98 (s, 3H, OCH_3), 4.85-5.15 (m, 2H, 2 x H-11), 5.50-5.90 (m, 1H, C-10), 5.95 (broad s, 1H, H-9), 7.24 (s, 1H, H-5'), 7.53 (d, 1H, J = 4,5 Hz, H-3'), 7.87 (s, 1H, H-8'), 8.71 (d, 1H, J = 4.5 Hz, H-2').

The esterified mixture of photoproducts showed four closely grouped major and several minor peaks by GCMS. The major peaks arose from two pairs of isomers.

Methyl esters of C-8 isomers of 12: m/z (rel. int.) M^+ 195(25), 136(100).

Methyl acetals of C-8 isomers of 11: m/z (rel. int.) M^+ 211(20), 180(40), 136(98), 75(100).

Methyl ester of 14: m/z (rel. int.) M^+ 217(100), 186(36), 158(53).

Compound 11: m/z (rel. int.) M^+ 165(14), 136(100).

Compound 13: m/z (rel. int.) M^+ 187(100), 186(45).

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