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PHOTOREACTIONS OF QUININE IN AQUEOUS CITRIC ACID SOLUTION

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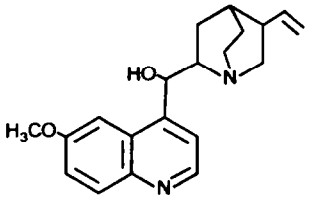
Abstract - Two novel compounds, 2'-(1,3-dicarboxy-2-hydroxyprop-2-yl)-quinine and the corresponding deoxyquinine derivative, have been identified together with deoxyquinine as major products of the irradiation of quinine in aqueous citric acid solution.

INTRODUCTION

Despite being known for more than a century[1] the photolability of quinine (1) has received scant study. Stenberg and co-workers[2,3] showed that deoxyquinine (2) was formed in 10% yield when quinine was irradiated in aqueous hydrochloric acid solution and Epling and Yoon [4] reported the cleavage to 6-methoxyquinoline (3) and 5-vinyl-quinuclidine-2-carboxaldehyde (4) in methanol. In view of these contrasting results it was of interest to establish the nature of the photoreactions responsible for the loss of quinine that occurs when a solution in aqueous citric acid is exposed to light.[5]



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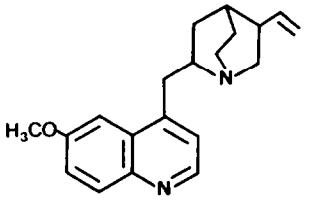

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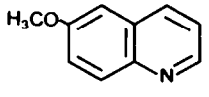

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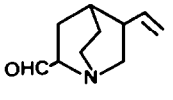

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RESULTS AND DISCUSSION

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 HPLC using UV detection at 250 nm. In the early stages of irradiation the solution showed three

peaks on the chromatogram in addition to that for quinine (Figure 1). After prolonged irradiation the solution no longer gave these three peaks suggesting that the compounds responsible reacted further to form products not detectable at 250 nm. The optimum yield of the three early formed photoproducts was attained after one hour's irradiation when approximately 80% of the quinine had reacted.

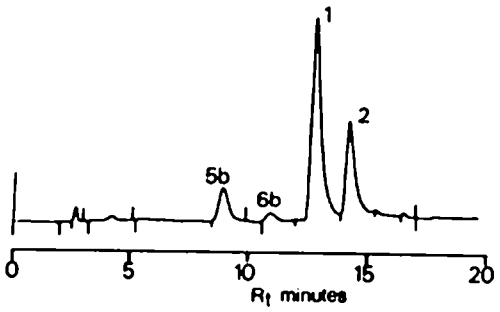
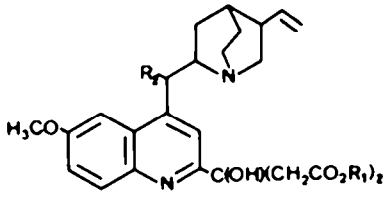


Fig. 1. HPLC separation of quinine (1) and photoproducts on LiChrosorb RP8.

Only that photoproduct corresponding to the slowest eluting HPLC peak was directly recoverable from the irradiated solution by solvent partition. It was obtained together with unreacted quinine when the irradiated solution was basified and extracted with chloroform. The photoproduct was separated from quinine by preparative TLC and shown to be deoxyquinine (2).

After extraction of quinine and deoxyquinine the irradiated solution was acidified and passed through a preparative C_{18} HPLC column. The remaining photoproducts were retained on the column which was then freed from acid by washing with water. Subsequent elution with methanol gave the photoproducts as a mixture not amenable to separation by TLC. Following evidence of the presence of carboxyl group(s) the mixture was esterified with methanolic HCl and examined by TLC. Two major components were detected and these were isolated by preparative TLC.

The mass spectrum of the more polar component showed a weak ion at m/z 498. Chemical ionisation mass spectrometry confirmed that this was the molecular ion and mass measurement gave an accurate mass consistent with the formula $C_{27}H_{34}N_2O_7$. The base peak observed in the spectrum at m/z 136 indicated that the photoproduct had retained the vinyl quinuclidine ring system of quinine. The IR spectrum contained bands indicative of hydroxyl groups (νmax 3480, 3300 cm^{-1}) and at least one carbonyl group (νmax 1735 cm^{-1}). Examination of the ^1H NMR spectrum showed a three proton aromatic methoxyl signal at δ 3.89 and a six proton signal for two identical ester methoxyls at δ 3.56. The aromatic proton region resembled that of quinine but the absence of the proton signal at lowest field (δ 8.55) suggested that substitution had occurred at C-2' of the quinoline ring. These results are best accommodated by structure 5a for the derivatised product and 5b for the original photoproduct.



5a : R_1 = CH_3 R_2 = OH
5b : R_1 = H R_2 = OH
6a : R_1 = CH_3 R_2 = H
6b : R_1 = H R_2 = H

The other esterified product was shown on the basis of the spectral data to be the corresponding deoxyquinine derivative, 2'-(1,3-dimethoxycarbonyl-2-hydroxyprop-2-yl)deoxyquinine (6a).

The saponification products 5b and 6b derived from 5a and 6a, respectively, corresponded in HPLC retention time to two of the major peaks shown by the solution in the early stages of irradiation.

The photo-induced formation of 5b and 6b from quinine and citric acid is analogous to the known photo-alkylation of quinoline at the 2- and 4-positions by aliphatic acids in benzene.[6,7] A plausible mechanism could involve the formation of radicals a and b from citric acid. While these radicals are formed on flash photolysis of aqueous citric acid solution[8] the use in the present study of a Pyrex filter opaque to light of wavelength <300 nm would have precluded their formation by this route. However, a possible source of the radicals is UV light activation of a quinine-citric acid complex (or salt).

a b

It has been established that 6b is formed if either 5b or deoxyquinine is irradiated in aqueous citric acid solution. There is no evidence that one or other pathway is particularly favoured but the simultaneous appearance of deoxyquinine and 6b during the irradiation of quinine may suggest that these products arise from a common intermediate.

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. Small-scale irradiations of deoxyquinine and 5b were performed in a test tube external to the Pyrex thimble.

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

Ultra-violet absorption spectra were recorded on a Perkin-Elmer Lambda 3 UV/VIS spectrometer in 1 cm path length cuvettes. Samples were prepared in methanolic HCl.

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

Analytical high performance liquid chromatography (HPLC) was carried out on an Altex/Beckman Series 340 liquid chromatograph comprising two 112 Solvent Delivery Modules, a 165 UV/VIS variable wave-length detector set at 250 nm, a 421 Controller, and a Universal injector fitted with a 20 µl loop. HPLC grade solvents, methanol and water, from Rathburn were used. Elution of photoproducts was effected from a LiChrosorb RP8 column (25 cm x 4.6 mm i.d.) using a concave gradient over thirteen minutes at a flow rate of 1.5 ml min^{-1}. The primary eluent was a solution of methanol-water-60% perchloric acid (15:84:1, v/v/v) and the secondary eluent was a solution of methanol-water-60% perchloric acid (60:39:1. v/v/v). Both mobile phases were degassed by ultrasonication for ten minutes prior to use.

Preparative HPLC was undertaken on a Waters Preparative LC 500 System fitted with a reversed-phase Prep. PAK C_{18} Cartridge (30 cm x 5.7 cm). Analytical TLC used Merck Silica-gel F254 (0.25 mm) plates developed with hexane-acetone-diethylamine (5:3:2, v/v/v). Photoproducts were detected on the fluorescent plates by quenching of 254 nm UV light and by fluorescence in 366 nm UV light. Visualisation with potassium iodoplatinate spray reagent was also used. All alkaloid photoproducts gave a violet colour with this reagent.

Quinine hydrochloride dihydrate (2.0 g) was dissolved in a solution of citric acid monohydrate (40.0 g) in water (100 mL). This solution was transferred to the photochemical reactor and diluted to volume (10 L) with distilled water. The 200 ppm quinine solution was irradiated for one hour whilst stirring mechanically. At regular intervals 2 mL aliquots were removed from the irradiated solution and were subjected to analysis by HPLC and by ultra-violet spectrometry against a reference solution of 0.4% citric acid.

The irradiated quinine solution (10 L), basified to pH 11 by the addition of sodium hydroxide solution (100 mL, 5 M), was extracted with chloroform (2 x 10 L). The combined extracts were dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure. The

resulting brown residue (500 mg) was shown by TLC to consist of quinine (R_f = 0.40) and a less polar compound (R_f = 0.55). Separation by TLC followed by crystallisation from ethanol gave the photoproduct as colourless plates.

MS: m/z (rel. int.), $M^{\cdot\cdot}$ 308(3.9), 307(2.3) 293(2), 198(4), 186(6), 185(7), 136(100), 81(6), 55(8), 42(8), 41(7), Accurate mass $M^{\cdot\cdot}$ 308.1857 (calc. 308.1889) for $C_{20}H_{24}N_2O$.

The compound had identical IR, UV, NMR and mass spectra to an authentic sample of deoxyquinine synthesised by the method of Pouwels and Veldstra.[9]

The aqueous phase (10 L) remaining after chloroform extraction was acidified to pH 2-3 with hydrochloric acid (50 mL, 10 M) and pumped at a flow rate of 50 mL min^{-1} onto a Prep. PAK C_{18} Cartridge (30 cm x 5.7 cm) that had been wetted with methanol (1 L) followed by water (2 L). The cartridge was washed with water (3 L) at a flow rate of 50 ml min^{-1} until the aqueous eluate was free from acid. The photoproducts were eluted with HPLC grade methanol (2 L) and the resulting solution was evaporated to dryness under vacuum to yield an amber residue (1.85g). Treatment of this residue with dry methanolic HCl afforded a mixture which was shown by TLC to contain the two esterified photoproducts (5a) and (6a) with R_f = 0.53 and 0.64, respectively. Purification by preparative TLC gave:-

Compound 5a

^{1}H-NMR (90 MHz): δ 1-0-3.0 (m, 11H, quinuclidine ring protons), 3.15 (m, 4H, 2xCH_2), 3.60 (s, 6H, 2xOCH_3), 3.85 (s, 3H, OCH_3), 4.80 - 5.10 (m, 2H, 2xH-11), 5.50 - 5.70 (m, 1H, H-10), 5.92 (broad s, 1H, H-9), 7.15 - 7.45 (m, 2H, J = 2.5, H-7', H-5'), 7.89 (d, 1H, J = 9, H-8'), 7.96 (s, 1H, H-3'). MS : m/z (rel. int.) $M^{\cdot\cdot}$ 498(0.2), 467(2), 136(100), 81(4), 55(2). CIMS : m/z (rel. int.) $(M+1)^+$ 499(100), 425(11), 136(56) Accurate mass $M^{\cdot\cdot}$ 498.2371 (calc. 498.2366) for $C_{27}H_{34}N_2O_7$. IR: νmax cm^{-1} 3480, 3300 (OH), 1735 (ester C=O), 1630, 1590, 1505, 1435, 995, 915. UV: λmax(nm) ε(L $mole^{-1}cm^{-1}$): 258 (25,200), 321 (3900), 345 (4300).

Compound 6a

^{1}H-NMR (90 MHz) : δ 1.00 - 3.00 (m, 11 H, quinuclidine ring protons), 3.15 (m, 4H, 2xCH_2), 3.60 (s, 6H, 2xOCH_3), 3.85 (s, 3H, OCH_3), 4.80-5.15 (t, 2H, 2xH-11), 5.60-6.00 (m, 1H, H-10), 7.20-7.45 (m, 2H, H-5', H-7'), 7.60 (broad s, 1H, H-3'), 7.91 (d, 1H, J = 9, H-8'). MS : m/z (rel. int.) $M^{\cdot\cdot}$ 482(2), 451(2) 411(1), 409(2) 136(100), 81(5), CIMS : m/z (rel. int.) $(M+1)^+$ 483(100), 409(8), 136(13) Accurate mass $M^{\cdot\cdot}$ 482.2385 (calc. 482.2417) for $C_{27}H_{34}N_2O_6$. IR: νmax 3300 (OH), 2950, 1745 (C=O), 1625, 1600, 1500, 1440, 1030, 1000, 925. UV: λmax(nm) ε(L $mole^{-1}cm^{-1}$) 258 (25,100), 323 (3920), 346 (4310).

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