RESEARCH PAPER

Received 10 September 1994
Indian J. Pharm. Sci., 1995, 57(6), pp. 237-239

4-Cyano-6-methoxyquinoline from Quinine

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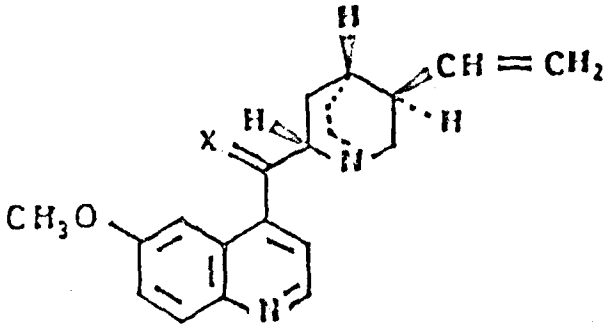
Quininone oxime when refluxed with phosphorus pentachloride in chloroform for 90 minutes underwent Beckmann fragmentation rather than rearrangement to give 4-cyano-6-methoxyquinoline.

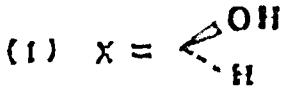
THE prevention and treatment of malaria, which appeared to have been controlled in the late fifties, have received a setback in the developing countries due to the development of drug resistance by malaria parasites to existing antimalarial agents such as chloroquine and pyrimethamine. This has initiated a search for new antimalarial drugs. Quinine (1) as an antimalarial agent is more toxic and less effective than chloroquine, but has provided a model for the search for more effective and less toxic drugs like mefloquine. Several structural alterations in the quinine molecule have been carried out, but none of the resulting compounds had antimalarial action superior to that of quinine.

In the present study it was thought of interest to prepare some quinine analogues. It was envisaged to introduce an extra nitrogen in the molecule through Beckmann rearrangement of the oxime 2 prepared from quinine (3). The resulting products, 4 and/or 5 were conceived to have different types of biological activities. However, the Beckmann rearrangement carried out with phosphorus pentachloride resulted in the fragmentation of the oxime rather than rearrangement to give 4-cyano-6-methoxy quinoline (6). Such fragmentation has been reported earlier in other molecules[1], but not with quininone oxime. The resulting product 6, though poor in yield, could serve as the starting material for the synthesis of 4-aminoalkyl substituted 6-methoxyquinolines, a class of potential medicinal interest, and other series.

Quinine (1) was oxidized by refluxing with benzophenone/potassium *tertiary*-butoxide in benzene to give quinione (3)[2]. Oximination of the quinione by the usual method employing hydroxylamine hydrochloride/pyridine was not successful. Quininone oxime (2) could be formed in the presence of sodium hydroxide using hydroxylamine hydrochloride[3]. The oxime on thin-layer chromatography using chloroform-methanol (8:2) was found to be a mixture of two isomers. The major isomer has been sucessfully separated through chromatographic procedure and has been obtained in pure crystalline form. Quininone oxime has earlier been reported as an uncrystallisable product[4].

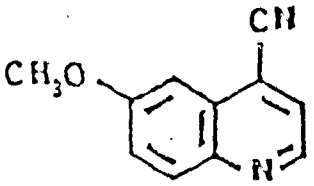
Attempts to carry out Beckmann rearrangement of the oxime (2) to get either 4 or 5 or mixture of both with thionyl chloride (in benzene, dioxane or ether), phosphorous oxychloride (in pyridine) or phosphorous pentachloride in cold (0-5°) (in chloroform) failed. Refluxing the oxime with phosphorous pentachloride for 90 minutes in chloroform, however resulted in Beckmann fragmentation rather than rearrangement to give 4-cyano-6-methyquinoline (6). The fragmentation product 6 showed the characteristic nitrile stretching at 2220 cm^{-1}. The PMR spectrum (CD $C1_3$) showed signals at δ9.0(d. for 1H. at C-2), 8.2 (d. for 1H. at C-3). Other ring protons appeared at 7.85 to 7.3 integrating for 3H.. The OCH_3 signal appeared as a singlet at δ4.0. The ^{13}C NMR spectrum ($CDC1_3$) showed a signal at



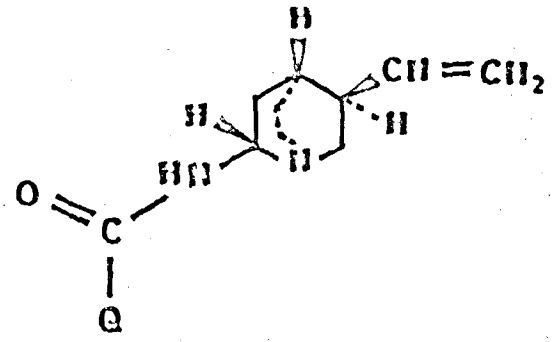
(1) X = 

(2) X = NOH

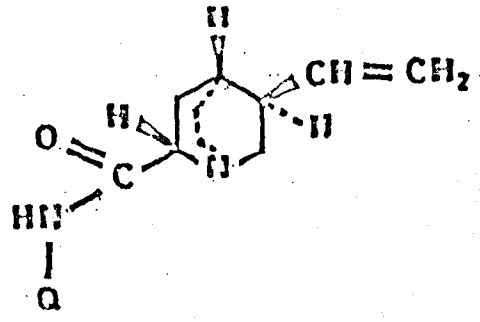
(3) X = O



(6)



(4) Q = 6-Methoxyquinol-4-yl



(5) Q = 6-Methoxyquinol-4-yl

124 ppm for cyano carbon and at 55 ppm for the methoxy carbon. The mass spectrum showed molecular ion peak at m/z 184. The other characteristic peak appeared at m/z 153 (base peak) due to the loss of methoxy group.

EXPERIMENTAL

The melting points reported are uncorrected. PMR spectra were recorded on Varian EM 390, 90 MHz model in $CDC1_3$ using TMS as internal reference (chemical shifts in δppm). ^{13}C NMR spectra were recorded on Jeol model FX 90 Q at 22.49 MHz and IR spectra in KBr (max, cm^{-1}). Mass spectra were recorded on VG micromass 7070 F model. Plates for TLC were prepared with silica gel G according to Stahl (E. Merck) and activated at 110° for 30 min, and were developed by spraying with modified Dragendorffs' reagent or exposure to iodine vapours. Anhydrous sodium sulphate was used as drying agent. Quinine sulphate of IP grade was purchased locally; from which the quinine base was obtained by the usual procedure.

Quininone (3)

Potassium *tertiary* - butoxide was prepared by completely dissolving potassium metal (4g) in *tert*-butanol (80 ml). The excess of *tert*-butanol was removed *in vacuo* and the solid cake broken up and dried until a mobile powder was obtained. To the dried powder anhydrous benzene (155 ml), quinine

(10g) and dry benzophenone (30 g) were added. The system was flushed with dry nitrogen and the mixture was refluxed on a water bath for 20 hr. The reaction mixture was allowed to cool and poured into crushed ice and then extracted with 10% v/v hydrochloric acid until the extract was nearly colourless. The combined acid extract was washed with ether and then dripped with stirring into an excess of ammonia solution in crushed ice. The quininone, precipitated as a pale yellow semi-solid, was extracted with ether. The aqueous layer was saturated with sodium chloride and extracted again with ether. The combined ether extract was washed with salt solution, dried and concentrated to yield 3 as pale yellow crystals (8.7g, 87.6%); m.p. 92-94° (lit [2] m.p. 106- 108°); IR : 1750, 1650; PMR : δ 9(d, 1H), 8(d,1H), 7.78 (1H), 7.62(1H), 7.4 (d,1H), 6.0(m, 1H), 5.1(m,2H), 4.2(m,1H), 3.98(s, 3H) and 3.2-1.4(1CH); ^{13}C NMR : δc 204 (> C=O), 159 and 148.

Quininone oxime (2)

To a solution of 3 in 15 ml of ethanol containing 2-3 drops of water were added hydroxylamine hydrochloride (2.5g) and sodium hydroxide (5g). The mixture was refluxed for 4 hr. After cooling, the mixture was diluted with water and extracted with chloroform. The combined organic layer was washed with water, dried and concentrated *in vacuo* to give a brown fluffy mass (2.3g; 88.5 %). TLC (chloroform-methanol, 8:2) revealed it to be a mixture. Resolution of the crude oxime (1.8 g) on a column of alumina gave a major crystalline fraction of the pure oxime (0.33 g,17.8 %); m.p. 150-152°; IR : 3500, 1670, 1408, 1250, 1042; PMR: δ11.35(S, 1H, exchanged with D_2O); ^{13}C NMR (CD_3OD) : δc 179 (> C=N), 160, 148; MS: m/z 337 (M^+).

4-Cyano-6-methoxyquinoline (6)

To a solution of the oxime 2 (4g) in chloroform (50 ml) were added 5 g of phosphorous pentachloride, and the mixture was refluxed for 90 min. After removal of the solvent under vacuum the residue was diluted with water and basified with sodium carbonate and extracted with chloroform. The combined chloroform extract was washed with water, dried and the solvent evaporated to yield a residue (2.69;65 %) which was chromatographed over a column of alumina (180g). Elution with petroleum ether (60- 80°)-chloroform (8:2) gave a residue which upon crystallization from petroleum ether afforded 6 (0.103g, 2.57 %), m.p. 135-139°; IR : 2220; PMR : 9.0(1H), 8.2(1H), 7.85-7.3 (3H) and 4.0(S, 3H); ^{13}C NMR ($CDCl_3$) : δc 124; 55; MS : m/z 184 (M^+), 153, (M^+-OCH_3).

ACKNOWLEDGEMENTS

The authors are thankful to the University Grants Commission, New Delhi for providing financial assistance; and to Dr. K.L. Bedi, Regional Research Laboratory, Jammu for recording the ^{13}C NMR spectra.

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4. Rabe, P., **Ann. Chem.**, 1909, 364, 330.