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1-ACETOXY-4-HYDROXYIMINO-1,4-DIHYDROQUINOLINE, A REACTIVE INTERMEDIATE DERIVED FROM THE POTENT CARCINOGEN 4-NITROQUINOLINE N-OXIDE

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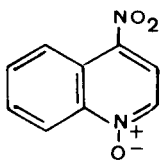
Summary :

The title compound, a new monoester of the carcinogenic metabolite 4-hydroxyaminoquinoline 1-oxide, has been prepared as its crystalline hydrochloride and its decomposition in acidic and basic media examined.

4-Nitroquinoline N-oxide (4-NQO) 1 is a synthetic carcinogen whose chemistry and biology have been extensively studied by Japanese workers[1]. Its metabolic transformation is known to involve reduction to 4-hydroxyaminoquinoline 1-oxide (4-HAQO), existing largely[2] as the tautomer 2,which is subsequently activated to a reactive "ultimate" derivative which is able to bind covalently to nucleic acids. The mono- and di-acetates 3 and 4 have been considered as models for this ultimate carcinogen. The diacetate 4 is a very unstable[3] compound which is obtained by acetylation[4] (Ac_2O/AcOH) of 4-HAQO 2 . The monoacetate 3 has been prepared by Kawazoe et al.[2] by treating 4 with dithiothreitol in DMSO. It is so reactive that it could not be isolated. This preparative procedure has been used recently by Bailleul et al.[5] to study the interaction of 3 with DNA and nucleosides.

We now report the isolation and some of the properties of the hydrochloride of the other monoacetyl derivative of 4-HAQO, i.e. 1-acetoxy-4-hydroxyimino-1,4-dihydroquinoline 5, which proves to be just as reactive as the related acetates 3 and 4.



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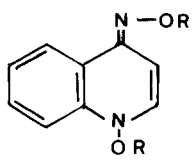
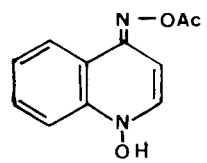


2 · R = H

4 R = Ac



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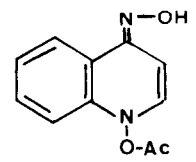
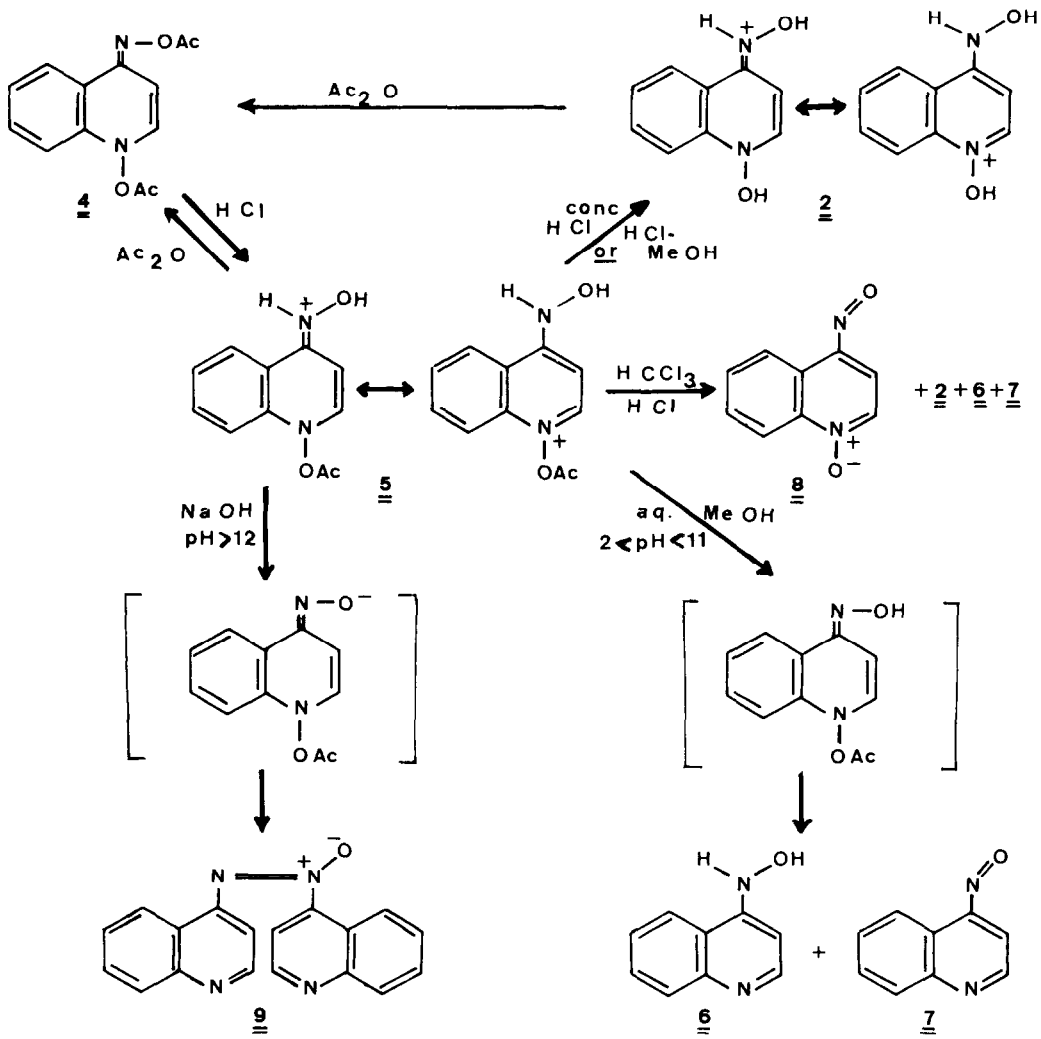


5

The new monoacetate 5 was obtained as its hydrochloride by selective cleavage of the oxime acetate function of diacetate 4 by HCl. The white powder was assigned the structure 5 on the basis of its chemical reactions and spectroscopic data[6]. The fact that compound 5 possesses the 4-HAQO skeleton 2 and that it corresponds to one of the two possible monoacetyl derivatives is indicated by the following reactions :

1/ 5 could be quantitatively reacetylated to 4 by treatment with Ac_2O. (This was established by the isolation of the reaction product and its identification with authentic 4. The quantitative nature of the reaction was proved by HPLC analysis).

2/ 5 was hydrolysed to 4-HAQO 2. (This latter compound was identified by its retention time on HPLC and by its reacetylation "in situ" to authentic bis-acetate 4).



Compound 5 is clearly different from its previously described isomer 3, as indicated by spectroscopic data, HPLC analysis and chemical reactivity. Furthermore the simultaneous presence of 3 and 5 during the acid methanolysis of 4 was established by low temperature NMR spectroscopy. Structure 5 can be assigned on this basis alone. It is further confirmed by the spectroscopic data. One absorption at 1825 cm^{-1}, which is indicative of the presence of the acetoxy group at position 1, is visible in the IR spectrum[7]. It corresponds to the high frequency band observed[8] for diacetyl 4 (1810 and 1760 cm^{-1}). In the NMR spectrum (acidic methanol) the acetate protons are visible at δ 2.60 ppm (peaks at 2.42 in 4)[6] and the H-2 and H-3 protons appear as doublets at δ 8.65 and 7.05 (J = 8Hz).

Compound 5 is extremely reactive. The crystalline hydrochloride can be kept for a few days in the dark at low temperature under an HCl atmosphere or in suspension in $CHCl_3$. However on further standing a complex mixture is obtained in which the nitroso derivatives 7 and 8 can be identified[9,10], along with the hydroxylamines 2 and 6.

In solution, its behaviour depends strongly on the pH of the medium. In concentrated aqueous hydrochloric acid (or in methanol saturated with dry HCl), it is quantitatively transformed to 4-HAQO 2. In neutral conditions however, in citrate buffer at pH 7, the formation of this compound is no longer observed and a mixture of hydroxylaminoquinoline 6 and nitrosoquinoline 7 is rapidly obtained (6 : 15 % ; 7 : 60 % at 18°C). The half lifetime of 5 was estimated to be about 2 mn in 50 : 50 CH_3OH-H_2O, pH 7, 15°. Similar behaviour is observed for 5 at all pHs ranging from 2 to 12. In basic conditions, in aqueous sodium hydroxide (pH > 12) there is immediate precipitation of an orange solid which is a complex mixture of quinolinylazoquinoline oxides[11] such as 9.

Compound 5 was routinely analysed by HPLC. It gives one sharp peak which does not correspond to the elution of the injected 5 but to the nitroso compound 7, instantly and quantitatively formed on the column[9,12].

The monoacetate 5 is a very reactive compound for which various kinds of reactivity have been observed - hydrolysis to 2, elimination of acetic acid to give 7 and redox reactions leading to 6, 7 and 8. Several reaction mechanisms can be envisaged for the two latter processes and analogies can be found in the literature, notably in the carcinogenic purine N-oxide series[13]. The pathways probably involve the protonated, neutral and deprotonated forms of 5 at the different pHs as shown.

Compound 5 is a close derivative of 4-HAQO, 2, a compound which has been demonstrated to be a metabolite of the carcinogenic 4-NQO. We are now investigating the possible reaction of 5 with nucleosides and DNA.

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NOTES AND REFERENCES

1. For a recent Review, see T. Sugimura "Carcinogenesis, Vol 6 : The Nitroquinolines", Ed. Raven Press, New York, 1981.

2. Y. Kawazoe, O. Ogawa and G.F. Huang, Tetrahedron, 36, 2933 (1980).
3 was also produced when diacetate 4 was treated with liquid ammonia. It was too sensitive to air oxidation to be purified.

3. M. Araki, Y. Kawazoe and C. Nagata, Chem. Pharm. Bull., 17, 1344 (1969).

4. Y. Kawazoe and M. Araki, Gann, 58, 485 (1967).

5. B. Bailleul, S. Galiegue and M.H. Loucheux-Lefebvre, in press.

6. 5 (hydrochloride) : mp 118-118.5°C ; IR(KBr) 1825 cm^{-1} ; NMR (CD_3OD-DCl) δ 2.6 (s, 3H, CH_3), 7.05 (d, 1H, J=8Hz, H-3), 8.65 (d, 1H, J=8Hz, H-2), 8.4 (m : 1H), 7.5-8 (m, 3H) ; UV (CH_3OH) λ_{max} 242 (ε =21000) 354 nm (ε = 11000) ; mass : m/e 219 : M^++1 (4) 202 (0.2) 174 (2.9) 160 (31) 144 (58) 129 (49) 128 (100) 117 (34).

7. Comparable high frequency absorption reported for N-oxide esters in the purine series. See for example ref. 13.

8. M. Enomoto, K. Sato, E.C. Miller and J.A. Miller, Life Sciences, 7, 1025 (1968).

9. An authentic sample of the new compound 7 was prepared by Ag_2CO_3 oxidation of 6. This material had mp 82°C (dec) ; NMR ($CDCl_3$) δ 6.1 (d, 1H, J=4Hz, H-3), 7.5-8.5 (m, 3H), 9.11 (d, 1H, J=4Hz, H-2), 9.7 (m, 1H, H-5) ; UV (CHC'_3) λ_{max} = 242 (ε = 20140) 364 (ε = 8400) ; mass : m/e 158 : M^+ (56.7), 144 (20) 128 (100) 117 (5.5) 101 (95.5).

10. R.A. Abramovitch and E.M. Smith, J. Het. Chem., 12, 969 (1975).

11. T. Kosuge, H. Zenda and H. Sawanishi, Chem. Pharm. Bull., 17, 2389 (1969) and preceding papers.

12. The analysis of 5 consequently included, in addition to the HPLC test, a reacetylation reaction of the product to 4 and HPLC examination. This analysis technique was also extended to compounds 2 and 6. HPLC was performed on μBondapak C18 using MeOH : H_2O pH 2.5.

13. J.C. Parham and M.A. Templeton, Tetrahedron, 36, 709 (1980), and refs there in ; R.A. Mathews and G. Stohrer, Chem. Biol. Interactions, 29, 57 (1980).

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