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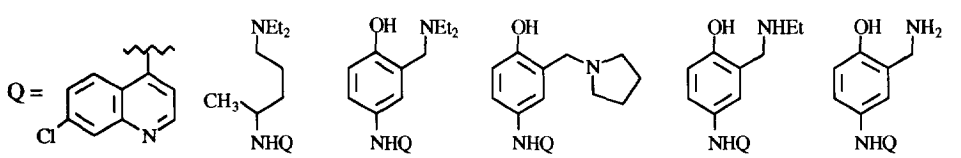
In Search of the Non-Polar Amopyroquin Metabolite. A Consideration of Polonovski-Type Reactivity

David J. Aitken*, Isabelle Jobet-Hermelin and Henri-Philippe Husson

Laboratoire de Chimie Thérapeutique, URA 1310 du CNRS, Faculté des Sciences Pharmaceutiques et Biologiques, Université René Descartes, 4 Avenue de l'Observatoire, 75270 Paris cedex 06, France.

Abstract: The Polonovski-Potier reaction was carried out on the *N*-oxide of amopyroquin in an attempt to mimic the metabolic process. The major reaction product was the previously unknown aldehyde. The dihydrobenzoxazine, potentially the unidentified non-polar metabolite, was prepared by an alternative route. Neither of these compounds was the metabolite sought.

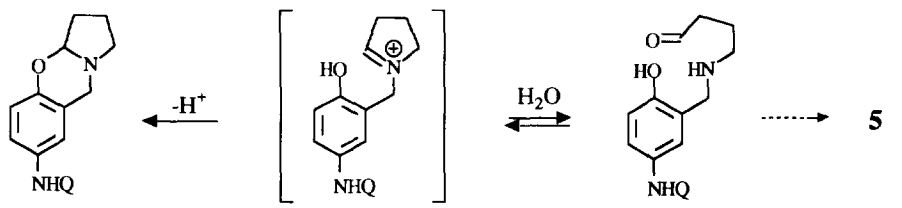
Malaria is one of the most serious parasitic diseases, accounting for over 1 million human deaths annually.[1] Since the 1940s, chloroquin (CQ) **1** has figured among the most effective antimalarial agents, but the recent appearance of CQ-resistant strains of *Plasmodium* has revived interest in other 4-amino-quinolines,[2] notably amodiaquin (ADQ) **2** and amopyroquin (APQ) **3**. Full pharmacological profiles of these compounds are necessary, however, before they can be safely used as alternatives to CQ in the treatment of malaria or as prophylactics.[3]



1 **2** **3** **4** **5**

Metabolic and pharmacokinetic studies[4-6] have shown that the major metabolite of ADQ in man is the monodesethyl derivative **4**, which accumulates rapidly in the blood and appears to be the active form of the drug.[4a] This derivative is eliminated over a period of several days, during which time other minor metabolites are formed, including the bisdesethyl derivative **5**. Rather less is known of APQ metabolism,[7] but a recent study by the Verdier group[8] of malaria patients treated with APQ indicated that the same primary amine **5** was a metabolite (T_{max} 11 h) and revealed the intermediate formation (T_{max} 3 h) of an unidentified component (APQM) of unusually low polarity. Blood plasma samples contained metabolite concentrations prohibitively low for feasible extraction, so we envisaged performing biomimetic chemical transformations on APQ in an effort to prepare and identify the putative metabolite.

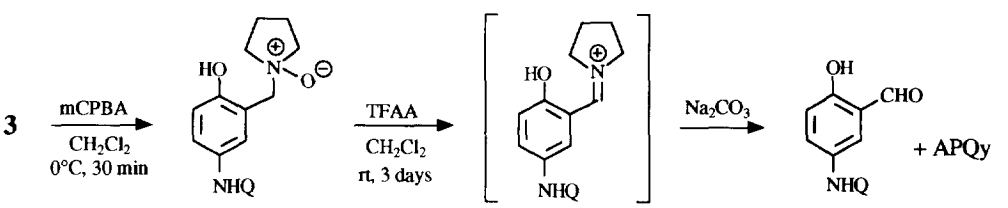
The low polarity of the new component suggested that it was unlikely to be a hydroxylated product. The structural similarities between APQ and ADQ led us to speculate that the same metabolic process should operate for both compounds, *i.e.* transformation at the tertiary aliphatic amine centre. One possible biomimetic system for ADQ could involve generation of an iminium ion centred on one of the ethyl substituents, ready hydrolysis of which should give the major metabolite **4**. We considered that an analogous iminium ion **A** located in the pyrrolidine ring of APQ would be less rapidly hydrolysed, due to reversible intramolecular condensation of the aminoaldehyde **7**, and might persist long enough to allow intramolecular trapping by the phenol to give dihydro-1,3-benzoxazine **6**, an interesting possible structure for the non-polar metabolite (Scheme 1). Through equilibration with **7**, slower cleavage of the second N-C bond would eventually produce the known metabolite **5**.



6 **A** **7**

Scheme 1

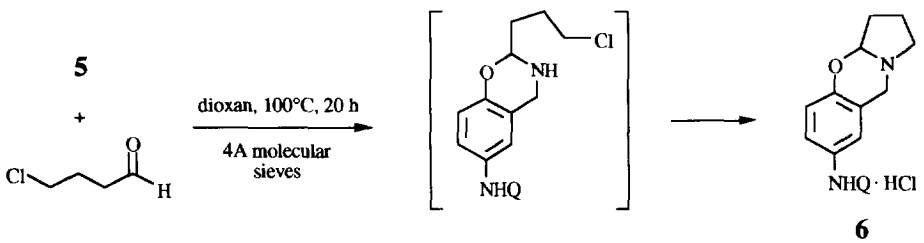
In the Polonovski reaction,[9,10] an iminium ion is generated from a tertiary amine *via* its *N*-oxide, and the Potier modification[10,11] allows stabilisation of the iminium to a sufficient degree to allow reaction with selected nucleophiles. This seemed a worthy system to probe the metabolism-mimetic reactivity of APQ.[12] In the event, the stable *N*-oxide **8** (APQO) was obtained chimioselectively in 72% yield by oxidation of APQ with mCPBA. Exposure of a solution of this compound in dichloromethane to excess trifluoroacetic anhydride (Polonovski-Potier conditions) over 3 days followed by basic aqueous work-up gave two new products in around 70% total yield (Scheme 2). The major product was identified as the aldehyde **9**, suggesting that the reaction had proceeded *via* the more stable benzylic iminium ion **B**. The minor component (APQy) was not identified,[13] and was rapidly degraded on attempted purification. No evidence for the formation of structure **6** was obtained.



8 **B** **9**

Scheme 2

The Polonovski system did therefore operate on the targeted centre of APQ, but generated the wrong iminium regioisomer for our hypothesis. Since other potentially biomimetic systems seemed likely to do the same,[14] we devised an alternative unequivocal synthesis of oxazine **6** (Scheme 3). The available[15] primary amine **5** was condensed in a one-pot reaction with 4-chlorobutyraldehyde[16] to give **6** as its hydrochloride in near-quantitative yield.



6

Scheme 3

HPLC coinjection of a blood serum sample containing APQM with each of the new compounds[17] **6**, **8**, **9** and the unidentified minor component from the Polonovski-Potier reaction showed that none of these structures corresponded to that of the non-polar metabolite. The iminium system may, of course, be an inappropriate choice here, and the possibility of different metabolic processes for ADQ and APQ cannot be excluded. We are presently considering alternative metabolism-mimetic reactions in the search for APQM.

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12. For a metabolism-mimetic example of the Polonovski-Potier reaction, see: Gessner, W.; Brossi, A. *Helv. Chim. Acta* **1984**, *67*, 2037.
13. UV spectral data (H_2O/MeOH/AcOH) suggested a reaction at the main chromophore centre, *i.e.* the quinoline system: APQ, APQO and aldehyde **9** all have (approximately) λ^1_{max} = 235 nm, λ^2_{max} = 345 nm, $\varepsilon_1/\varepsilon_2$ = 1.13, while APQy had λ^1_{max} = 235 nm, λ^2_{max} = 330 nm, $\varepsilon_1/\varepsilon_2$ = 0.56.
14. For example, trityl tetrafluoroborate generates conjugated iminiums from tetrahydroisoquinolines: de Costa, B.R.; Radesca, L. *Synthesis* **1992**, 887.
15. Prepared in five steps following the original Parke-Davis synthesis: Burckhalter, J.H.; Tendick, F.H.; Jones, E.M.; Jones, P.A.; Holcomb, W.F.; Rawlins, A.L. *J. Am. Chem. Soc.* **1948**, *70*, 1363.
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APQO **8**: δ_H ($CD_3OD/CDCl_3$) 1.82 (2H, m), 2.08 (2H, m), 3.22 (4H, m), 4.33 (2H, s), 6.34 (1H, d), 6.71 (1H, d), 6.88 (1H, d), 6.99 (1H, dd), 7.14 (1H, dd), 7.56 (1H, d), 7.88 (1H, d), 7.99 (1H, d); δ_C ($CD_3OD/CDCl_3$) 20.9, 66.9, 68.2, 100.2, 117.3, 118.6, 121.0, 122.6, 125.2, 126.2, 128.1, 128.6, 130.2, 135.2, 148.1, 150.3, 150.5, 156.4; MS (CI/CH_4) *m/z* 370 and 372 $[MH]^+$
aldehyde **9**: δ_H ($CDCl_3$) 6.59 (1H, d), 7.12 (1H, d), 7.43 (1H, dd), 7.51 (1H, dd), 7.55 (1H, d), 7.91 (1H, d), 8.03 (1H, d), 8.45 (1H, d), 9.96 (1H, s); δ_C (DMSO-d_6) 102.0, 119.0, 119.7, 123.9, 124.7, 125.4, 126.1, 128.7, 132.8, 133.9, 135.1, 150.0, 150.5, 153.1, 159.5, 191.9; IR (nujol) ν 1657 cm^{-1}; MS (CI/NH_3) *m/z* 299 and 301 $[MH]^+$
oxazine **6**: δ_H (DMSO-d_6) 1.8-2.1 (4H, m), 2.73 (1H, m), 2.98 (1H, m), 3.82 (1H, d), 4.31 (1H, d), 5.09 (1H, d), 6.54 (1H, d), 6.78 (1H, d), 7.06 (2H, m), 7.52 (1H, dd), 7.86 (1H, d), 8.47 (1H, d), 8.48 (1H, d); δ_C (DMSO-d_6) 21.9, 32.6, 46.6, 49.8, 91.6, 101.8, 117.9, 119.0, 120.9, 124.3, 124.9, 125.6, 125.7, 128.6, 133.0, 134.8, 150.3, 150.6, 152.0, 153.0; MS (CI/NH_3) *m/z* 352 and 354 $[MH]^+$.

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