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N-ACETYL-N-OXO-1,4-BENZOQUINONE IMINE, OBSERVATION OF AN ACYL NITRONE

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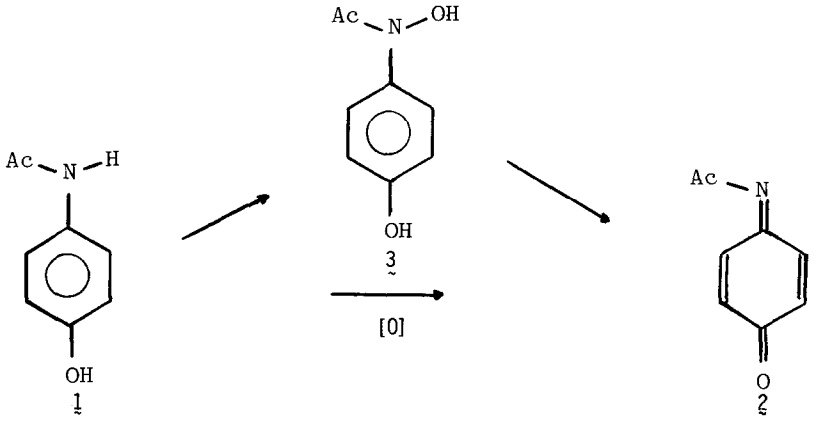
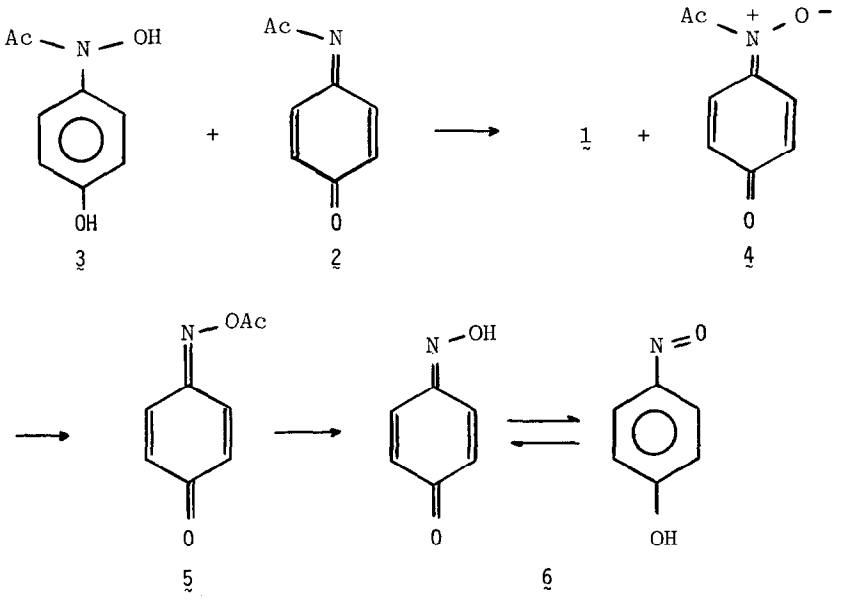
SUMMARY: N-Acetyl-N-oxo-1,4-benzoquinone imine, an N-acyl nitrone has been prepared and its intramolecular rearrangement to N-acetoxy-1,4-benzoquinone imine observed using ^{1}H-NMR spectroscopy.

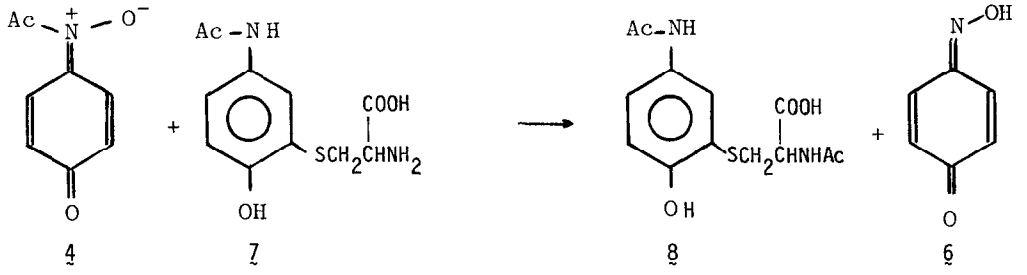
The analgesic paracetamol (1) is linked with liver necrosis in man and experimental animals when taken in high doses[1]. Its toxicity has been attributed to an electrophilic metabolite N-acetyl-1,4-benzoquinone imine (2) which may bind to cell macromolecules[2]. The mechanism of its formation is at present a matter of controversy with current evidence[3,4] favouring a direct oxidative route (1 → 2) by-passing the putative intermediate, N-hydroxyparacetamol (3).



During decomposition studies of 3 we[4] and others[3] have suggested that a highly unstable N-acyl nitrone, N-acetyl-N-oxo-1,4-benzoquinone imine (4) was formed as a result of the oxidation of 3 by 2; the decomposition products isolated are readily explained by rearrangement of the nitrone (4) to N-acetoxy-1,4-benzoquinone imine (5) followed by hydrolysis of 5 to p-nitrosophenol (6).

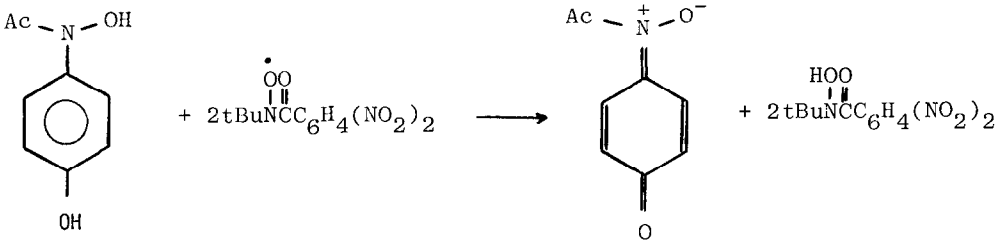


Additional evidence[5] that 4 was an intermediate was provided in the synthesis of the cysteine conjugate of paracetamol where the acetylated byproduct, paracetamol mercapturic acid (8) was isolated. When 5 was found to be unable to acetylate the cysteine conjugate (7) the active species was postulated to be the N-acyl nitrone (4).



To validate the above suggestions we set out to prepare 4 and observe some of its properties. N-Acyl nitrones have been previously suggested as reactive intermediates in the oxidation of N-alkyl hydroxamic acids[6,7,8]. Though too reactive to be observed, their presence was inferred from trapping experiments and from their behaviour as powerful acylating agents. We expected that the extended conjugation of 4 would lead to a more stable entity than the simple N-acyl nitrones. We now report the preparation of N-acetyl-N-oxo-1,4-benzoquinone imine (4) and its dimethyl analogue (9).

N-Hydroxyparacetamol (3) was smoothly oxidised to nitrone 4 at -75° in *deutero*-acetone by two equivalents of N-3,5-dinitrobenzoyl-N-t-butyl nitroxyl[9] (10). The reaction could be followed visually by the disappearance of the colour of the green radical and the formation of the yellow-brown nitrone.

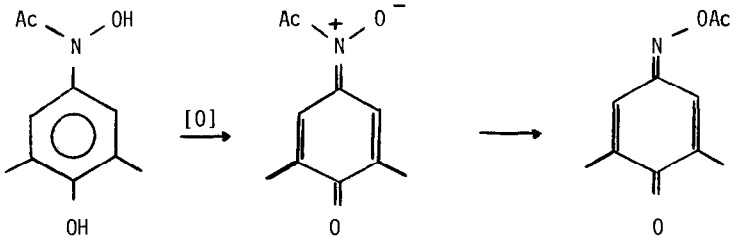


3 10 4 11

4 appeared to be stable indefinitely at -75°, but on warming the solution turned pale yellow forming the rearranged product, N-acetoxy-1,4-benzoquinone imine (5), which was isolated via silica gel chromatography[10]. The above sequence of reactions was followed by ^{1}H-NMR spectroscopy using the acetyl methyl group as a probe. The conversion of 3 → 4 resulted in a shift of the methyl resonance[11] from δ2.10 to δ2.69. On warming to -55° the methyl signal moved to δ2.33 and the spectrum corresponded to that of an authentic sample of 5[12].

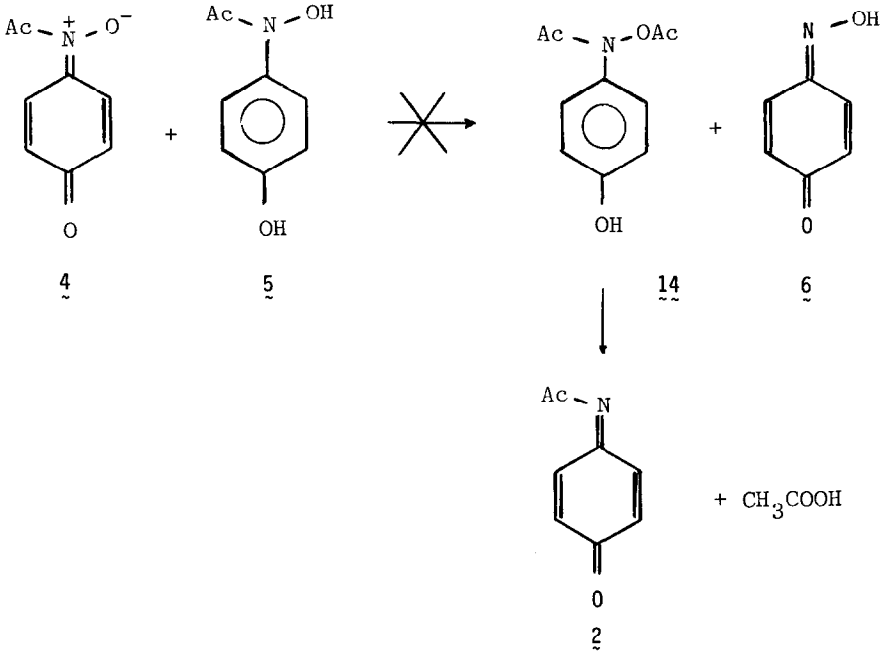
The acyl nitrone 4 was shown to be a strong acylating agent converting aniline to acetanilide at -60° in 50% isolated yield. In contrast the oxime acetate (5) does not acylate aniline even at room temperature.

Oxidation of 3,5-dimethyl-N-hydroxyparacetamol (12) with the radical 10 yielded the corresponding acyl nitrone (9). The substituted nitrone (9) was more stable than 4 and did not rearrange to the oxime acetate (13) until the temperature reached -15°.



12 9 13

While the exact mode of N-acyl nitrone rearrangement is unknown, we have excluded the pathway below by the careful addition of stoichiometric quantities of the oxidant 10; neither excess 3 nor signals corresponding to 14, 6 or 2 were observed in the proton NMR spectrum.



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10. Some decomposition to the p-nitrosophenol occurred on chromatography.
11. All other resonances in the spectrum could be completely accounted for and were assigned either to 11 or the complex quinonoid protons of 4.
12. Prepared by the procedure of R. Norris and S. Sternhell, *Aust. J. Chem.*, 24, 1449 (1971).

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