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A NEW NITRATION PRODUCT, 3-NITRO-4-ACETAMIDOPHENOL, OBTAINED FROM ACETAMINOPHEN WITH NITROUS ACID

Takanobu MATSUNO, Tomoko MATSUKAWA, Yoshiharu SAKUMA, and Takehisa KUNIEDA*
Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto 862, Japan

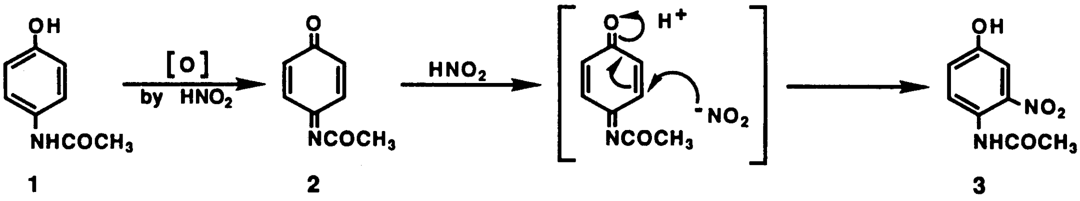
Treatment of acetaminophen with an excess sodium nitrite under mildly acidic to neutral conditions results in smooth formation of new 3-nitro-4-acetamidophenol via N-acetyl-p-benzoquinone imine as an oxidation intermediate, which is a well-known, widely explored metabolite.

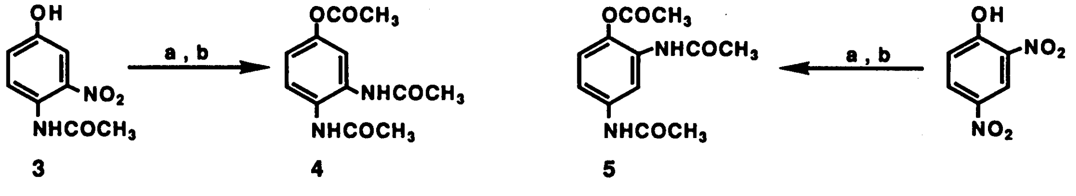
KEYWORDS acetaminophen; sodium nitrite; nitration; N-acetyl-p-benzoquinone imine; 3-nitro-4-acetamidophenol

There is still considerable interest in the metabolic chemistry of the widely used analgesic and antipyretic drugs acetaminophen (p-acetamidophenol)[1] and phenacetin,[2] and related compounds.[3] A recent paper[4] on the reaction of p-acetaminophen with nitrite under gastric conditions has promted us to report our results on a new nitration product.

As part of synthesis study of methoxatin, we have found quite smooth formation of 3-nitro-4-acetamidophenol (3) on the treatment of acetaminophen (1) with sodium nitrite commonly used as a food additive at the relatively wide pH range of 3 to 7.[5] Thus, p-acetamidophenol (1) was treated at 0°C with a five-molar excess of sodium nitrite in aqueous acetic acid at pH 4 or in a phosphate-buffer solution at pH 7 to give the 3-nitrated phenol (3)[6] (mp 139°C) in 81% yield. The structure of this product was unequivocally determined by reductive conversion to 3,4-diacetamidophenyl acetate (4)[6] (mp 181°C) which was distinctly different from the authentic 2,4-diacetamidophenyl acetate (5)[6] (mp 195°C) derived from 2,4-dinitrophenol. In contrast to the previous observation,[4] no nitration occurred at the 2-position of the phenol in this reaction.

This type of aromatic nitration with nitrous acid probably involves the initial formation of an oxidation intermediate, N-acetyl-p-benzoquinone imine (2), followed by the Michael-type addition of nitrite ion. Intermediacy of the quinone imine is suggested by the fact that treatment of the quinone imine purely isolated[7] with sodium nitrite under mildly acidic or neutral conditions resulted in smooth formation of the 3-nitrated product (3) (22% yield), and the nitration of 1 was greatly facilitated by treatment with equimolecular amounts of hydrogen peroxide (at 0°C) followed by the addition of nitrite to give nearly quantitative yield of 3 (above 94%).





a) Zn , CH_3COOH ; b) $(CH_3CO)_2O$, pyridine

The reactive intermediate quinone imine (2) is well recognized as an important hepatotoxic metabolite of the p-aminophenol type of analgesics,[1,2,8] and is believed to make nonenzymatically in vivo a covalent bonding with nucleophiles such as the thiol groups on proteins. Our mode of nitrite addition to the quinone imine at the 3-position is in strong contrast to the previous reports that nucleophiles such as the methanethiol,[9] cysteine[10] and glutathione[10] moieties as well as chloride ions[3a] would react with the quinone imine metabolite (2) at the 2-position to give the 2-substituted phenols.

In conclusion, treatment of acetaminophen with an excess nitrous acid gave a high yield of the nitration product, 3-nitro-4-acetamidophenol, contrary to the expectation that nitration would take place at the 2-position. The smooth nitration described in this paper may be of significance particularly in connection with the metabolism of the analgesics, p-acetaminophen and related drugs, since nitrite serves as an oxidizing agent and a good source of nucleophile.

Further structural studies of the nucleophile adducts derived from the quinone imine metabolite are in progress.

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6) Characterized by elemental and spectral analyses. Spectral data are as follows.
(3): ^{1}H-NMR (DMSO-d_6) δ 2.04 (s,3H), 7.02 (d,1H,J=9.0Hz), 7.72 (d.d,1H,J=9.0Hz and 2.4Hz), 8.87 (d,1H,J=2.4Hz). IR (KBr) 3296, 1664 and 1546 cm^{-1}. MS m/z 196 (M$^+$).
(4): ^{1}H-NMR (DMSO-d_6) δ 2.03 (s,3H), 2.15 (s,6H), 7.16 (d,1H,J=9.0Hz), 7.54 (d.d,1H,J=9.0Hz and 3.0Hz), 7.60 (d,1H,J=3.0Hz). IR (KBr) 1768 and 1673 cm^{-1}. MS m/z 250 (M$^+$).
(5): ^{1}H-NMR (DMSO-d_6) δ 2.01 (s,3H), 2.04 (s,3H), 2.24 (s,3H), 6.92 (d,1H,J=9.6Hz), 7.41 (d.d,1H,J=9.6 and 2.4Hz), 7.96 (d,1H,J=2.4Hz). IR (KBr) 1759 and 1671 cm^{-1}. MS m/z 250 (M$^+$).
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