Preparation of *N*-Hydroxyphenacetin and Formation of 1-Acetyloxindoles from Keten and *N*-Phenylhydroxylamines

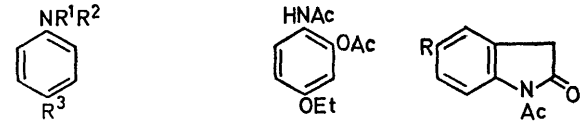
By I. C. CALDER and P. J. WILLIAMS*

(*Department of Organic Chemistry, University of Melbourne, Parkville, Victoria, Australia* 3052)

Summary *N*-Hydroxyphenacetin has been synthesised, and the reaction of phenylhydroxylamines with an excess of keten has been shown to give 1-acetyloxindoles in addition to the expected phenylhydroxylamine *NO*-diacetates.

THE minor urinary metabolites of phenacetin (I), which could account for its chronic nephrotoxicity,[1] may arise from initial *N*-hydroxylation of the drug.[2] Klutch *et al.*[3] were unsuccessful in preparing *N*-hydroxyphenacetin (III) and Nery[2] used an indirect method to search for it as a metabolite in rat urine. Because of this and our own interest in the nephrotoxicity of phenacetin metabolites, we report a straightforward synthesis of *N*-hydroxyphenacetin (III) and also its novel reaction with keten.

Reduction of 4-nitrophenetole with zinc dust and ammonium chloride in aqueous ethanol,[4] gave *N*-(4-ethoxyphenyl)-hydroxylamine (II). Treatment of the freshly prepared hydroxylamine in ether solution at room temperature with 1 equiv. of keten gave the required *N*-acetylhydroxylamine (III), which was isolated after extraction with base in 46% yield. The product was purified† by a single recrystallisation from petroleum–benzene; 104 °C, ν_{max} (KBr) 3110 and 1615 cm^{-1}. The 60MHz n.m.r. spectrum was similar to that of phenacetin except for a small downfield shift of the ethoxy-protons (2–3 Hz). The residue from the

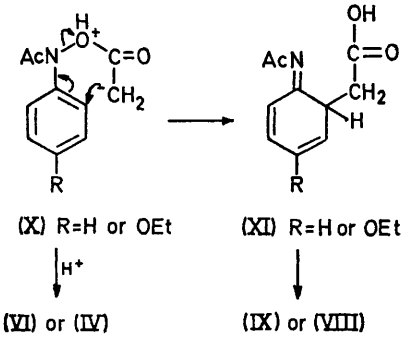


(I) R^1=Ac, R^2=H, R^3=OEt
(II) R^1=H, R^2=OH, R^3=OEt
(III) R^1=Ac, R^2=OH, R^3=OEt
(IV) R^1=Ac, R^2=OAc, R^3=OEt
(V) R^1=H, R^2=OH, R^3=H
(VI) R^1=Ac, R^2=OAc, R^3=H

(VII)

(VIII) R=OEt
(IX) R=H

† Satisfactory analytical data were obtained for all new compounds.



extraction consisted of 4-nitrophenetole, contaminated with a little 4,4′-diethoxyazoxybenzene.

Treatment of (III) with an excess of keten in ether–chloroform at room temperature gave a mixture of two products in the ratio of 1:3 (n.m.r.). Heating this mixture in 40—60° petroleum during attempted crystallisation gave 2-acetoxyphenacetin (VII), identified by comparison with an authentic sample[5] (n.m.r., t.l.c., mixed m.p.). This arose by a sigmatropic rearrangement[6] of the major component the *NO*-diacetate (IV). The minor component from treatment of (III) with an excess of keten was isolated by preparative t.l.c. of the mother liquors and identified from its i.r., mass, and n.m.r. spectra as 1-acetyl-5-ethoxyoxindole (VIII).

As in the case of the 4-ethoxy-compound, treatment of *N*-phenylhydroxylamine[7] (V) in ether solution with an excess of keten gave two products, the *NO*-diacetate (VI) and 1-acetyloxindole (IX) in a ratio of 3:2. The proportions of the two products were the same from reactions in chloroform solution either at room temperature or at reflux, but at −70 °C the *NO*-diacetate (VI) was the sole product. Compounds (VI) and (IX) were identified by comparison with authentic specimens (i.r., n.m.r., t.l.c., and mixed m.p.). The *NO*-diacetate (VI) was prepared[8] as an oil, and 1-acetyloxindole was synthesised by a two-step reduction of isatin[9] followed by acetylation with acetic anhydride. The alternative cyclic product, 1-acetylindoxyl, was prepared[10,11] and shown to be different from (IX).

The addition of keten to the *N*-acetylhydroxylamines may involve an intermediate such as the dipolar species (X). This could either transfer proton to yield the *NO*-diacetates (IV) and (VI), or undergo a sigmatropic rearrangement[6,12] to (XI) which could then cyclise to the oxindoles (VIII) and (IX).

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