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NEIGHBOURING GROUP PARTICIPATION BY OXIMATE ANION

F.L. Scott, J.C. Riordan and A.F. Hegarty

Department of Chemistry, University College,
Cork, Ireland

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The oximes of certain Mannich bases cyclize under basic conditions to yield isoxazolines.[1] These results suggest that the oximate anion can play the role of a powerful neighbouring group towards saturated carbon, and to examine this idea further, we have checked, extended and added to the previous data. When the methiodide of β-dimethylamino-propiophenone oxime (Ia, $X=\overset{+}{N}(CH_3)_3.\bar{I}$) was refluxed with ten equivalents of ethoxide ion in ethanolic solution for six hours, a 50% yield of 3-phenylisoxazoline (II), m.p. 63-65° and a 40% yield of phenyl vinyl ketoxime (III) m.p. 109-110°, together with a trace of β-ethoxypropiophenone oxime (IVa, Y=OEt) was obtained. The structure of (II) was confirmed by n.m.r. spectroscopy. All spectra were run[2] in deuterochloroform with tetramethyl silane as an internal standard. The spectrum of compound (II) showed a multiplet at τ 2.58 (J 5cps), due to aromatic CH, and two triplets, one at τ5.56 (J 10cps), due to the pair of hydrogens labelled (b) in (II), and a second triplet (τ6.69, J 10cps) due to the hydrogens labelled (a) in (II).[3] Similarly obtained, the n.m.r. spectrum of substance (III) showed a very strong aromatic CH absorption at τ2.59, a quartet due to methylene hydrogen ($=CH_2$) at τ4.34 (J 5cps) and a weak oxime-OH signal at τ0.67[4,5].

The formation of substance (II) is superficial evidence for the process we were seeking namely reaction A, (Figure 1). However compound (II) may also arise from any of the sequence of processes B + F, B + C + D, E + D. When substance (III) was refluxed for 6 hours with 10 equivalents of ethoxide ion in ethanol, it was recovered in 55% yield and less than 10% of compound (IVa) was formed. Substantial polymerization[6] was also detected in the run. When compound (III) was treated with a threefold excess of ethoxide ion under milder conditions, namely for 30 minutes at 50° it was recovered in 87% yield[7]. Thus reaction F does not take place under our conditions. We next prepared

(IVa) unambiguously[8] and have found that in the presence of base it forms neither (II) nor (III), hence reactions D, or the reversal of C do not occur under our selected conditions. Thus the formation of (IIa) from (Ia) using the technique reported above, does indeed correspond to reaction A[9].

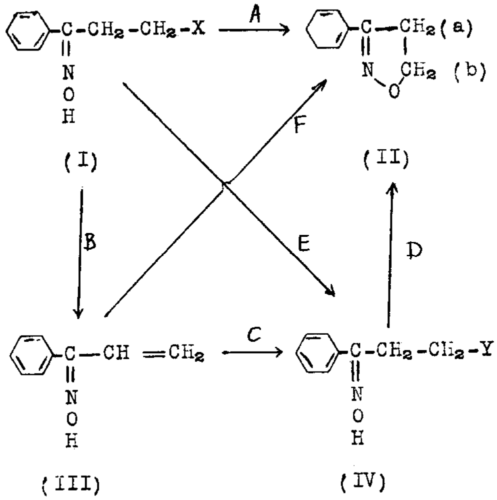

Figure I

When compound (Ia) was treated with a ten-fold excess of hydroxide ion, for 15 minutes at 25°, substance (III) was the only product isolated and that in 58% yield. The predominance of elimination over cyclization in the aqueous medium (relative to their mutual extents in ethanolic solution) may be due to a number of concurrent effects - a variation in the oximate anion concentration with change of solvent[10a] -- though this alone should not be decisive; the stronger basicity of ethoxide ion compared to hydroxide ion (though this should operate towards favouring elimination in ethanol[10b]); the effect of solvent variation on the transition state structure,[10b] and of solvation changes on nucleophilicities[10c] etc.. Lack of space precludes any further discussion of these individual and / or combined effects here. It is interesting to note that when the reaction terminus in (I) is made more sterically accessible (as it is for example in compound (Ib), the methiodide of β-morpholinopropiophenone) then cyclization and elimination are encountered in aqueous solution. Thus treatment of substance (Ib) with a twenty-fold excess of hydroxide ion in aqueous solution for 1 hour at 50° affords a 27% yield of substance (II) and a 63% yield of compound (III).

The ease of cyclization of substance (Ia) to compound (II) is clearly much more rapid than when oximate ion displaces an aryl halide moiety[9] and it appears somewhat slower than the corresponding elimination reactions of Mannich bases themselves.[11] The precise rate of cyclization is currently being probed. Reaction A above corresponds to the oximate anion effectively losing its ambident[12] character (for steric reasons) and operating via its oxygen terminus. The results, namely the essential absence of reaction E, confirm the superiority of oximate anion as a nucleophile towards saturated carbon[cf. 12] compared to ethoxide ion. The present unequivocal establishment of reaction A now permits us to competetively assess (Reactions A. vs. E) the effectiveness of oximate vs. other nucleophiles towards saturated carbon, and this is being explored.

REFERENCES

1. Z.-Y,Kyi and W. Wilson, J. Chem. Soc. 798(1953).

2. We are indebted to Dr. D. Hollis (Varian Associates, Palo Alto) for determining the n.m.r. spectra and for assistance in their interpretation. The spectra were run on an A-60 Varian Associates Spectrometer (60 Mc./sec.)

3. For compilations of τ-values, see L.M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, London (1960).

4. N.m.r. data have been recently reported for the oximes of some other unsaturated ketones, G. Slomp and W.J. Wechter, Chem. & Ind. **41**, (1962).

5. The structural assignments we have made using n.m.r. data are corroborated by i.r. data and agree with those of Kyi and Wilson, who used u.v. absorption data as structural criteria.

6. Compare some analogous results reported by Ferry and McQuillin, loc.cit. and also e.g. V. Horak, J. Michl and P. Zuman, Tetrahedron Letters, No. 21, 744 (1961).

7. The slow reaction of (III) with ethoxide is puzzling, particularly since vinyl ketones readily add on such anions, see N. Ferry and F.J. McQuillin, *J. Chem. Soc*. 103 (1962). One could postulate that the oximate ions possess some nitrosocarbanionic character (*cf.e.g*. F. Nerdel and I. Huldschinsky *Chem. Ber*. **86**, 1005 (1953)), which conjugates with the vinylic moiety (cf. H.J. Ringold and S.K. Malhotra, *J. Amer. Chem. Soc.* **84**, 3402 (1962), and inhibits addition of nucleophiles. This carbanionic character of the oximate anion shows itself in reactions with perchloryl fluoride (J.P. Freeman, *J. Amer. Chem. Soc.* **82**, 3869 (1960), but not in alkylation reactions, P.A.S. Smith and J.E. Robertson, *J. Amer. Chem. Soc.* **84**, 1197 (1962). Compound (III) does add on amines readily in ethereal solution.

8. By the reaction of hydroxylammonium hydrochloride, β-ethoxypropiophenone and sodium acetate, contrast T. Matsumoto, T. Nishida, and H. Shirahama, *J. Org. Chem.* **27**, 79 (1962).

9. The use of oximate anion to displace intramolecularly an aryl halide moiety is well-known (and of course represents oximate anchimerism also) and has recently been investigated quantitatively, see the interesting paper of J.F. Bunnett and S.Y. Yih, *J. Amer. Chem. Soc*. **83**, 3805 (1961) for details and pertinent references.

10. (a) For acidity data for various oximes see O.L. Brady and N.M Chokshi, *J. Chem. Soc*. 946 (1929) and C.V. King and A.P. Marion, *J. Amer. Chem. Soc*. **66**, 977 (1944); (b) for an interesting discussion on these and related points see K.A. Cooper, M.L. Dhar, E.D. Hughes, C.K. Ingold, B.J. MacNutty and L.I. Woolf, *J. Chem. Soc*. 2043 (1948), see also J.F. Bunnett, *Angewandte Chem. International Edition* **1** 225 (1962). (c) Compare R.F. Hudson and M. Green, *J. Chem. Soc.* 1055 (1962).

11. Ferry and McQuillin, *loc.cit.*

12. Smith and Robertson, *loc.cit*. have studied quantitatively the ambident character of oximate ion via its tendency to undergo both N- and O-alkylation.