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THE INVOLVEMENT OF OXIME GROUPS WITH NEIGHBOURING ACYL FUNCTIONS

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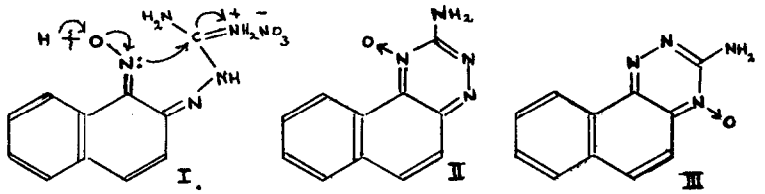
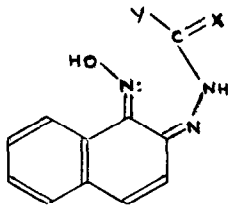
We have shown recently (1) that the formation of isoxazolines by treating the oximes of β-aroylethyltrimethyl ammonium iodides with ethoxide ion involves the oximate anion as a powerful nucleophile, with its normally ambident character (2) being restricted (for steric reasons) to reactivity at the oxygen atom alone. We have also reported, much earlier (3), another cyclization reaction in which again the ambident character of an oxime moiety is restricted (also on steric grounds) to attack via a single atom but in this case, via its nitrogen atom exclusively. This latter reaction also differs from our more recent work in that it involves an intramolecular attack by an oxime function at an acyl (rather than alkyl) carbon atom. The particular reaction reported involved the facile conversion of 1,2-naphthoquinone-1-oxime guanylhydrazone nitrate (I) to a substituted 1,2,4-triazine-4-oxide (II), merely by gently warming an aqueous suspension of compound (I) for a brief period.



I. II III

We began a reexamination of this reaction by considering whether the reaction occurred when the location of the oxime and hydrazone functions in the naphtnalene ring were reversed. When we endeavoured to make the necessary guanyl hydrazone of 1,2-naphthoquinone 2-oxime, under conditions where compound (I) forms easily (namely by mixing equimolar quantities of substituted quinone oxime and aminoguanidine nitrate in warm aqueous ethanol in the presence of some very dilute acid as catalyst) no hydrazone resulted. However, when the medium was made appreciably more acid (0.5 to 1.0 N), the guanylhydrazone nitrate of 1,2-naphthoquinone-2-oxime (Ia), yellow needles, m.p. 159-160° was formed in 77% yield. On boiling this compound in water, it also rapidly (and quantitatively) cyclized to the substituted triazine (III), m.p. 279-281°. Thus the steric hindrance (to hydrazone formation) encountered at the 1-naphthyl position did not obtrude in the oxime participation reaction. Two experiments were performed to determine whether the favourable proximity of the oxime (donor) and amidinium (acceptor) groups in

(I) and related compounds was necessary for cyclization. Thus, diacetylmonoxime guanylhydrazone nitrate (IV), m.p. 215°, was synthesized and duly refluxed in aqueous solution for 6 hours. While 58% of compound (IV) was recovered reaction did occur, but it represented disproportionation rather than intramolecular cyclization - the products obtained being dimethylglyoxime (22%), diacetylguanyl osazone nitrate (27%) and diacetylmonoxime (4%).

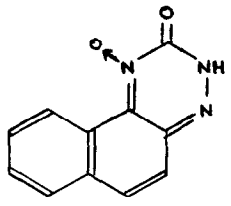


V, a, X = O, Y = NH_2

b, X = $NH_2^+.NO_3^-$, Y = NHC_6H_5

c, X = NH, Y = $NHNO_2$

d, X = $NH_2^+.I^-$, Y = SCH_3



VI

An intermolecular oxime-amidine interaction was next attempted, by refluxing equimolar quantities of acetophenone oxime and benzaldehyde guanylhydrazone nitrate in ethanolic solution for 3 hours. Both compounds were recovered in better than 85% yields and no product corresponing to oxime-amidine interaction was detected (4).

To define more precisely the role of the acceptor function in these oxime-acceptor cyclizations we have examined the behaviour of an additional number of acylhydrazones of 1,2-naphthoquinone-1-oxime (V). When 1,2-naphthoquinone-1-oxime was refluxed with one equivalent of semicarbazide hydrochloride, together with one equivalent of sodium acetate, in aqueous ethanolic solution for 1 hour, the corresponding semicarbazone (Va), m.p. 191° (5) was obtained. When this substance was heated in glacial acetic acid solution for seven minutes on a steam-bath, (or when the original substituted quinone oxime was refluxed with semicarbazide hydrochloride without sodium acetate), then the product was the substituted triazinone-4-oxide (VI), m.p. 167°, (decomp.) (monohydrate), or m.p. 217° (decomp.) (anhydrous form). It is apparent that the neutral carbamyl moiety has but a poor attraction for the oximino function, but that the protonated form $-\overset{\overset{+}{OH}}{\overset{\|}{C}}-NH_2$ resembling as it does the amidinium function in compound (I), facilitates oxime addition and ultimately cyclization. The weak electrophilicity of the neutral carbamyl group towards a neighbouring oxime function was also overcome by increasing the nucleophilic potency of the latter, by converting it to an anion. Thus when compound (Va) was refluxed in 10% aqueous potassium carbonate solution for 10 minutes (and the cooled solution was then acidified with dilute acid), then the triazinone (VI) was obtained in ca. 80% yield.

The triazinone-N-oxide (VI) loses its N-oxide function very easily - the reduced triazinone (VII) m.p. 272-3° (6) being obtained in 85% yield after the substance (VI) has been refluxed in 50% aqueous ethanol for two hours. The compound (VI) also deoxygenated when it was refluxed with triphenylphosphine for 10 hours in benzene-dioxane solution to yield the reduced material (VII) in 75% yield. Such facile deoxygenations cannot be attributed to the nature of the 1,2,4-triazine system since we found that the triazine N-oxide (II) was not appreciably reduced after being refluxed either for 10 hours in 50% aqueous ethanol, or for 10 hours with triphenylphosphine in 3:1 toluene n-butanol as solvent. The ease of deoxygenation observed with compound (VI) relative to substance (II) is comparable to the difference in ease of deoxygenation between aliphatic and heterocyclic N-oxides (7) and for similar reasons. Infrared spectral data show that while substance (II) is an aminotriazine, compound (VI) is a triazinone, with its heterocyclic ring in a reduced and quasialiphatic state.

Compound (VI) was also readily reduced in an aqueous suspension with sodium dithionite to yield an unstable dihydromaterial, m.p. ca. 200° (decomp.) which was isolated but not further examined (8). This, on oxidation with aqueous-ethanolic ferric chloride solution, also yielded the substituted triazine (VII). The structure of material (VII) was confirmed by two independent syntheses, (i) by the reaction of 3-amino-1,2-as-naphthotriazine (9) with sodium nitrite in 50% H_2SO_4, a reaction which gave compound (VII)

in 79% yield; (ii) by the action of 10% aqueous potassium carbonate solution on 1,2-naphthoquinone-2-semicarbazone, when substance (VII) was obtained in 64% yield. A by-product of this latter reaction was 1-naphthol (11%) - the result apparently of an activated Kischner-Wolff-Staudinger reaction under exceptionally mild conditions.(10)

4-Phenylaminoguanidine nitrate condensed smoothly with 1,2-naphthoquinone-1-oxime to yield the corresponding hydrazone (Vb), m.p. 132°. When this was refluxed in aqueous solution, compound (II) was obtained in quantitative yield, aniline nitrate being very easily eliminated. Two other acylhydrazone derivatives were also investigated, a nitroguanyl hydrazone (Vc) and an S-methylisothiosemicarbazone salt (Vd). The acyl moieties in these systems showed themselves to be more effective electrophiles towards neighbouring oxime than either their amidinium or carbamyl analogues. Thus, when 1,2-naphthoquinone-1-oxime was treated with nitroaminoguanidine in warm aqueous ethanol, in the presence of a trace of dilute nitric acid conditions that do not lead to triazine formation with substances (I), (Ia), (Va) or (Vb) a 70% yield of compound (II) resulted, corresponding to an extremely facile loss of nitramide. Under similar conditions during an attempt to form the hydrazone (Vd), methyl mercaptan was copiously evolved, and substance (II) was formed in 40% yield, together with other so-far-unidentified air-sensitive materials. The high electrophilicity of the nitroguanyl group towards neighbouring oxime was still not sufficient to cause inter-

molecular reaction. Thus, when a mixture of equimolar quantities of benzaldehyde nitroguanylhydrazone and of acetophenone oxime was refluxed for 10 hours in aqueous ethanol, both compounds were recovered quantitatively.

This work was carried out during the tenure by one of the authors (F.J.L.) of a State Maintenance Allowance for Research. Satisfactory analyses have been obtained for all new compounds reported.

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2. See, for example, P.A.S. Smith and J.E. Robertson, J.Am.Chem.Soc. 84, 1197 (1962).

3. F.L.Scott and J. Reilly, Nature, 169, 584 (1952).

4. For an interesting discussion of inter- versus intramolecular displacements at acyl functions, see M.L. Bender, Chem. Revs. 60, 53 (1960).

5. This material has been reported without explicit preparative details by J. Thiele and W.Barlow, Ann. 270, 311 (1898).

6. Thiele and Barlow (loc.cit.), S.C.De, J.Indian Chem. Soc. 4, 183 (1927), and R.Fusco and G. Bianchetti, Gazz. Chim. Ital. 87, 438 (1957) have all reported preparing this compound, but no source quotes its m.p.

7. See for example, L.Horner and H. Hoffmann, Angew.Chem. 68, 480 (1956) and E. Howard Jr., and W.F. Olszewski, J.Am.Chem.Soc. 81, 1483 (1959).

8. O.Diels, Ann. 429, 1, (1922) has claimed to have prepared this compound. He describes obtaining it by a complicated series of reactions as white needles, m.p. 299°C. His report implies the material is reasonably stable. However, by analogy with the relative ease of oxidation of other reduced naphthotriazines (Thiele and Barlow loc.cit.) it seems unlikely that the compound obtained by Diels is a dihydrotriazine.

9. This compound was prepared by the method of Fusco and Bianchetti, (loc.cit.). We have found that it can also be obtained (in 40% yield) by refluxing 1,2-naphthoquinone-2-guanylhydrazone nitrate in aqueous solution for 10 hours.

10. W. Seibert, Chem. Ber. 80 494 (1947).