The Reaction of Aromatic Nitroso-compounds with Enamines. Part I. The Reaction of Nitrosobenzene with 1-Morpholin-1-ylcyclohexene

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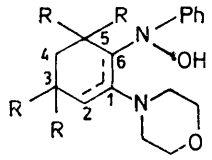
The reaction of nitrosobenzene with 1-morpholin-1-ylcyclohexene gives the hydroxylamine (1; R = H) as the initial product. On standing (1; R = H) rearranges into *N*-(2-hydroxy-2-morpholin-1-ylcyclohexylidene)aniline (2). The reactions of (1; R = H) and (2) are discussed.

THE reaction of nitrosobenzene with mono-olefins has until recently received little attention.[1] Ingold and Weaver [2] claimed to have isolated oxazetidines from the reaction of nitrosobenzene with styrene, diethylmethylene malonate, and 1,1-diphenylethylene. These structural assignments were refuted by Lapworth [3] and later confirmed as incorrect by Hepfinger *et al.*[4] Sullivan [5] reported the reaction of various substituted nitrosobenzenes with 2,3-dimethylbut-2-ene and concluded that the nitroso-group underwent an 'ene' addition to the olefin to yield an unsaturated hydroxylamine intermediate which then was oxidised further to an alkenyl aryl nitroxide. The nature of the ene reaction was confirmed by Knight [6] who was able to isolate *N*-alkenyl-*N*-phenylhydroxylamines from nitrosobenzenes and allylic olefins. Our interest in enamines led us to investigate their reaction with aromatic nitroso-compounds and the preliminary findings form the subject of this paper.

The initial product from the reaction of nitrosobenzene and 1-morpholin-1-ylcyclohexene was a red oil. Direct characterisation of this compound as (1; R = H) was not possible since on standing it slowly rearranged into a crystalline imine which is shown below to have structure

[1] For a recent review of nitrosoarene–olefin reactions, G. T. Knight and B. Pepper, *Tetrahedron*, 1971, **27**, 6201.
[2] C. K. Ingold and S. D. Weaver, *J. Chem. Soc.*, 1924, **125**, 1456.
[3] G. N. Burkhardt, A. Lapworth, and J. Walkder, *J. Chem. Soc.*, 1925, **127**, 1748; G. N. Burkhardt and A. Lapworth, *ibid.*, p. 2458.
[4] N. F. Hepfinger, C. E. Griffin, and B. L. Shapiro, *Tetrahedron Letters*, 1963, 1361, 1365.
[5] A. B. Sullivan, *J. Org. Chem.*, 1966, **31**, 2811.
[6] G. T. Knight, *Chem. Comm.*, 1970, 1016.

(2). However when the morpholine enamine of 3,3,5,5-tetramethylcyclohexanone was reacted with nitrosobenzene under identical conditions, the corresponding crystalline hydroxylamine (1; R = Me) was obtained. The i.r. spectra of both (1; R = H) and (1; R = Me)



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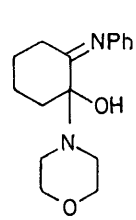

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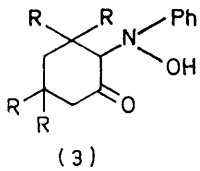

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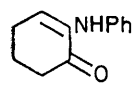

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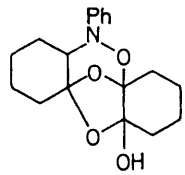

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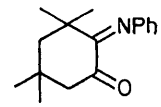

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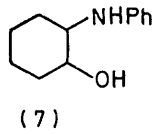

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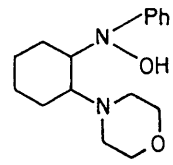


(8)

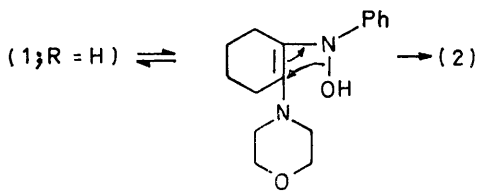
showed broad OH bands in the region 3370—3380 and intensified enamine double bond absorption at 1643 cm^{-1}. Attempts to confirm the structure of (1; R = H) by n.m.r. spectroscopy were unsuccessful; severe line broadening occurred presumably due to the presence of nitroxyl radicals resulting from atmospheric oxidation. A rapidly-determined n.m.r. spectrum of (1; R = Me) in [$^2H_5$]pyridine revealed that the enamine double bond was located completely in the trisubstituted position; two broad singlets were observed, the first at τ 5·27 due to the enaminic 2-H and the second at 6·10 attributable to 6-H.

Hydrolysis of (1; R = H) gave the hydroxyamino-ketone (3; R = H) after 5 min. After a much longer hydrolysis time (15 h) the major product was the amino-ketone (4) resulting from dehydration of (3; R = H); a small amount of a highly crystalline product $C_{18}H_{23}NO_4$ was also isolated. The absence of carbonyl absorption in the i.r. spectrum of this compound and the presence of only one hydroxy-signal in the n.m.r. suggested that the remaining three oxygen atoms were present as ether linkages. Its u.v. and mass spectra suggested that it readily decomposed into cyclohexane-1,2-dione. On treatment with base, the u.v. absorption in ethanol (originally 240 nm) shifted to 308 and decreased to 265 nm on reacidification. The wavelength of these absorptions agree well with those of pure cyclohexane-1,2-dione determined in the same solvent. The base peak (> *m/e* 100) in the mass spectrum of this compound corresponded to ionised cyclohexane-1,2-dione (*m/e* 112). A structure for this product is (5) formed by direct condensation of the hydroxyamino-ketone (3; R = H) with cyclohexane-1,2-dione, the latter compound arising from hydrolysis of (4).

In contrast to (1; R = H), the hydrolysis of (1; R = Me) was much slower presumably as a result of the steric hindrance of the four methyl groups. After 15 h, a moderate yield of the hydroxyamino-ketone (3; R = Me) was obtained. Under basic conditions this compound was converted to the imino-ketone (6).

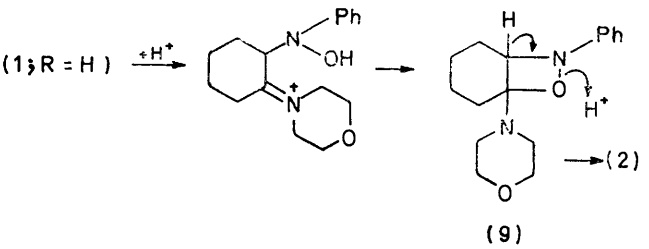
The structure of the imine (2) was established as follows. Its i.r. spectrum showed a sharp band at 3375 (OH) and strong absorption at 1672 cm^{-1} attributable to the imine double bond. The inherent instability of (2) was reflected in its rapid transformation to the unsaturated ketone (4) which occurred even on reduction with sodium borohydride in ethanol solution to give finally the amine (7) as the major product.

The formation of (2) from (1; R = H) can be envisaged as occurring by two possible routes. The first requires isomerisation of the enamine double bond in (1; R = H) to the tetrasubstituted position followed by a cyclic rearrangement to give (2) (Scheme 1). The second



SCHEME 1

route involves postulating the presence of an intermediate 7-oxa-8-azabicyclo[4.2.0]octane (9) which then undergoes cleavage to yield the desired product (2) (Scheme 2).



SCHEME 2

The formation of authentic oxazetidine intermediates analogous to (9) has been reported by Haszeldine *et al.*[7] in the reaction of trifluoronitrosomethane with fluoro-substituted olefins and allenes, and recently by Gill [8] in the reaction between nitrosoarenes and ketenimines.

Reduction of (1; R = H) with sodium borohydride in ethanol gave the expected hydroxylamine (8). This

[7] D. Barr, R. N. Haszeldine, and C. J. Willis, *J. Chem. Soc.*, 1961, 1351; D. H. Coy, R. N. Haszeldine, M. J. Newlands, and A. E. Tipping, *Chem. Comm.*, 1970, 456.
[8] J. T. Gill, *Diss. Abs.*, 1971, 22,653.

route has been used to prepare a whole series of *N*-substituted hydroxylamines by variation of the initial enamine and aromatic nitroso-compound. These compounds and their biological properties will be discussed elsewhere.

EXPERIMENTAL

General experimental methods have previously been described.[9]

The Reaction of Nitrosobenzene with 1-*Morpholin*-1-*ylcyclohexene*.—The enamine (28 g) in dry benzene (50 ml) was added over 5 min to a stirred suspension of nitrosobenzene (16 g) in dry benzene (50 ml) maintained at 0—5°. The mixture was stirred for a further 15 min at 0—5° and then 30 min at room temperature. Removal of the solvent gave (1; R = H) as a red oil, $\nu_{max.}$ 3375 (OH) and 1643 (enamine C=C) cm^{-1}. It was stirred with ether (20 ml) for 15 h, the ether was removed and the residue was stored at 0—5° for 48 h when it began to crystallise. Trituration with ether gave N-(2-*hydroxy*-2-*morpholin*-1-*ylcyclohexylidene*)*aniline* (2) (10·3 g) which crystallised from acetone–light petroleum, m.p. 89—93°. Cooling the ethereal mother liquors for a further 24 h at 0° furnished an additional quantity (4·5 g) of (2), m.p. 87—92° (Found: C, 69·9; H, 8·3; N, 10·3. $C_{16}H_{22}N_2O_2$ requires C, 70·05; H, 8·1; N, 10·2%); $\nu_{max.}$ 3375 (N–OH), 1672 (C=N), and 1595 (ArC=C) cm^{-1}.

Reaction of 3,3,5,5-*Tetramethyl*-1-*morpholin*-1-*ylcyclohexene and Nitrosobenzene*.—The enamine was prepared from the ketone and morpholine in benzene solution by azeotropic removal of the water formed in the reaction. It distilled with b.p. 92—95° at 0·5 mmHg (lit.,[10] b.p. 95—100° at 0·7 mmHg). The enamine (8 g) in dry benzene (10 ml) was added to a stirred suspension of nitrosobenzene (3·5 g) in dry benzene (25 ml) at 0—5°. The solution was stirred for 15 min at 0—5° and then a further 45 min at room temperature. The solvent was removed to give the crystalline 3,3,5,5-*tetramethyl*-1-*morpholin*-1-*yl*-2-N-*phenylhydroxyaminocyclohexene* (1; R = Me) (4·7 g) which was collected, washed with ether, and recrystallised from acetone–light petroleum in fine needles (4·2 g), m.p. 146—147° (decomp.) (Found: C, 72·6; H, 8·8; N, 8·5. $C_{20}H_{30}N_2O_2$ requires C, 72·7; H, 9·15; N, 8·5%); $\nu_{max.}$ 3480 (N–OH), 1643 (enamine C=C), and 1590 (ArC=C) cm^{-1}; τ (C_5D_5N) 6·1br (s, 1H, 6-H), 5·27br (s, 1H, olefinic 2-H), and 2·30—3·63 (m, 5H, Ph).

Hydrolysis of the Hydroxylamine (1; R = H).—(i) *For* 5 *min*. Nitrosobenzene (10 g) and the enamine (20 g) were allowed to react as before. A buffer solution of sodium acetate (15 g) and acetic acid (30 ml) in water (100 ml) was then added and the mixture was stirred vigorously for 5 min. Dilute hydrochloric acid was added (pH 2) and the benzene layer was separated. The aqueous layer was extracted once with ether and the combined organic layers were washed with water and dried. Removal of the solvent followed by trituration of the residue with ether gave 2-N-*phenylhydroxyaminocyclohexanone* (3; R = H) (5·8 g) which crystallised from acetone–light petroleum in fine needles, m.p. 118—119° (Found: C, 70·35; H, 7·3; N, 7·0. $C_{12}H_{15}NO_2$ requires C, 70·2; H, 7·4; N, 6·8%); $\nu_{max.}$ 3380 (N–OH), 1712 (cyclohexanone C=O), and 1593 (ArC=C) cm^{-1}; τ 5·80 (t, 1H, *J* 8 Hz, C*H*–N) and 2·2—3·3 (m, 5H, Ph).

(ii) *For* 15 h. The procedure was carried out as above except that the product was hydrolysed for 15 h. The benzene layer was then separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with water and dried. The residue (15·3 g) after removal of solvent yielded a small amount (1·6 g) of crystalline 4a,10a-*epoxy*-6-*phenylperhydrodibenzo*[b,f][1,4,5]*dioxazepin*-11a-*ol* (5) on trituration with ether. Recrystallisation of (5) from acetone gave needles, m.p. 169—172° (variable; decomp.) (Found: C, 68·3; H, 7·1; N, 4·4. $C_{18}H_{23}NO_4$ requires C, 68·1; H, 7·15; N, 4·4%); *m/e* 317 and 112; $\lambda_{max.}$(EtOH) 240 (ε 10,400), $\lambda_{max.}$(EtOH–NaOH) 308 nm; reacidification gave $\lambda_{max.}$ 265 nm (cyclohexane-1,2-dione, $\lambda_{max.}$(EtOH–NaOH) 311; reacidification gave $\lambda_{max.}$ 266 nm); τ 6·60 (t, 1H, *J* 7·5 Hz, C*H*–N), (m, 5H, (s, 1H, exchangeable with D_2O, OH), and 2·4—3·2 4·63 Ph).

The remaining material (13·7 g) was distilled. The fraction (8·7 g) with b.p. 126—129° at 0·7 mmHg solidified on cooling and was recrystallised from light petroleum (b.p. 40—60°) to give 2-*anilinocyclohex*-2-*enone* (4), m.p. 52—53·5° (Found: C, 76·9; H, 7·1; N, 7·5. $C_{12}H_{13}NO$ requires C, 77·1; H, 7·0; N, 7·5%); $\nu_{max.}$ 3385 (NH), 1660 (C=O), 1628 (CH=CH), and 1598 (ArC=C) cm^{-1}; τ 3·63 (t, 1H, *J* 4·5 Hz, olefinic H) and 2·5—3·3 (m, 5H, Ph).

Hydrolysis of the Hydroxylamine (1; R = Me).—A solution of (1; R = Me) (6 g) in benzene (20 ml) was stirred with a buffer solution of sodium acetate (3 g) and acetic acid (6 ml) in water (20 ml) for 15 h. The benzene layer was separated and the aqueous layer was extracted with chloroform (50 ml). The combined organic layers were washed with water and dried. Removal of solvent gave 3,3,5,5-*tetramethyl*-2-N-*phenylhydroxyaminocyclohexanone* (3; R = Me) which crystallised from ether–light petroleum in fine needles (3·05 g), m.p. 132—134° (Found: C, 73·6; H, 8·6; N, 5·0. $C_{16}H_{23}NO_2$ requires C, 73·55; H, 8·9; N, 5·35%); $\nu_{max.}$ 3385 (N–OH), 1701 (cyclohexanone C=O), and 1596 (ArC=C) cm^{-1}; τ 8·96 (s, 6H, 2 × Me), 8·67 and 8·72 (s, 6H, 2 × Me), 5·97br (s, 1H, C*H*–N), and 2·4—3·5 (m, 5H, Ph).

Dehydration of (3; R = Me).—The ketone (3; R = Me) (2 g) and piperidine (0·5 ml) in benzene (40 ml) were maintained at 70—80° for 5 h. Removal of benzene gave an orange crystalline residue which yielded yellow rods of 3,3,5,5-*tetramethyl*-2-N-*phenyliminocyclohexanone* (6) (1·29 g), m.p. 72—75° (from ether–light petroleum) (Found: C, 78·9; H, 8·5; N, 5·4. $C_{16}H_{21}NO$ requires C, 79·0; H, 8·7; N, 5·75%); $\nu_{max.}$ 1711 (cyclohexanone C=O), 1650 (C=N), and 1591 (ArC=C) cm^{-1}; $\lambda_{max.}^{EtOH}$ 286 (ε15,600) and 354 (3400) nm; τ 8·90 (s, 6H, 2 × Me), 8·72 (s, 6H, 2 × Me), 7·60 and 8·17 (m, 2H, 2 × CH_2), and 2·6—3·4 (m, 5H, Ph).

Hydrolysis of the Imine (2).—A buffer solution comprising sodium acetate (3 g) and acetic acid (6 ml) in water (20 ml) was added to a solution of the imine (2) (6 g) in benzene (20 ml) and the mixture was stirred vigorously for 5 min. The benzene layer was separated and the aqueous layer was extracted with chloroform. The combined organic layers were washed with water and dried. Removal of the solvent followed by trituration of the residue with light petroleum at 0° gave the amino-ketone (4) (0·92 g) identified by its i.r. spectrum and m.p. The mother liquors after removal of (4) were evaporated to dryness, dissolved in ether, and the ethereal layer was washed with dilute hydrochloric acid and dried. Removal of ether gave an additional quantity (1·4 g) of (4), again identified by its i.r. spectrum and m.p.

[9] J. W. Lewis, P. L. Myers, and M. J. Readhead, *J. Chem. Soc.* (*C*), 1970, 771.

[10] P. W. Hickmott and J. R. Hargreaves, *Tetrahedron*, 1967, **23**, 3151.

Reduction of the Imine (2).—The imine (2) (3 g) and sodium borohydride (1 g) were reacted in ethanol (50 ml) for 15 h. The reaction mixture was poured into water (200 ml) and acidified (pH 2) with dilute hydrochloric acid. The mixture was extracted once with ether and the organic layer was discarded. The aqueous layer was basified with ammonia (*d* 0·88) and extracted with ether. Removal of the solvent gave a crystalline residue (2·06 g) which yielded needles of 2-*anilinocyclohexanol* (7) (1·62 g), m.p. 72—74° (from ether–light petroleum) (Found: C, 75·2; H, 8·8; N, 7·1. $C_{12}H_{17}NO$ requires C, 75·35; H, 9·0; N, 7·3%); $\nu_{max.}$ 3315 (NH + OH) and 1608 (ArC=C) cm^{-1}; τ 6·73 (m, 1H, C*H*–N), 6·06 (m, 1H, C*H*–O), and 2·6—3·7 (m, 5H, Ph).

Reduction of (1; R = H).—The product from nitrosobenzene (10 g) and 1-morpholin-1-ylcyclohexene (17 g) was dissolved in ethanol (50 ml) at 0° and sodium borohydride (3·8 g) added. Work-up as before gave impure N-(2-morpholin-1-ylcyclohexyl)phenylhydroxylamine (8). The *hydrochloride* salt was crystallised from ethanol–ether (9·0 g), m.p. 218—221° (Found: C, 61·3; H, 7·7; N, 8·9; Cl, 11·9. $C_{16}H_{25}N_2O_2Cl$ requires C, 61·4; H, 8·05; N, 8·95; Cl, 11·3%); $\nu_{max.}$ 3250 (N–OH) and 1595 (ArC=C) cm^{-1}

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