Ketenimines as Intermediates to Heterocycles. Part 3.[1] Rearrangement of 3-Iminoisoxazolines to 2-Imino-oxazolines

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N-Substituted hydroxylamines (2) add to 2-benzoyl-*N*,2-diphenylvinylideneamine (1) and the adducts are easily dehydrated to give the 3-iminoisoxazolines (4). Compounds (4) with 2-aryl substituents rearrange spontaneously to give the 2-imino-oxazolines (5) or (6), but the 2-methyl derivative is more stable and only rearranges on heating. 2-Imino-3-acylaziridines (8) or (9) are assumed to be the intermediates; the expected 2-imino-oxazoline (5b) was isolated among the products during an attempted synthesis of 1,3-diphenyl-2-phenylimino-3-benzoylaziridine (8b) from benzoylphenylcarbene and diphenylcarbodi-imide.

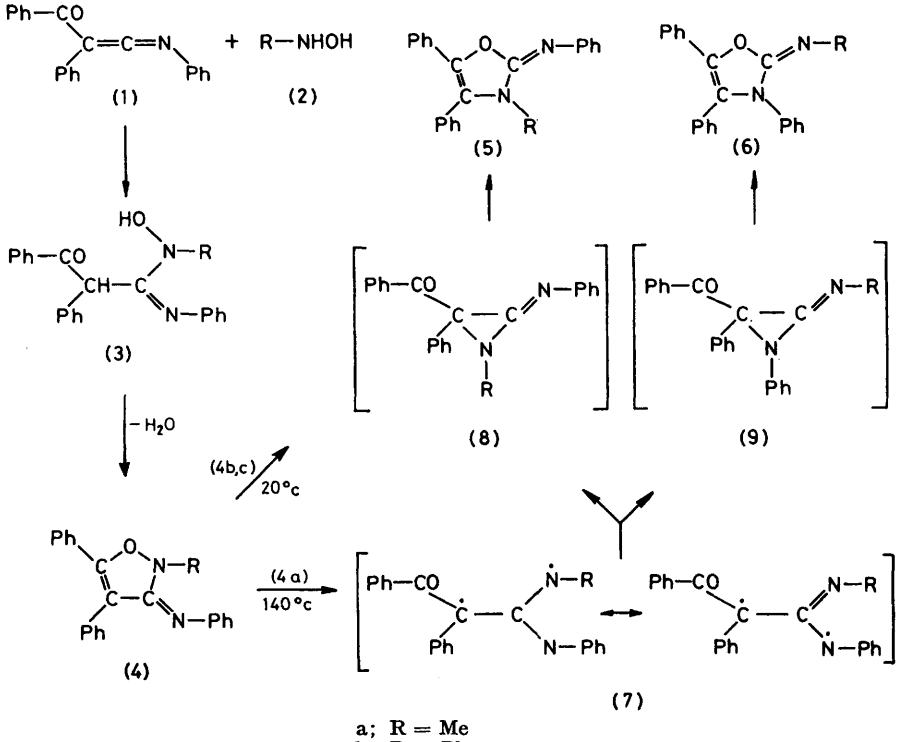
THE reaction between 2-benzoyl-*N*,2-diphenylvinylideneamine (1) † and *N*-phenylhydroxylamine (2b) has been shown to produce 3,4,5-triphenyl-2-phenylimino-oxazoline (5b = 6b).[1,2] In order to identify the mechanism of the rearrangement involved in this reaction, we treated the ketenimine (1) with other hydroxylamino derivatives and reinvestigated the reaction with *N*-phenylhydroxylamine, with the aim of isolating intermediates.

RESULTS

When the ketenimine (1) was treated with *N*-methylhydroxylamine (2a) at room temperature, a product of addition and dehydration was obtained, identified as the isoxazoline (4a). On the other hand, the reactions of the ketenimine (1) with the *N*-arylhydroxylamines (2b) or (2c) led respectively to the oxazoline (5b = 6b), as already reported,[1,2] and to a mixture of the oxazolines (5c) and (6c). The iminoisoxazoline (4a) underwent thermal rearrangement to the two isomers (5a) and (6a).

The imine (5c), like (5b = 6b),[2] was easily hydrolysed in dilute acid to the corresponding oxazolin-2-one; in contrast, the imines (4a), (5a), and (6a) are apparently insensitive to acid hydrolysis. The imine (6a) was hydrolysed by bases to *N*-(α-benzoylbenzyl)-*N'*-methyl-*N*-phenylurea, which spontaneously dehydrated to give 1-methyl-3,4,5-triphenylimidazolin-2-one.

The structures assigned to the products were supported by their spectroscopic properties. The mass spectra of



a; R = Me
b; R = Ph
c; R = *p*-MeC_6H_4

compounds (5) and (6) are characterized by base peaks corresponding to the fragments $[Ph–C{\equiv}N–R]^+$ and $[Ph–C{\equiv}N–Ph]^+$, respectively; mass-analysed ion kinetic

† Previously named as *C*-benzoyl-*CN*-diphenylketenimine.

energy (MIKE) spectra [3] of the molecular ions (5a—c) and (6a, b) showed that these fragment ions are generated in one step from the corresponding molecular ions. The mass spectrum of compound (4a) is almost identical to the sum of the spectra of the isomers (5a) and (6a) (two main fragments at *m/z* 118 $[Ph-C\equiv N-Me]^+$ and 180 $[Ph-C\equiv N-Ph]^+$), thus showing that thermal rearrangement occurs in the source of the mass spectrometer.

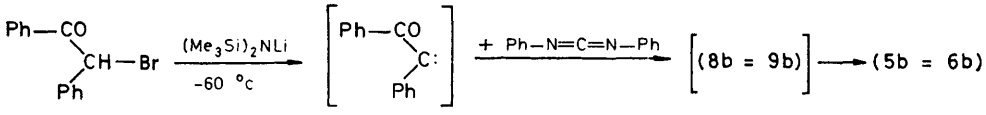
The chemical shifts of the carbon atoms bearing no hydrogen atoms were obtained from the low-noise ^{13}C n.m.r. spectra of compounds (4a), (5a—c), and (6a, b); their values are reported in the Experimental section. Only the iminoisoxazoline (4a) exhibits a signal to higher field of the aromatic region (δ 110.69 p.p.m.); this is ascribed to C(4) of the isoxazoline ring, which is not bound to heteroatoms. Similar shifts are known for C(4) in furan (δ 109.8 p.p.m.), pyrrole (δ 108.4), and pyrazole (δ 104.7) systems.[4]

We have been able to show that the iminoisoxazoline (4b) is an intermediate, by carrying out the reaction between the ketenimine (1) and *N*-phenylhydroxylamine (2b) under milder conditions: at 0 °C, the adduct (3b) can be isolated before it evolves to give further products. This adduct (3b) is rather stable in the solid state at room temperature, but in solution it is slowly converted into 3,4,5-triphenyl-2-phenylimino-oxazoline (5b = 6b). The intermediate (3b) was dehydrated without extended rearrangement by treatment of a cold solution in methylene dichloride with silica gel. The iminoisoxazoline (4b) thus obtained could be stored at −78 °C; its spectroscopic behaviour is closely related to that of the parent iminoisoxazoline (4a): i.r. (CH_2Cl_2), $\nu_{C=N}$ 1 620 (4b) and 1 610 cm^{-1} (4a); u.v. (CH_2Cl_2), $\lambda_{max.}$ 270 and 357, extending up to 440 nm (4b, qualitative), $\lambda_{max.}$ 260 (log ε 4.24) and 340 (log ε 3.90) extending up to 450 nm (4a); ^{13}C n.m.r. ($CDCl_3$), C-4 δ 110.74 (4b) and 110.69 (4a) p.p.m.

At room temperature in methylene dichloride solution, the rearrangement of the iminoisoxazoline (4b) to the imino-oxazoline (5b = 6b) was complete in 3 h; this reaction was followed by either i.r. or u.v. spectroscopy (two isosbestic points, at 283 and 348 nm), the final spectra being identical with those of a sample of pure (5b = 6b).

DISCUSSION

As already pointed out,[1] the final products (5a—c) and (6a—c) are obtained by a mechanism involving presumably the unstable iminoacylaziridines (8a—c) and (9a—c), by analogy with known similar reactions.[5-7] The intermediates (4b) and (4c) are in fact less stable than we supposed earlier.



(10)

This view is supported by the result of an attempted synthesis of the aziridine (8b = 9b), from benzoylphenylcarbene (10) and diphenylcarbodi-imide: the oxazoline (5b = 6b) was isolated in low yield from the product mixture.

The N–O bond in isoxazoline derivatives has already been reported to be weaker in *N*-aryl than in *N*-alkyl compounds.[5,6] In the iminoisoxazolines (4a—c) a similar feature was observed; the rearrangement of the imine (4a) requires prolonged heating at 140 °C, affording a mixture of the isomers (5a) and (6a) in almost equal amounts, while the imine (4c), like (4b), rearranges at room temperature, to give a mixture in which (5c) predominates over the isomeric (6c). This suggests that the imine (4c) rearranges mainly to the iminoaziridine (8c) *via* a concerted process. For the imine (4a), a stepwise pathway *via* the delocalised radical (7a) is assumed to be predominant, in order to explain the almost random production of the iminoaziridines (8a) and (9a), and thence of the imines (5a) and (6a).

The final rearrangement of iminoacylaziridines (8) and (9) to the respective imino-oxazolines (5) and (6) has not been investigated in detail. Some other iminoaziridines are reported to decompose to isonitriles and imino-compounds;[8,9] subsequent 1,4-addition of the isonitrile to the hetero-1,3-diene unit would account for the production of the final imino-oxazolines (5) and (6), by analogy with the known conversion of 1-ethoxycarbonyl-2-phenylimino-3,3-bis(trifluoromethyl)-aziridine into 2-ethoxy-5-phenylimino-4,4-bis(trifluoromethyl)-Δ^2-oxazoline.[9] However, no scrambled products [*e.g.* (5b)] were detected in the rearranged mixture from the iminoisoxazoline (4a). Therefore we are in favour of an intramolecular mechanism, either concerted, as previously proposed,[1] or possibly *via* dipolar intermediates, as reported recently for the rearrangement of 1-phenyl-2-t-butyl-3-t-butyliminodiaziridine to 2-t-butyl-3-t-butylaminoindazole.[10]

EXPERIMENTAL

M.p.s were measured on a RCH Kofler apparatus. N.m.r. spectra were recorded in deuteriochloroform solution with Bruker WP 80 (^{13}C: only the chemical shifts of carbon atoms without hydrogen are reported) and Perkin-Elmer R 32 (^1H) spectrometers. I.r. spectra were recorded for potassium bromide pellets using a Perkin-Elmer 457 spectrophotometer and u.v. spectra for methanolic solutions using a Cary 14 spectrophotometer. High-resolution mass spectra were recorded on a Varian MAT 311 mass spectrometer.

2,4,5-Triphenylisoxazolium perchlorate, 2-benzoyl-*N*,2-diphenylvinylideneamine (1), and 3,4,5-triphenyl-2-phenylimino-oxazoline (5b = 6b), *m/z* 388 (71%, M^+), 283 (6%, M^+ − PhCO), 194 (7%, M^{2+}), 180 (100%, $Ph-N\equiv C-Ph^+$), 165 (13%, fluorenyl$^+$), 119 (2%, $PhNCO^+$), 105 (6%, $PhCO^+$), and 77 (49%, Ph^+), were prepared as previously described.[2,11]

2-Methyl-4,5-diphenyl-3-phenyliminoisoxazoline (4a).—*N*-Methylhydroxylamine hydrochloride (5 g, large excess) in methylene dichloride (130 ml) was treated at 0 °C with triethylamine (11 ml), and then with a solution of 2,4,5-

triphenylisoxazolium perchlorate (4.4 g) in methylene dichloride (80 ml). The mixture was stirred for 1.5 days at room temperature washed with water, dried, and concentrated. The residue was crystallised from ethanol to give yellow crystals of the *isoxazoline* (4a), m.p. 133—135 °C, yield 70% (Found: C, 80.75; H, 5.6; N, 8.45. $C_{22}H_{18}N_2O$ requires C, 81.0; H, 5.6; N, 8.6%); $\nu_{C=N}$ 1 612 cm^{-1}; ^1H n.m.r. CH_3 at δ 3.25; ^{13}C n.m.r. δ 110.69, 127.49, 129.87, 148.85, 159.92, and 162.05 p.p.m.; $\lambda_{max.}$ 258 (log ε 4.21), 265 sh (4.20), and 315 sh (3.85) nm; *m/z* 326 (96%, M^+), 309 (4%, $M^+ - OH$), 297 (12%, $M^+ - MeN$), 249 (4%, $M^+ - Ph$), 235 (7%, $M^+ - PhN$), 221 (1.5%, $M^+ - PhCO$), 180 (52%, $Ph-N{\equiv}C-Ph^+$), 165 (2%, fluorenyl$^+$), 118 (91%, $Me-N{\equiv}C-Ph^+$), 105 (85%, $PhCO^+$), and 77 (100%, Ph^+). The iminoisoxazoline (4a) was unaffected by heating in refluxing aqueous ethanolic sulphuric acid.

3-Methyl-4,5-diphenyl-2-phenyliminooxazoline (5a) *and 2-Methylimino-3,4,5-triphenyloxazoline* (6a).—2-Methyl-4,5-diphenyl-3-phenyliminoisoxazoline (4a) (1.13 g) was refluxed in xylene (60 ml) for 10 h. The residue from the concentrated solution was chromatographed on a silica gel column (diethyl ether as eluant) to give the *oxazoline* (5a), m.p. 124—126 °C (from EtOH) (0.37 g) (Found: C, 81.1; H, 5.6; N, 8.6. $C_{22}H_{18}N_2O$ requires C, 81.0; H, 5.6; N, 8.6%) and the isomeric *oxazoline* (6a), m.p. 173 °C (from EtOH) (0.3 g) (Found: C, 80.8; H, 5.5; N, 8.6%); t.l.c. (silica gel plates, Merck F_{254}, Et_2O as eluant): R_F 0.47 (5a), and 0.1 (6a); $\nu_{C=N}$ 1 670 (5a) and 1 700 cm^{-1} (6a); ^1H n.m.r. CH_3 at δ 2.13 (5a) and 3.12 (6a); ^{13}C n.m.r. δ 124.82, 128.02, 128.65, 135.40, 135.50, and 151.47 p.p.m. (5a); 124.72, 127.54, 128.17, 134.82, 146.91, and 150.21 p.p.m. (6a); $\lambda_{max.}$ 280 (log ε 4.05), 287 sh (4.04), and 308 sh nm (3.96) (5a); 291 (4.03) and 317 (4.05) nm (6a); *m/z* 326 (86%, M^+), 235 (1%, $M^+ - NPh$), 221 (8%, $M^+ - PhCO$), 180 (11%, $Ph-N{\equiv}C-Ph^+$), 165 (7%, fluorenyl$^+$), 118 (100%, $Me-N{\equiv}C-Ph^+$), 105 (7%, $PhCO^+$), 104 (16%), and 77 (35%, Ph^+) (5a); 326 (70%, M^+), 310 (2%, $M^+ - CH_4$), 269 (2%, $M^+ - MeNCO$), 221 (1%), 180 (100%), 165 (14), 118 (7), 105 (5), and 77 (52) (6a). The two imino-oxazolines (5a) and (6a) are not in equilibrium: each of them is stable in refluxing xylene.

Both compounds are unaffected by acid treatment even under more severe conditions than those reported for the hydrolysis of the imino-oxazoline (5b = 6b).[2]

In boiling aqueous ethanolic potassium hydroxide the imine (5a) is very stable, whereas the imine (6a) was converted into an unstable product, m.p. 161—162 °C (from benzene): i.r. 1 680 cm^{-1}; ^1H n.m.r. δ 5.21, 3.47, 2.77 (ratio 1 : 1 : 3) and aromatic multiplet. This compound [probably *N*-(α-benzoylbenzyl)-*N'*-methyl-*N*-phenylurea], either in solution or in the solid state, spontaneously gave *1-methyl-3,4,5-triphenylimidazolin-2-one*, m.p. 196—199 °C (from methanol), identical with a sample prepared from *N*-methyl-*N'*-phenylurea and benzoin in acetic acid (Found: C, 80.7; H, 5.8; N, 8.6. $C_{22}H_{18}N_2O$ requires C, 81.0; H, 5.6; N, 8.6%); i.r. 1 685 cm^{-1}; ^1H n.m.r. CH_3 at δ 3.22.

4,5-Diphenyl-2-phenylimino-3-p-tolyloxazoline (5c) *and 3,4,5-Triphenyl-2-p-tolylimino-oxazoline* (6c).—A solution of the ketenimine (1) in methylene dichloride prepared from 2,4,5-triphenylisoxazolium perchlorate (1 mmol) [2] was added dropwise at room temperature to a stirred solution of *N-p*-tolylhydroxylamine (1.05 mmol) in the same solvent (10 ml). The solvent was then removed *in vacuo*, methanol (5 ml) added to the residue, and the clear solution set aside overnight. A precipitate comprising the oxazoline (5c) containing a small impurity of the isomer (6c) was collected (283 mg, 70%) and recrystallised from acetonitrile (4 ml): 252 mg, m.p. 176 °C (Found: C, 82.8; H, 5.8; N, 7.0. Calc. for $C_{28}H_{22}N_2O$: C, 83.6; H, 5.5; N, 7.0%); $\nu_{C=N}$ 1 685 cm^{-1}; ^1H n.m.r. CH_3 at δ 2.20; ^{13}C n.m.r. δ 124.67, 127.78, 128.22, 132.44, 135.55, 137.34, 147.10, and 149.29 p.p.m.; $\lambda_{max.}$ 282 nm (log ε 4.27) and 308 sh (4.20); *m/z* 402 (92%, M^+), 297 (6%, $M^+ - PhCO$), 201 (9%, M^{2+}), 194 (100%, $tol-N{\equiv}C-Ph^+$), 180 (11%, $Ph-N{\equiv}C-Ph^+$), 165 (15%, fluorenyl$^+$), 119 (3%, $PhNCO^+$), 105 (5%, $PhCO^+$), 91 (32%, $C_7H_7^+$), and 77 (17%, Ph^+).

The mother liquor, analysed by t.l.c. (silica gel Merck F_{254}, eluant CH_2Cl_2 + cyclohexane, 3 : 1), contained the imine (4c), R_F 0.26, and several by-products with R_F values of 0.56 (azoxytoluene), 0.43, 0.35, 0.19, 0.15 (benzoylphenylacetanilide), 0.12, and 0. The spot at R_F 0.19 was due to 3,4,5-triphenyl-2-*p*-tolylimino-oxazoline (6c). Its mass spectrum was recorded for a sample extracted from the silica gel layer; *m/z* 402 (62%), 309 (7), 297 (7), 295 (6), 194 (26), 180 (100), 167 (12), 165 (11), 149 (54), 105 (51), 91 (24), and 77 (70). The fragment at *m/z* 194 might arise from an impurity comprising the isomeric imine (5c).

The imine (5c), when heated in refluxing dilute aqueous ethanolic sulphuric acid for 10 h, was hydrolysed to the known [12] 4,5-diphenyl-3-*p*-tolyloxazolin-2-one; $\nu_{C=O}$ 1 740 cm^{-1}; $\lambda_{max.}$ 292 nm (log ε 4.22); ^1H n.m.r. CH_3 at δ 2.27.

N-Phenyl-N-(1-phenylimino-2-benzoyl-2-phenylethyl)-hydroxylamine (3b).—The ketenimine (1) in methylene chloride (1 mmol in 50 ml) was added to a stirred solution of *N*-phenylhydroxylamine (2b) (1 mmol) in the same solvent (10 ml) at 0 °C. The solvent was removed *in vacuo*, and the residue treated with methanol (5 ml) and then with water (20 ml); the precipitate of the *hydroxylamine* (3b) was collected, dried, and crystallised from light petroleum (or simply washed): m.p. 101—104 °C, yield 53% (Found: C, 80.1; H, 5.6; N, 7.1. $C_{27}H_{22}N_2O_2$ requires C, 79.8; H, 5.5; N, 6.9%), i.r. 3 510 and 1 650 cm^{-1}; ^1H n.m.r. δ 3.5 br and 4.35 (m, ArH); u.v. $\lambda_{max.}$ 216 (log ε 4.65) and 289 nm (4.47). When the potassium bromide pellet which was used to record the i.r. spectrum was heated at 80 °C for 1 h, the same i.r. spectrum as that of the imine (5b = 6b) was obtained. Compound (3b) is quite stable at room temperature.

2,4,5-Triphenyl-3-phenyliminoisoxazoline (4b).—A solution of the intermediate (3b) (177 mg) in methylene dichloride (7 ml) was stirred with silica gel for 5—10 h at −10 °C, the reaction progress being followed by i.r. spectroscopy: the absorption at 1 650 cm^{-1} (3b) decreased, while that at 1 620 cm^{-1} (4b) increased. The solution was filtered, the solid washed with diethyl ether (50 ml), and the solvents were removed at low temperature from the combined solutions. If some rearranged product (5b = 6b) was present (absorption at 1 680 cm^{-1}), the residue was chromatographed on a silica gel column at 0 °C, with methylene dichloride–diethyl ether (20 : 1) as eluant. The appropriate fractions were concentrated in the cold, and the residual oil crystallised from light petroleum between 0 and −60 °C: the yellow solid, decanted from the mother liquor, was stored in solid carbon dioxide. Its rearrangement to the imine (5b = 6b) was easily followed, in methylene dichloride solution, by i.r. or u.v. spectroscopy, and was complete in a few hours: ^{13}C n.m.r. δ 110.98, 126.71, 129.43, 139.77, 148.70, 155.26, and 160.94 p.p.m. (4b); 124.53, 127.68, 128.12, 135.07, 135.69, 146.86, and 149.04 p.p.m. (5b = 6b).

Reaction of Benzoylphenylcarbene (10) *with Diphenylcarbodi-imide*.—A 10% solution of 2-bromo-2-phenylacetophenone in anhydrous tetrahydrofuran was added dropwise to a solution of lithium hexamethyldisilazane [13] in the same solvent, cooled at −75 °C, under nitrogen. After addition of a solution of diphenylcarbodi-imide in the same solvent, the temperature was maintained at −55 °C for several hours. 2-Phenylimino-3,4,5-triphenyloxazoline (5b = 6b) was isolated in low yield (2%) by column chromatography on silica gel with methylene dichloride as eluant and recrystallisation from methanol and identified by i.r. comparison with an authentic sample.

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REFERENCES

[1] Part 2, F. De Sarlo, *J. Chem. Soc., Perkin Trans. 1*, 1980, 385.
[2] F. De Sarlo and G. Renzi, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1113.
[3] R. G. Cooks, J. H. Beynon, R. M. Caprioli, and G. R. Lester, 'Metastable Ions,' Elsevier, Amsterdam, 1973, p. 42.
[4] J. B. Stothers, 'Carbon-13 NMR Spectroscopy,' Academic Press, New York and London, 1972, p. 253.
[5] J. E. Baldwin, R. G. Pudussery, A. K. Qureshi, and B. Sklarz, *J. Am. Chem. Soc.*, 1968, **90**, 5325.
[6] I. Adachi, R. Miyazaki, and H. Kanō, *Chem. Pharm. Bull.*, 1974, **22**, 70.
[7] A. R. Gagneux and R. Göschke, *Tetrahedron Lett.*, 1966, 5451.
[8] H. Quast and P. Schäfer, *Tetrahedron Lett.*, 1977, 1057.
[9] E. G. Ter-Garbiélyan, N. P. Gambaryan, and Yu. V. Zeifman, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1978, 1888.
[10] H. Quast, personal communication, *Heterocycles*, in the press.
[11] D. J. Woodman, M. Tontapanish, and J. V. Van Ornum, *J. Org. Chem.*, 1971, **36**, 1685.
[12] H. McCombie and J. W. Parkes, *J. Chem. Soc.*, 1912, **101**, 1997.
[13] E. H. Amonoo-Neizer, R. H. Shaw, D. O. Skovlin, and B. C. Smith, *J. Chem. Soc.*, 1965, 2997.