Reaction of Benzoyl(phenyl)acetaldehyde with *N*-Phenylhydroxylamine : a Re-examination

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N-(2-Benzoylstyryl)-*N*-phenylhydroxylamine (3), the primary condensation product between benzoyl(phenyl)-acetaldehyde (1) and *N*-phenylhydroxylamine (2) has been isolated, and its tautomerism studied. This compound readily dehydrates to *C*-benzoyl-*CN*-diphenylketen imine (5) which, in turn, gives the final products by addition, respectively, of water [benzoyl(phenyl)acetanilide (12)], acetic acid [acetylated benzoyl(phenyl)acetanilide (7)], *N*-phenylhydroxylamine [2-phenylimino-3,4,5-triphenyloxazoline (10)], or benzoylphenylacetaldehyde [2-benzoylstyryl [*N*-phenyl(benzoyl)phenylacetimidate or tautomer (9), produced].

THE title reaction [1] has been re-investigated,[2] and the product obtained in acetic acid solution has now correctly been identified as *N*-acetyl(benzoyl)phenylacetanilide (7). The reaction has been reported [2] to take place *via* several unisolated intermediates, *i.e.* *N*-phenyl-*N*-(2-benzoylstyryl)hydroxylamine (3a), 2,4,5-triphenylisoxazolium (4) acetate, *N*-phenyl(benzoyl)-phenylketen imine (5), and finally two unstable *O*-acetyl derivatives of benzoyl(phenyl)acetanilide, which sequentially rearrange to the product (7). The 2,4,5-triphenylisoxazolium (4) was isolated as a perchlorate by carrying out the reaction in ethereal perchloric acid.

In ethanol, a condensation product between benzoyl-(phenyl)acetaldehyde (1) and *N*-phenylhydroxylamine (2) in 2 : 1 molar ratio has been isolated [1,2] and formulated [2] as a tautomer of 2-benzoylstyryl *N*-phenyl-(benzoyl)phenylacetimidate (9). In addition, another condensation product between (1) and (2) in 1 : 2 molar ratio is obtained in yields depending upon the reaction conditions [(10), m.p. 180 °C]. When an excess of either (1) or (2) is employed the main reaction product is either compound (9) or (10) respectively. Compound (10) ($C_{27}H_{20}N_2O$) was formerly described as a pyrroline derivative ($C_{28}H_{24}N_2O$),[1] and believed to arise from product (9).[1,2] Possibly, compound (10) was present as an impurity, since it cannot be obtained from pure samples of (9).

The condensation product $C_{27}H_{20}N_2O$ was converted, by acid treatment, into aniline and 3,4,5-triphenyl-oxazolin-2-one (11), the latter identified by comparison (i.r.) with a sample prepared *via* the benzoin phenylurethane.[3] Only aromatic protons appear in the ^1H n.m.r. spectrum of compound (10), and significant i.r. absorption occurs at 1 693vs (C=N) and 1 655w cm^{-1} (C=C). On this basis, possible structures for the product $C_{27}H_{20}N_2O$ are restricted to 3,4,5-triphenyl-2-phenylimino-oxazoline (10), corresponding to the carbonyl compound (11) and to 2,4,5-triphenyl-3-phenylimino-isoxazoline: thermal rearrangement of isoxazolin-3-ones to oxazolin-2-ones is known to occur.[4] A third isomer, *i.e.* 2,3,4-triphenyl-5-phenyliminoisoxazoline, is not considered because it cannot give the hydrolysis product (11). The u.v. spectrum (solvent methanol) of the imine (10), $\lambda_{max.}$ 282 nm (log ε 4.27) and *ca.* 310sh nm (log ε 4.22), indicating extended conjugation seems in favour of the 3-phenyliminoisoxazoline structure: similarly 2,3,4-triphenylisoxazolin-5-one has $\lambda_{max.}$ 312 (log ε 4.11) [5] [*cf.* 3,4,5-triphenyloxazoline-2-one (11) $\lambda_{max.}$ 291 (log ε 4.19) and 3-methyl-4,5-diphenyloxazolin-2-one $\lambda_{max.}$ 290.5 (log ε 4.15)] and an inflection at 220 nm (log ε 4.20).[6]

The most reasonable structure for the product $C_{27}H_{20}N_2O$ seems, therefore, to be that of 3-phenylimino-2,4,5-triphenylisoxazoline: its formation from the keten imine (5) and *N*-phenyl-hydroxylamine (2), see later, can be understood in terms of nucleophilic attack by the nitrogen atom of (2), followed by intramolecular condensation. However, the structure of 3,4,5-triphenyl 2-phenylimino-oxazoline cannot be excluded with certainty since a rearrangement would account for its formation; further work on this is in progress.†

We succeeded in isolating two reaction intermediates: the initial condensation product (3) was prepared from a concentrated alcoholic reaction mixture below 10 °C; the keten imine (5) from 2,4,5-triphenylisoxazolium (4) perchlorate.

The first reaction intermediate (3), previously formulated as the hydroxylamino-derivative (3a),[1,2] can also be obtained by mild oxidation of *N*-phenyl-*N*-(2-benzoyl-2-phenylethyl)hydroxylamine (8), *via* a reaction sequence described [7] for the synthesis of a similar compound.‡ Disregarding geometrical isomerism, the compound may exist as any one of the tautomeric

† There is now chemical evidenc that compound $C_{27}H_{20}N_2O$ is 2-phenylimino-3,4,5-triphenyloxazoline (10).

‡ This was formerly described as a nitrone,[7,8] and more recently as 3-(*N*-hydroxyanilino)acrylophenone.[9]

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[5] J. B. Hill, *Tetrahedron Letters*, 1975, 3283.
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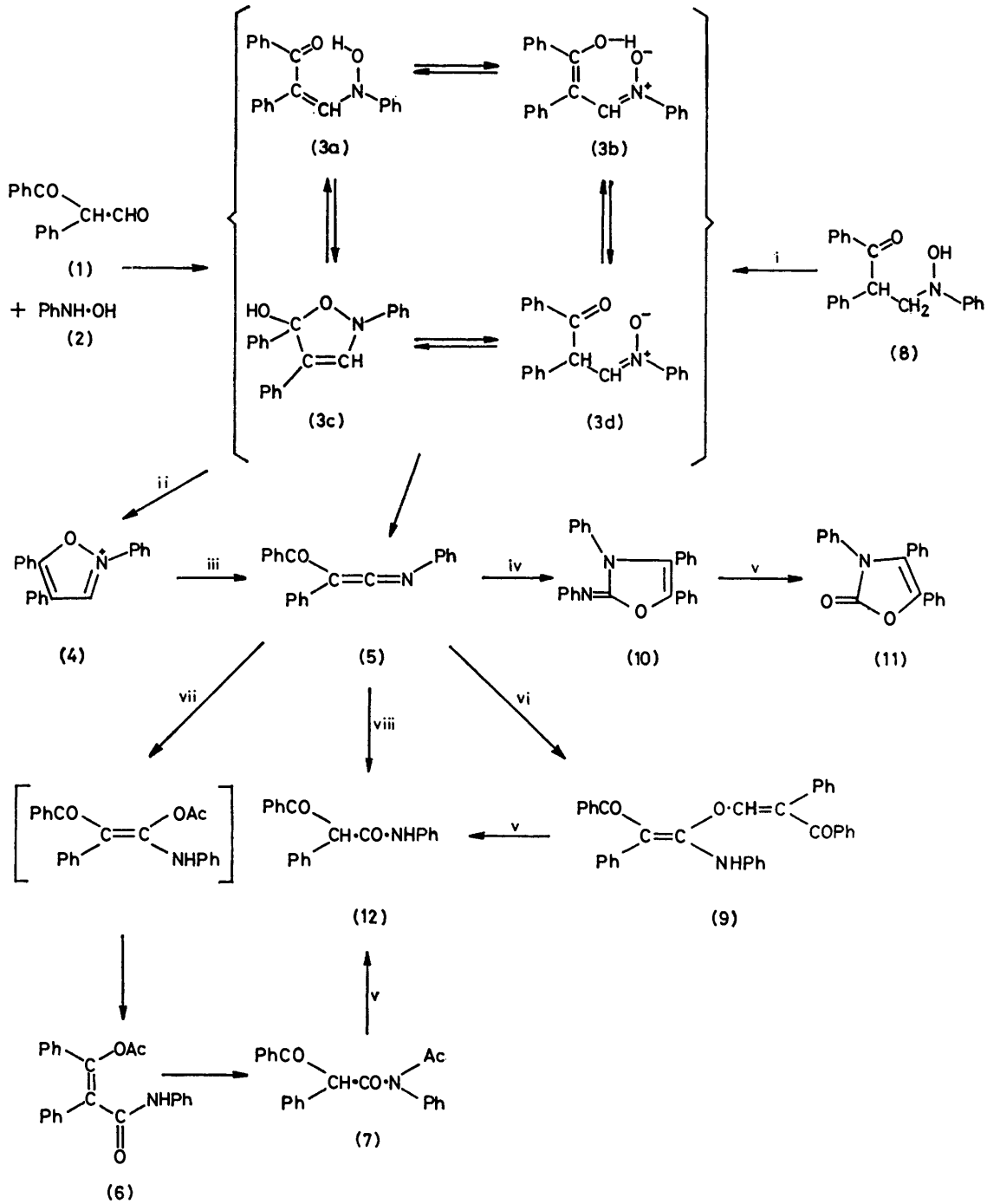
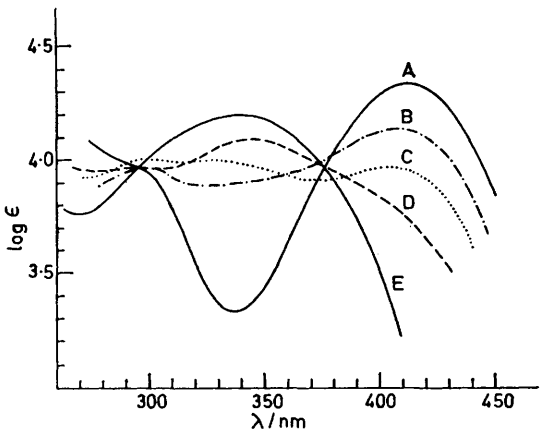
structures (3a—d). Both in the solid state and in solution the compound shows the absence of carbonyl absorption whilst no OH absorption can be identified



Reagents: i, PhNO or $K_3[Fe(CN)_6]$; ii, H^+; iii, NEt_3 or AcO^-; iv, PhNH·OH (2); v, H_3O^+; vi, PhCO·CH(Ph)·CHO (1); vii, AcOH; viii, H_2O

sulphoxide compound (3) shows a modified i.r. spectrum: thus, broad ν_{OH} absorption at 3 150 cm^{-1} and $\nu_{C=O}$ at 1 625 cm^{-1} are found, while the absorption at 1 565 cm^{-1} with certainty. Evidence in favour of structure (3b) is provided by the band at 1 565 cm^{-1} [ν(C=N)] which is ascribed to the nitrone group. Absorption arising from the hydroxy-group in structure (3b) is absent owing to very strong intramolecular association. In dimethyl lamost disappears. In terms of structure (3a) this is explained as hydrogen bonding with the solvent. In dioxan, intermediate behaviour is observed, with the compound in part as the (3b) form (internally hydrogen-bonded, $\nu_{C=N}$ at 1 565 cm^{-1}), and in part as (3a) (hydrogen

bonded with the solvent, ν_{OH} at 3 320 cm^{-1}, $\nu_{C=O}$ at 1 625 cm^{-1}). The electronic spectra of compound (3) in various solvents (range 280—450 nm, see Figure) accord with the behaviour described above: in tetrachloromethane the conjugated system of structure (3b) gives rise to absorption at 412 nm (log ε 4.33), and in dimethyl sulphoxide (3a) gives a $\lambda_{max.}$ at 338 nm (log ε 4.19). In methanol, or dioxan, or mixtures of solvents, intermediate spectra are observed. In the ^1H n.m.r. spectrum of product (3) in tetrachloromethane solution, the hydroxylic proton of structure (3b) appears as a sharp singlet at *ca.* δ 12.25, while the other non-aromatic proton is concealed by the aromatic pattern. The ^1H n.m.r. spectrum in dimethyl sulphoxide shows both the olefinic proton (*ca.* δ 8.2) and the hydroxylic proton (*ca.* δ 7.7) of structure (3a): the signal at δ 7.7 disappears



Electronic spectra of compound (3) in various solvents. A = CCl_4, B = CCl_4–Me_2SO (20 : 1), C = dioxan, D = MeOH, E = Me_2SO

upon addition of D_2O. The unusual shift of the hydroxylic proton in the form (3b) is ascribed to the chelate structure.

The nitrone (3) is quite stable in the solid state, but in solution undergoes dehydration to the keten imine (5). This process, very easy in those solvents in which structure (3a) predominates, is evidenced by i.r. spectroscopy: the spectrum of (3) in ethanol shows after a few minutes $\nu_{C=C=N}$ at 2 025 cm^{-1}, which later disappears. The keten imine (5) in turn is converted in solution into benzoylphenylacetanilide (12): the nitrone (3) in dimethyl sulphoxide gave, with time, the same ^1H n.m.r. spectrum as the anilide (12).

Unlike other nitrones containing α-hydrogen atoms, which are known to exist as dimers,[10] the nitrone (3) shows in chloroform the molecular weight expected for a monomer. This behaviour is ascribed to binding of the labile hydrogen atom in the highly stable hydrogen-bonded structure [(3a) or (3b)]: dimerization is thus prevented. Similar, monomer structures have been reported.[7,8,11]

The *N*-acetylanilide (7) can be obtained from either the nitrone (3) or the keten imine (5) with acetic acid; from isoxazolium (4) perchlorate, product (7) is obtained only by treatment with a base (triethylamine, acetate ions) in acetic acid.[2]

Either compound (9) or (10) is easily obtained by treatment of the nitrone (3) or the keten imine (5) with (1) or (2) respectively. The isoxazolium (4) perchlorate reacts with benzoylphenylacetaldehyde (1) only in the presence of a base,[2] to give the product (9), and with *N*-phenylhydroxylamine (2) to give the salt of the imine (10) with perchloric acid: the requirement of a base suggests intermediacy of the keten imine (5).

In view of the easy dehydration of compound (3) to the keten imine (5), it is even possible that, at least in ethanol, the isoxazolium (4) is not an intermediate at all.

EXPERIMENTAL (with Dr. M. MAOGGI)

Instruments used were: Hitachi–Perkin-Elmer 115 osmometer (for molecular weights); Perkin-Elmer spectrometers model 337 (for i.r. spectra), model 124 (for u.v. spectra), and model R 32 (for ^1H n.m.r. spectra).

Condensation of Benzoyl(phenyl)acetaldehyde (1) *with* N-*Phenylhydroxylamine* (2) *in Ethanol*.—In absolute ethanol, at temperatures above 10 °C, mixtures of compounds (9) and (10) were obtained [benzoyl(phenyl)acetanilide was found among the by-products] in variable relative amounts depending on reaction conditions (temperature, reagents molar ratio, rate of reagents admixture, *etc.*). At 5 °C the nitrone (3) was isolated. Mixtures were analysed by t.l.c.: on silica gel plates (Merck F_{254}, 0.25 mm), with benzene–diethyl ether (100 : 4) as eluant, R_F values were as follows: (1), 0.41; (2) 0.04; (9), 0.16; (3), 0.43; and (10), 0.36.

Trimethyl-(2-benzoyl-2-phenylethyl)ammonium methylsulphate was prepared from 3-dimethylamino-1,2-diphenylpropan-1-one [12] and dimethyl sulphate in diethyl ether: m.p. 172—174 °C (from ethanol) (Found: C, 59.8; H, 6.6; N, 3.7. $C_{19}H_{25}NO_5S$ requires C, 60.1; H, 6.6; N, 3.7%).

N-*Phenyl*-N-(2-*benzoyl*-2-*phenylethyl*)*hydroxylamine* (8).—An equimolecular mixture of the above methyl sulphate and *N*-phenylhydroxylamine in dilute acetic acid was treated with dilute aqueous sodium hydroxide, according to a known procedure.[7] The precipitated product (8), decanted from the mother liquor, was washed with water, then light petroleum: m.p. 124—125 °C (Found: C, 78.9; H, 6.2; N, 4.75. $C_{21}H_{19}NO_2$ requires C, 79.5; H, 6.0; N, 4.4%).

N-(2-*Benzoylstyryl*)-N-*phenylhydroxylamine* (3).—(*a*) *By oxidation*. A solution of the hydroxylamino-derivative (8) (2 mmol) in methylene chloride (10 ml) was shaken during 15 min with an aqueous solution of potassium ferricyanide (4 mmol) and sodium hydrogen carbonate (4 mmol). The organic layer afforded on concentration the product (3), m.p. 107—108 °C (yield 65%) (Found: C, 79.8; H, 5.5; N, 4.2%; *M*, 290.5. $C_{21}H_{17}NO_2$ requires C, 80.0; H, 5.4; N, 4.4%; *M*, 315.4). Oxidation with nitrosobenzene was carried out in ethanol at 30 °C: some of the imine (10) was found in the mother liquor.

(*b*) *By condensation*. Benzoyl(phenyl)acetaldehyde (1) (5 mmol) in ethanol (30 ml) was added dropwise at 5—10 °C

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to a suspension of *N*-phenylhydroxylamine (2) (5 mmol) in ethanol (5 ml). Stirring was continued for 2 h after which the yellow product was collected (52%, crude). Samples prepared by different methods had identical i.r. spectra.

C-*Benzoyl*-CN-*diphenylketen imine* (5).—Pure 2,4,5-triphenylisoxazolium (4) perchlorate * (1 mmol) was dissolved in methylene chloride (50 ml) and the solution vigorously stirred for 10 min at room temperature with 1M-aqueous sodium carbonate (20 ml). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The keten imine (5) was collected, m.p. 117—119 °C (yield 85%) (Found: C, 84.3; H, 5.2; N, 4.7. $C_{21}H_{15}NO$ requires C, 84.8; H, 5.1; N, 4.7%). In boiling ethanol the keten imine (5) was converted in part into benzoyl(phenyl)-acetanilide (12), besides an unidentified product, with $R_F = 0.56$ (t.l.c., same conditions as above).

2-*Phenylimino*-3,4,5-*triphenyloxazoline* (10).—(*a*) *By condensation.* Benzoyl(phenyl)acetaldehyde (1) (5 mmol) was added at 50 °C to a stirred solution of *N*-phenylhydroxylamine (2) (10 mmol) in anhydrous ethanol (15 ml). The mixture was maintained at 50—60 °C for 0.5 h, while the product began to separate; it was then cooled and the precipitate collected (crude yield 50%), m.p. 179—180 °C (from ethanol) (Found: C, 83.2; H, 5.2; N, 6.9%; *M*, 386. $C_{27}H_{20}N_2O$ requires C, 83.5; H, 5.2; N, 7.2%; *M*, 388.5).

(*b*) *From the nitrone* (3). The nitrone (3) was stirred at 50—60 °C for 2 h with *N*-phenylhydroxylamine (2) in anhydrous ethanol: the imine (10) was collected after cooling.

(*c*) *From the* 2,4,5-*triphenylisoxazolium* (4) *perchlorate.* The isoxazolium (4) perchlorate was maintained at 50 °C in anhydrous ethanol with an excess of *N*-phenylhydroxylamine (2) for 3 days: the salt of the imine (10) with perchloric acid was collected after cooling, it crystallized as needles from ethanol, m.p. 249—252 °C (decomp.) (Found: C, 66.1; H, 4.4; N, 5.7. $C_{27}H_{21}ClN_2O_5$ requires C, 66.3; H, 4.3; N, 5.7%). This salt was treated in a dropping funnel with ether and aqueous sodium carbonate: the imine (10) was recovered by concentration of the ethereal solution. The imine (10) was obtained directly from the isoxazolium (4) perchlorate and *N*-phenylhydroxylamine (2) with triethylamine in methylene chloride.

(*d*) *From the keten imine* (5). Some imine (10) was obtained by addition of the keten imine (5) to a solution of *N*-phenylhydroxylamine (2) in anhydrous ethanol at 50—60 °C. Better yields (55%) were obtained by dissolving the reagents in methylene chloride at room temperature, removing the solvent, adding ethanol, and setting the mixture aside for several days. Samples of the imine (10) prepared by different methods had identical i.r. spectra and t.l.c. behaviour.

3,4,5-*Triphenyloxazolin*-2-*one* (11).—A solution of the imine (10) in ethanol with diluted aqueous sulphuric acid was refluxed and then concentrated and cooled. The precipitate was collected, washed with water, and recrystallized from ethanol to give needles, m.p. 214—216 °C (lit.,[3] m.p. 214—214.5 °C). The product (11) was found to be identical to a sample prepared by a literature method [3] (i.r. and t.l.c. comparison).

2-*Benzoylstyryl* N-*Phenyl*(*benzoyl*)*phenylacetimidate* (9).—(*a*) By condensation. *N*-Phenylhydroxylamine (2) (10 mmol) was added during 10 min at 33 °C to a stirred suspension of benzoyl(phenyl)acetaldehyde (1) (10 mmol) in anhydrous ethanol (8 ml). After 2 h at room temperature the precipitate was collected, thoroughly washed with ether [yield 40% with respect to (1)] and then recrystallized from benzene; it had m.p. 173—175 °C (decomp.) (Found: C, 83.0; H, 5.4; N, 2.5%; *M*, 530. $C_{36}H_{27}NO_3$ requires C, 82.9; H, 5.2; N, 2.7%; *M*, 521.6). Product (9) is decomposed to give benzoyl(phenyl)acetanilide (12) by refluxing it in ethanol with a trace of diluted sulphuric acid for 2 h.

(*b*) The ester (9) was prepared by treatment of the nitrone (3) with benzoyl(phenyl)acetaldehyde (1) in ethanol at room temperature.

(*c*) From the keten imine (5) and benzoyl(phenyl)acetaldehyde (1) in anhydrous ethanol at room temperature, the ester (9) was isolated in poor yield (13%) by column chromatography (same conditions as for t.l.c.). In methylene chloride the reaction was slower (1.5 days), giving the ester (9) among other products.

* This was prepared as described in the literature [2] and recrystallized twice from methanol: it deflagrates at 140 °C (lit.,[2] m.p. 137—138 °C decomp.).

[7/1199 *Received*, 7*th July*, 1977]