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ADDITION OF PYRIDINE AND ISOQUINOLINE TO BENZOYLCARBONITRILE OXIDE[1]

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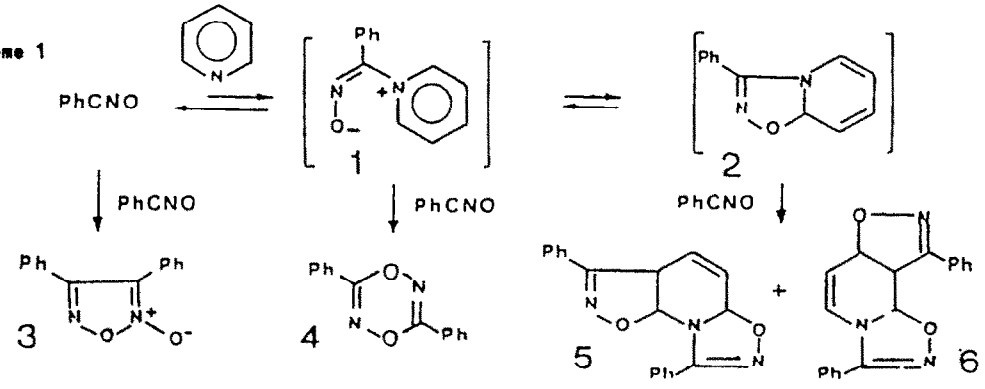
Abstract: Addition of pyridine to benzoylcarbonitrile oxide affords a fragile zwitterionic adduct, which slowly reverts to the addends, leading ultimately to benzoyl isocyanate and products deriving from it. A moderately stable cycloadduct is obtained in the reaction with isoquinoline.

In polar solvents pyridine catalyzes the dimerization of benzonitrile oxide (BNO) affording quantitatively the "abnormal" 1,4,2,5-dioxadiazine dimer 4[2] while in apolar solvents the two site-isomeric biscycloadducts 5 and 6 could be obtained in yields up to 50% along with the "normal" dimer, furoxan 3, as well as with some dioxadiazine 4 (Scheme 1).[3] A reasonable mechanism, which accounts for the remarkable solvent effect on the product distribution and the high dipolarophilic activity of the aromatic pyridine in apolar solvents, involves two different labile intermediates, zwitterion 1 and monocycloadduct 2.[3] Addition of pyridine to BNO affords the zwitterion 1, which is the overwhelming labile species in polar solvents and leads quantitatively to the dioxadiazine dimer. Apolar solvents slow down the addition step, as shown by the formation of furoxan 3, and promote the electrocyclic closure of the zwitterion to the labile monocycloadduct 2, which contains a rather reactive dienamine moiety and adds regiospecifically the nitrile oxide carbon at the β and δ positions to yield the site-isomeric biscycloadducts 5 and 6.

The proposed mechanism is qualitatively consistent with the ease of nucleophilic additions to nitrile oxides[4] and with the well-known tendency of pyridinium salt to form covalent species (pseudo bases) in apolar solvents.[5] In a search of more direct evidence for the proposed

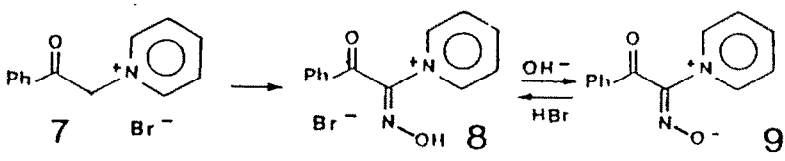
Scheme 1



intermediates, we explored the possibility of increasing their stability by appropriate modifications of the reactants. We have already succeeded in stabilizing the monocycloadducts relative to the reactants by reducing the loss of aromaticity involved in the cycloaddition. Quinoline and isoquinoline indeed add BNO to yield isolable monocycloadducts.[3] In order to increase the stability of the zwitterion we have conceivably to provide delocalization of charges. Some indication of the feasibility of this approach comes from a paper of Kröhnke and Kübler, who described in 1937 the fragile but isolable zwitterion 9 (Scheme 2).[6] Nitrosation of phenacyl pyridinium bromide 7 afforded the isonitroso phenacyl pyridinium bromide 8, which could be reversibly deprotonated, yielding the yellow zwitterion 9. A related isoquinolinium zwitterion was similarly obtained.

We report here a study on the reaction of benzoylcarbonitrile oxide (BZNO) to pyridine. The reaction with isoquinoline has also been investigated.

Scheme 2



RESULTS AND DISCUSSION

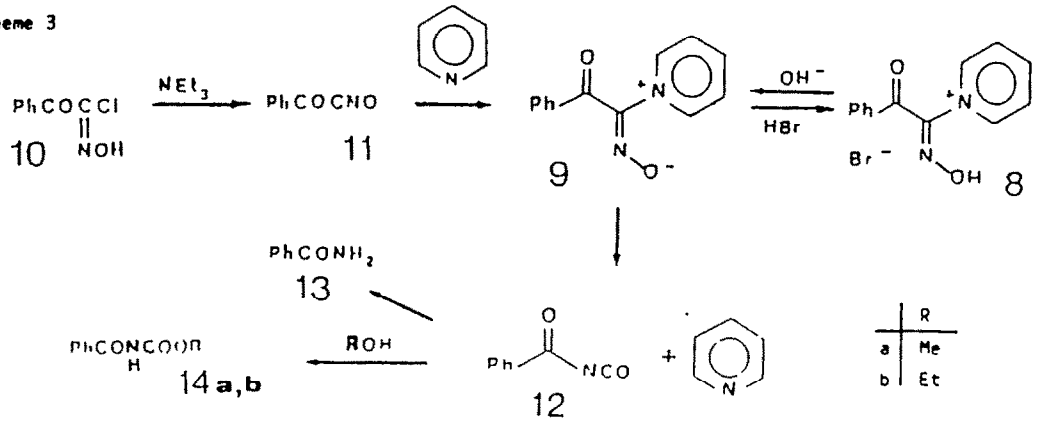
Zwitterion 9 from pyridine and benzoylcarbonitrile oxide

When BZNO 11 was generated *in situ* from phenylglyoxylohydroximoyl chloride 10 and triethylamine (1 equiv) in ether in the presence of pyridine (3 equivs), the ethereal solution turned intensely orange and the yellow zwitterionic adduct 9 promptly separated in 63% yield (Scheme 3). The yellow needles, m.p. 60–1°C dec. from water, show a broad IR absorption at 3400 cm^{-1}, attributable to water of crystallization and a C=O absorption at a rather low frequency (1620 cm^{-1}), suggesting that the carbonyl group is delocalizing negative charge.[7] It is identical with a sample of 9, $C_{13}H_{10}N_2O_2.2H_2O$, prepared according to the procedure of Kröhnke and Kübler. By treatment with 2N HBr 9 is converted into the indefinitely stable colourless salt 8, which shows a normal PhC=O absorption at 1672 cm^{-1}.

The zwitterion 9 is by itself rather unstable, even in the solid state. When the yellow needles are left on a plate or stored, the colour fades after a few days and colourless crystals of pure benzamide 13 are formed. The adduct is slightly soluble in water and alcohols (MeOH, EtOH) or in dipolar aprotic solvents (DMF, DMSO), yielding yellow and orange-red solutions, respectively. The stability of the zwitterion in solution depends strongly on the solvents, as judged by the fading of the colour of the solutions. In water fading takes place over a week, in alcohols or dipolar aprotic solvents in a few hours. In aprotic polar and apolar solvents (e.g. CH_3CN, ether) the adduct is only very slightly soluble and the weakly coloured orange solutions faded rather quickly, in just a few minutes. This behaviour supports the idea of an enhanced stability of the zwitterion in the protic and aprotic dipolar solvents due to efficient solvation. In the case of reactions performed in alcohols, evaporation of the solvent affords methyl and ethyl N-benzoyl carbamates 14a and 14b while in the other cases benzamide 13 could be identified as the major decomposition product along with pyridine.

The decomposition of the zwitterion could be monitored by NMR. When a sample of 9 was dissolved in CD_3OD only aromatic protons attributable to 9 could be observed at the beginning. Subsequent scanning clearly showed the appearance of the signals of pyridine and those of methyl N-benzoyl carbamate 14a. The decay takes place with a half-life of approximately 15–20 minutes at 35°C. In

Scheme 3



DMSO-d_6 the decomposition of 9 is somewhat faster and the spectral changes are more complex. In a parallel experiment evidence for the formation of benzoyl isocyanate in a DMSO solution of 9 could be gained by IR measurements which clearly show the appearance of the isocyanate band of benzoylisocyanate at 2225 cm^{-1}. The band reaches its maximum intensity in approx. 15 minutes. After addition of water to the DMSO solution benzamide (13) could be isolated.

The mechanism of the decomposition of 9 is however not so simple as implied in the unimolecular decay of Scheme 3. Since in the addition runs, by generating BZNO in the presence of excess pyridine, the orange colour of the reaction mixtures lasted significantly longer than expected from the behaviour of the pure 9, we tested the influence of pyridine on its decomposition. In the Figure, line a shows the decay of the absorbance at 350 nm of a 10^{-3}M solution of 9 at 35.5°C. In the presence of 5-50 equivs of pyridine the decay is strongly inhibited, as shown by lines b and c. This suggests that the first step of the decomposition is the reversible dissociation of 9 into pyridine and BZNO 11. The intermediacy of the elusive BZNO could be proved by trapping 11 with a very active dipolarophile, norbornene. In the presence of 20 equivs of norbornene the decay profile (line d) resembles that of pure 9 (a) but the cycloadduct of BZNO to norbornene, 15, is formed almost quantitatively, instead (Scheme 4). As expected, in the presence of the very reactive norbornene (20 equivs), addition of pyridine (5-50 equivs) does not affect the rate of decomposition and the decrease of the absorbance looks like line d. Interestingly, the inhibition by pyridine is also suppressed in the presence of a small excess of triethylamine. Line e shows the decrease of the absorbance in the presence of 4 equivs of triethylamine and the decay profile remains unaffected by addition of pyridine. These findings account for the lack of inhibition by pyridine when 9 was generated in situ from salt 8 and a slight excess of triethylamine.

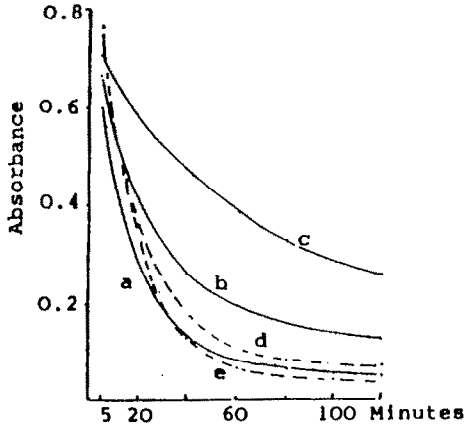
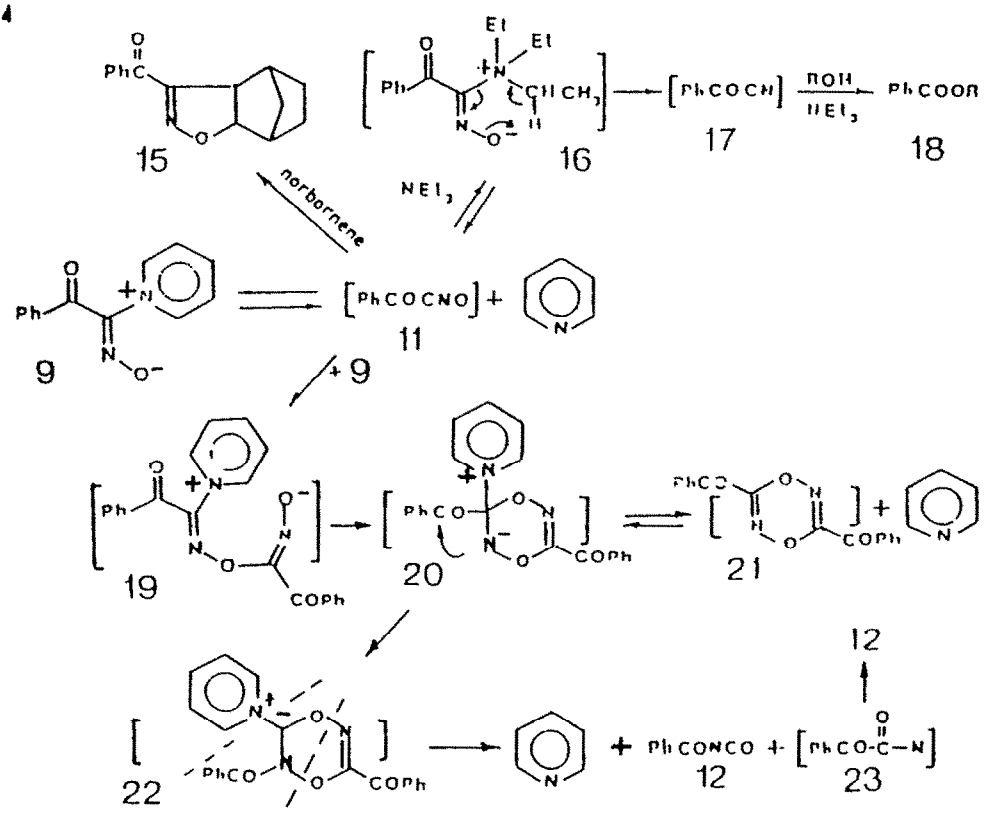


Figure. Solid lines show the decrease of absorption at 350 nm, 35.5°C, of a 10^{-3}M solution of 9 in methanol without (a) and with pyridine added, 5 equivs (b) and 50 equivs (c). Dashed lines show the decay of 9 in the presence of 20 equivs norbornene (d) or 4 equivs triethylamine (e)

Scheme 4



The intriguing effect of triethylamine in cycloadditions of BZNO is well-known.[8] Dipolarophiles of moderate activity afford only low yields of cycloadducts when triethylamine is used for the in situ generation of the nitrile oxide and, for synthetic purposes, procedures avoiding the use of bases in the generation of acylnitrile oxides have been successfully devised.[8,9] We found that treatment of phenylglyoxylohydroximoyl chloride 10 with triethylamine (3 equivs) in methanol affords methyl benzoate 18 as the main product (59%). The formation of 18 can be accounted for by assuming the same mechanism proposed for the deoxygenation of aromatic nitrile oxides induced by triethylamine in polar solvents.[10] Reversible addition of triethylamine to BZNO affords zwitterion 16, whose fragmentation leads to benzoyl cyanide 17. In alcoholic solvents and in the presence of bases, 17 is known[11] to undergo an easy displacement of CN^-, giving alkyl benzoates 18. Alternatively direct displacement of CNO^- from BZNO could also be conceived.

In the absence of any added trapping agent the reaction apparently follows the same pathway proposed for the pyridine catalyzed dimerization of aromatic nitrile oxides to dioxadiazines.[2] The nucleophilic oxygen of zwitterion 9 traps BZNO affording the extended zwitterion 19 and its cyclic form 20. Loss of pyridine from 20 should lead to the unknown 3,6-dibenzoyl-1,4,2,5-dioxadiazine 21. In this case, however, the intermediate 20 can undergo an easy migration of the benzoyl group to the nucleophilic nitrogen[12] affording the rearranged species 22, whose fragmentation leads formally to pyridine, benzoyl isocyanate and acylnitrene 23, a discussed precursor of isocyanates in Curtius-type rearrangements.[13] Evidence for a subsequent reaction between zwitterion 9 and BZNO 11 can be gained from the Figure. A comparison of the initial values of the absorbance of line a and lines d or e clearly shows that the amount of zwitterion 9 at the beginning of the UV

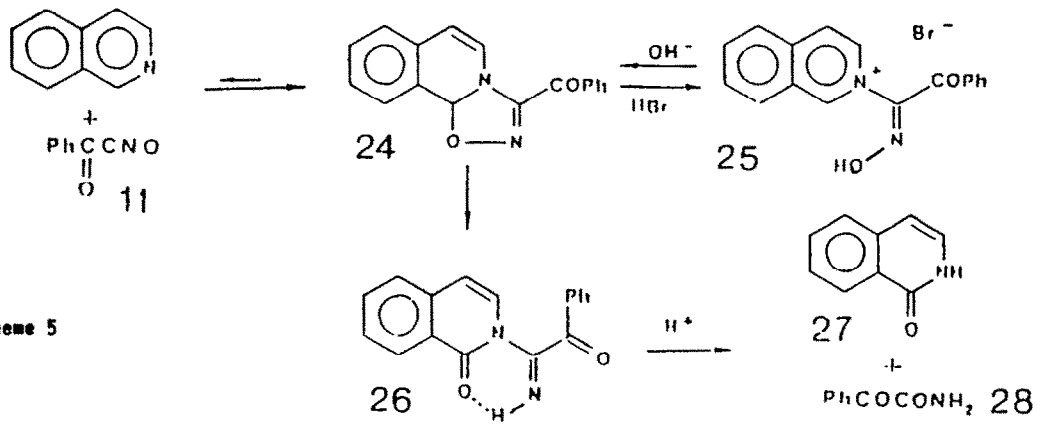
determinations is significantly higher when trapping agents like norbornene and triethylamine were added. In several experiments the initial absorption of the solution of 9 remained 10-20% less than that of the same solution with norbornene added. Thus, in the time necessary for the preparation of the samples for the UV determinations (approx. 5 minutes) there must be a leakage of 9 in the solutions containing only 9 and the subsequent reaction between 9 and 11 provides a reasonable pathway. In the presence of norbornene or triethylamine, BZNO 11 is trapped by the added trapping agents faster than it reacts with zwitterion 9 and no leakage of 9 is observed.

Cycloadduct of benzoylcarbonitrile oxide to isoquinoline

Generation of BZNO 11 from the phenylglyoxylohydroximoyl chloride 10 and 2 equivs of triethylamine at 0°C in ether in the presence of isoquinoline (2 equivs) afforded an intensely yellow reaction mixture. The yellow cycloadduct 24, m.p. 68-9 °C dec., could be isolated in 64% yield and is identical with the product $C_{17}H_{12}N_2O_2$ obtained by deprotonation of the isonitrosophenacyl isoquinolinium bromide 25 with K_2CO_3 according to the Kröhnke and Kübler protocol[6] (Scheme 5). As in the case of the adduct of pyridine, cycloadduct 24 could be converted quantitatively into the indefinitely stable salt 25 by treatment with 2N HBr. The cyclic structure 24 follows from the normal PhCO absorption at 1665 cm^{-1}. The NMR spectrum shows the oxadiazoline proton as a singlet at 6.80 δ and the olefinic protons as doublets at 7.22 and 5.95 δ. The chemical shift of the oxadiazoline proton is almost identical with the analogous proton of the BNO cycloadduct with isoquinoline (6.76 δ),[3] whereas the olefinic protons α and β to nitrogen are deshielded by the proximate benzoyl group by 0.7 and 0.3 ppm, respectively.

The cycloadduct is fragile. A short boiling in ethanol afforded colourless crystals of the isomeric product 26, m.p. 119°C. This same product 26 could be isolated in fair yields in the cycloaddition runs, when only a stoichiometric amount of triethylamine was used for the in situ generation of BZNO. We found that cycloadduct 24 easily isomerizes to 26 in solution at room temperature. The isomerization takes place in a few hours at room temperature in solvents of different polarity (e.g. benzene, acetonitrile), but is inhibited in the presence of triethylamine, a well-known radical scavenger in polymerization[14] or autoxidation[15] reactions, and in solutions kept in the dark under nitrogen. This demonstrates that the isomerization is due to the presence of air and is a free-radical process initiated by the abstraction of the oxadiazoline proton.

The structure of the ring opened product 26 is consistent with spectroscopic data. The IR spectrum shows a NH absorption at 3230 cm^{-1} and a strong carbonyl absorption at 1660 cm^{-1}, attributable to PhCO. Compound 26 can be easily cleaved to isocarbostyril 27. A solution of 26 in ethanol affords after a few hours colourless crystals of 27. In benzene solution 26 is fairly



Scheme 5

stable but addition of p-toluenesulfonic acid causes an immediate cleavage to 27 and phenylglyoxylamide 28. Addition of triethylamine also causes cleavage, affording after a few hours 27 and benzoic acid.

After having elucidated the general behaviour of cycloadduct 24, we could finally test its stability towards cycloreversion. When a benzene solution of 24 and excess norbornene (20 equivs) was kept under nitrogen or in the presence of triethylamine for 1 month, a quantitative yield of the BZNO adduct to norbornene, 15, and isoquinoline was obtained. Cycloreversion takes place with an half-life of approximately 1 week at room temperature.

CONCLUSION

A fragile zwitterion is formed in the reaction of BZNO and pyridine or by deprotonation of the Kröhnke's salt 8. The charge delocalization provided by the benzoyl substituent is apparently efficient enough to make the zwitterion more stable than the reactants. Charge delocalization stabilizes the zwitterion and also weakens its tendency to cyclization and reversion since the benzoyl substituent is not expected to stabilize the cyclic covalent form and the nitrile oxide, resp., at a similar degree. When dissolved in solvents the main reaction of the zwitterion is reversion to the addends, as evidenced by trapping experiments with norbornene, and the rate of reversion depends strongly on the solvent in a predictable way. In the absence of trapping agents the equilibrium is not reached because of the subsequent reaction of the zwitterion with BZNO. This reaction leads ultimately to a rearrangement to benzoylisocyanate or products deriving from it.

A cycloadduct is isolated in the reaction of BZNO and isoquinoline. Attempts to generate the corresponding zwitterion from Krönke salt 25 also afford the cycloadduct and the facile cyclization can be attributed to the smaller loss of aromaticity.[16] The cycloadduct is fragile in the presence of air, which initiates a free-radical isomerization to isocarbostyril derivatives. In the absence of air a slow cycloreversion to the addends could be detected.

EXPERIMENTAL

All m.ps are uncorrected. Elemental analyses were done on a C. Erba 1106 elemental analyzer. ^{1}H-NMR spectra were recorded on a Bruker WP80SY spectrometer in $CDCl_3$ solutions, unless otherwise stated. Chemical shifts are expressed in ppm from internal tetramethylsilane (δ) and coupling constants are in hertz (Hz). IR spectra (nujol mulls) were recorded on a Perkin-Elmer 197 spectrophotometer and UV spectra on a Perkin-Elmer Lambda 5 spectrophotometer, equipped with thermostatted cell transport assembly and automatic multicell programmer. Column chromatography and TLC: silicagel H 60 and GF_{254} (Merck) respectively, eluant cyclohexane: EtOAc 9:1 to 7:3. The identification of samples from different experiments was secured by mixed m.ps and superimposable IR spectra.

Materials - Phenylglyoxylohydroximoyl chloride 10 was prepared according to an Organic Syntheses procedure.[17] Phenacyl pyridinium bromide 7[18] and phenacyl isoquinolinium bromide[19] were obtained by reaction of phenacyl bromide with the appropriate heterocyclic base.
Methyl N-benzoyl carbamate 14a,[20] and ethyl N-benzoyl carbamate 14b[21] were prepared from the commercially available benzoyl isocyanate (Aldrich) and anhydrous methyl and ethyl alcohol, resp. Carbamate 14a: colourless crystals m.p. 117-8°C from diisopropyl ether; ν_{NH} 3240 and $\nu_{C=O}$ 1775 and 1740 cm^{-1}; NMR (CD_3OD): 7.85-7.95 δ (m, 2H, ortho-Hs), 7.5-7.6 δ (m, 3H, meta and para Hs), 3.83 δ (s, 3H, OCH_3). Carbamate 14b: colourless crystals m.p. 112°C from diisopropyl ether; ν_{NH} 3280 and ν_{CO} 1775 and 1750 cm^{-1}.
The isonitroso phenacyl pyridinium bromide 8[6] separated out in a 47% yield by treatment of a solution of 7 (5.6 g) in water (30 ml) with sodium nitrite (1.4 g) and 2N HBr (10 ml) at 0°C and keeping at 0°C for 1 day. The salt crystallized from ethanol in colourless crystals m.p. 147°C, $\nu_{C=O}$ 1672 cm^{-1}. The NMR spectrum in DMSO-d_6 showed the OH broad singlet at 14.5 δ, pyridine protons at 9.32 δ (d, 2H, J=5, ortho-Hs), 8.97 δ (t, 1H, J=8, para-H) and 8.47 δ (m, 2H, meta -Hs) and benzoyl protons at 8.16 δ (m, 2H, ortho-Hs) and 7.5-7.8 δ (m, 3H, meta and para Hs). The isonitroso phenacyl isoquinolinium bromide 25[6] was obtained in a 50% yield by treatment of a solution of phenacyl isoquinolinium bromide (1.6 g) in 66% EtOH (15 ml) with excess isoamyl nitrite (1.4 g) and 1 N NaOH (1 ml) at 0°C. After standing 12 hrs at 0°C, addition of 2N HBr (2 ml) caused

precipitation of the salt, colourless crystals m.p. 161-2°C dec. from ethanol; $\nu_{C=O}$ 1660 cm^{-1}. The NMR spectrum in DMSO-d_6 showed a broad singlet at 14.5 δ (OH), a singlet at 10.32 δ (1-isoquinolinic H) and a complex multiplet at 7.5-9 δ for all the other protons.

Reaction of BZNO with pyridine: To a stirred and ice-cooled solution of phenylglyoxylohydroximoyl chloride **10** (0.183 g, 1 mmole) in diethyl ether (25 ml) a stoichiometric amount of triethylamine (0.142 ml) was added. The colourless crystals of triethylamine hydrochloride separated out. Pyridine (0.24 ml, 3 mmoles) was added and the suspension turned out intensively orange while an orange-yellow solid separated out along with triethylamine hydrochloride. After 0.5 hr the precipitate was filtered off and washed with ice water (10 ml) leaving 0.158 g (63%) of the zwitterionic adduct **9** which could be crystallized from water. Adduct **9** (150 mg) was dissolved in water preheated at 50°C (15 ml) and immediately cooled in ice, giving yellow needles (90 mg), m.p. 60-1°C dec; $\nu_{C=O}$ 1620 cm^{-1} and ν_{OH} 3400 cm^{-1} (broad). The NMR spectrum in DMSO-d_6 showed immediately after the dissolution the ortho pyridine protons at 8.67 δ (d, J=5) and all the other aromatic protons as multiplets at 8.1-8.4 δ and 7.5-7.7 δ. In CD_3OD the ortho pyridine protons fall at 8.50 δ (d, J=5) and the other aromatic protons are multiplets at 8.1-8.3 δ and 7.4-7.6 δ.

In a duplicate experiment anhydrous ether was used. After addition of triethylamine, the triethylamine hydrochloride was filtered off and pyridine was added to the filtered solution. A highly unstable orange solid separated out. Addition of one drop of water converted it to a yellow solid, identical (IR) to the zwitterionic adduct described above. Similar results were obtained when pyridine was added first and then triethylamine.

The zwitterionic adduct is identical with a sample of the yellow compound $C_{13}H_{10}N_2O_2 \cdot 2H_2O$ obtained by deprotonation of isonitroso phenacyl pyridinium bromide **8** according to the Krohnke and Kübler protocol.[6] To the stirred and ice-cooled suspension of the finely powdered salt **8** (0.5 g, 1.7 mmoles) in ice water (50 ml), a solution of 1 N K_2CO_3 (10 ml) was added. After stirring 0.5 hr at 0°C the yellow product (230 mg, 53%) was filtered off. The product was dissolved in 25 ml of water preheated at 50°C and immediately cooled, giving yellow needles m.p. 60-1°C dec. When a sample of the yellow **9** was treated with 2N HBr, it was converted in the colourless crystals of isonitroso phenacyl pyridinium bromide **7**, identical with an authentic specimen. Yellow solutions of **9** in water are immediately decolourised by acidification with 2N HBr.

Decomposition of zwitterion **9** - The yellow needles of zwitterion **9** could be stored for months at -20°C. At room temperature they remained unchanged only for a few hours. The colour of the needles faded after 1-2 days while pyridine was released and colourless crystals of pure benzamide **13**, m.p. 128-9°, were formed.

In solution decomposition of **9** takes place with a rate which depends heavily on the solvent. In water and alcohols (MeOH, EtOH) the yellow needles were slightly soluble giving yellow solutions. The colour of the solution in water faded after 1-2 weeks and evaporation of the solution left benzamide **13**. The solutions in methanol and ethanol faded in a few hours and evaporation of the solvents afforded methyl N-benzoyl carbamate **14a**, and ethyl N-benzoyl carbamate **14b**, which crystallized from diisopropyl ether in colourless crystals, m.p. 117°C and 112°C, resp., and were identical with authentic materials. The yellow needles of **9** were fairly soluble in dipolar aprotic solvents (DMSO, DMF) giving orange solutions whose colour faded in a few hours. In the common aprotic solvents (ether, benzene, acetone, acetonitrile) **9** was only very slightly soluble, giving weakly coloured orange solutions. In these solvents the orange colour disappeared in a few minutes while the unsoluble yellow needles turned out colourless. Evaporation of the solvents gave a residue, which crystallized from diluted ethanol affording benzamide **13**. In some cases crystallization of the residue afforded small amounts of the less soluble dibenzoylurea, colourless crystals m.p. 208-9°C from ethanol, identical with an authentic specimen obtained by treatment of benzoylisocyanate with water.[20]

The decomposition of **9** in CD_3OD could be monitored by NMR. When a sample of **9** was dissolved in CD_3OD and the spectrum immediately taken, only the signals of **9** were apparent at 8.50 δ (d), 8.1-8.3 δ (m) and 7.4-7.6 δ (m). Subsequent scannings showed the appearance of a doublet at 8.40 δ, attributable to the ortho-protons of pyridine, and a multiplet at 7.8-7.9 δ attributable to the ortho-protons of the carbamate **14a** and the para-proton of pyridine. Assignments were secured in duplicate experiments by addition of pyridine and carbamate **14a** to the reaction mixtures. After 15-20 minutes at 35°C, integration indicated a 1:1 mixture of **9** and its decomposition products. After 1 day the spectrum showed a 1:1 mixture of pyridine and carbamate **14a**. The decomposition of **9** in DMSO-d_6 was monitored by NMR but the results were less clear-cut. The initial spectrum showed the signals of **9**, i.e. 8.67 δ (d), 8.1-8.4 δ (m) and 7.5-7.7 δ (m). Subsequent scannings showed rather complex changes in the region between 7.5 and 8.4 δ. After 20 minutes the signals of **9** disappeared and a doublet at 8.67 δ, attributable to the ortho-protons of pyridine, and a complex multiplet extending from 7.5 to 8.4 δ were present. In a parallel experiment the decomposition of a solution of **9** in DMSO was monitored by IR. A sample of **9** was dissolved in DMSO and the solution quickly transferred in a IR liquid cell. Repetitive scannings of the 2200 region showed the increase of a band at 2225 cm^{-1} within the first 10-15 minutes. The band is identical to the isocyanate band recorded for a DMSO solution of benzoyl isocyanate. Addition of water to the DMSO

solution after 2 hours afforded benzamide 13, which was isolated by column chromatography.

Kinetic of the decomposition of 9 in methanol - A solution of 9 in methanol showed UV maxima at 258 nm (log ϵ 3.8) and 292 nm (log ϵ 3.9). The latter maximum tailed towards the visible region and at 350 nm the ϵ is still significant (log ϵ 3.1). Kinetic determinations were performed at 350 nm since the products of decomposition (pyridine and carbamate 14a) and the BZNO adduct to norbornene, 15 [λ_{max} 265 nm (log ϵ 3.94), 277 (log ϵ 3.92)] had no absorption at this wavelenght.

A 0.001M solution of 9 was prepared dissolving a sample of 9 (13.1 mg) in 50 ml of methanol kept at 35.5°C. Six samples (2.5 ml) of the solution were placed in 6 thermostatted (35.5°C) couvettes and 10-50 μl of 1-2 M methanolic solution of the additives (pyridine, triethylamine, norbornene) were added with microsyringes. After vigorous shaking the kinetic determinations started. The preparation of the samples required approximately 5 minutes. The absorbance was determined with cycles of 2.5 minutes. The decay profiles are gathered in the Figure.

Zwitterion 9 was also generated in situ by treating a 10^{-3} M solution of salt 8 in methanol with triethylamine (5 equivs). The decay profile resembled that of line e in the Figure.

Decomposition of 9 in the presence of norbornene - A sample of 9 (131 mg, 0.5 mmoles) was dissolved in a solution of norbornene (0.94 g, 10 mmoles) in methanol (25 ml). After 1 day at r.t. the solution was evaporated giving a residue. Column chromatography afforded 0.1 g (83%) of the BZNO cycloadduct to norbornene 15, colourless crystals m.p. 50-1°C from petroleum ether.

The product is identical with a sample prepared by cycloaddition of BZNO to norbornene. To a stirred and ice-cooled solution of phenylglyoxylohydroximoyl chloride 10 (0.91 g, 5 mmoles) and norbornene (0.94 g, 10 mmoles) in diethyl ether (50 ml) a stoichiometric amount of triethylamine (0.71 ml) in ether (5 ml) was added over a 10 minutes period. After keeping 1 day at r.t., triethylamine hydrochloride was filtered off and the filtrate was evaporated leaving a residue. Crystallization from petroleum ether afforded 0.74 g (62%) of 15, colourless crystals m.p. 50-1°C; $\nu_{C=O}$ 1640 cm^{-1}; NMR: 1.05-1.70 δ (m, 6H), 2.65 δ (s, 2H), 3.55 δ (d, J=8, 4-isoxazolinic proton), 4.68 δ (d, J=8, 5-isoxazolinic proton), 7.3-8.25 δ (m, 5H). (Found: C, 74.29; H, 6.45; N, 5.91. $C_{15}H_{15}NO_2$ requires: C, 74.66; H, 6.27; N, 5.81%). Similar adducts have been described.[22]

Reaction of phenylglyoxylohydroximoyl chloride 10 and triethylamine (3 equivs) in methanol - Excess triethylamine (0.36 ml, 3 mmoles) was added to a solution of phenylglyoxylohydroximoyl chloride 10 (0.18 g, 1 mmole) in methanol (10 ml). After 1 day the mixture was evaporated. Addition of water (10 ml) gives a solution with a suspended oil, which was extracted with ether. The ethereal solution was dried and evaporated leaving the oily methyl benzoate (80 mg, 59%), identical (IR, NMR) with a commercial sample.

Cycloaddition of BZNO to isoquinoline - To a stirred and ice-cooled solution of phenylglyoxylohydroximoyl chloride 10 (0.37 g, 2 mmoles) in diethyl ether (50 ml), 2 equivs of isoquinoline (5.2 g) and then 2 equivs of triethylamine (0.57 ml) were added. The colourless crystals of triethylamine hydrochloride separated out while the solution turned out intensively yellow. After 1 hr the colourless crystals of triethylamine hydrochloride were filtered off and the filtrate was evaporated under vacuum, leaving a residue. Grinding with chilled ethanol (5 ml) afforded cycloadduct 24 (0.35 g, 64%), which crystallized from ethanol containing one drop of triethylamine in yellow needles m.p. 68-9°C dec; $\nu_{C=O}$ 1660 cm^{-1}, NMR: 5.95 δ (d, J=8, 1H), 6.80 δ (s, 1H), 7.22 δ (d, J=8, 1H), 7.2-7.7 δ (m, 7H) and 8.25 δ (m, 2H).

The cycloadduct 24 is identical with the yellow compound $C_{17}H_{12}N_2O_2$ obtained by deprotonation of isonitroso phenacyl isoquinolinium bromide 25 according to the Krönke and Kübler protocol.[6] A solution of 0.2N K_2CO_3 was added to a stirred and ice-cooled solution of salt 25 (0.3 g) in EtOH (25 ml) and H_2O (50 ml) over a 10 minutes period. After 0.5 hr at 0°C, the yellow cycloadduct 24 was filtered off in a quantitative yield (0.23 g). Crystallization from ethanol containing a drop of triethylamine afforded yellow needles m.p. 68-9°C dec. The yellow needles are converted into the colourless salt 25 by treatment with 2N HBr.

Isomerization of cycloadduct 24 - When cycloadduct 24 was crystallized from ethanol and the boiling solution was not immediately cooled, the isomeric product 26 separated out slowly, colourless crystals m.p. 119-124°C dec., with complete fusion above 180°C; ν_{NH} 3230 cm^{-1}; $\nu_{C=O}$ 1660 cm^{-1}, NMR (acetone-d_6): 6.92 δ (d, J=7.5, 1H), 7.5-8.0 δ (m, 8H), 8.16 δ (d, J=7.5, 1H), 10.5 δ (br s, 1H). (Found: C, 73.93; H, 4.28; N, 10.06. $C_{17}H_{12}N_2O_2$ requires: C, 73.90; H, 4.38; N, 10.12%).

The isomerization of cycloadduct 24 takes place easily in solution at r.t.. The yellow solutions of 24 (20 mg) in some common solvents (10 ml) like benzene, diethyl ether, acetone and acetonitrile faded after 1 day. The isomerization could be monitored by TLC or NMR and had an half-life of approximately 3-4 hours. The isomerization is inhibited by adding triethylamine (one drop) or in solutions kept in the dark under nitrogen.

Isomer 26 was isolated in the cycloaddition of BZNO to isoquinoline when only a stoichiometric amount of triethylamine was used. Grinding of the residue with ethanol afforded isomer 26 in fair yields (50%).

Cleavage of isomer 26 to isocarbostyril 27 - Isomer 26 can be cleaved rather easily to yield isocarbostyril 27, colourless crystals m.p. 211-214°C from ethanol or chloroform; $\nu_{C=O}$ 1630 cm^{-1}; NMR (DMSO-d_6): 6.55 δ (d, J=7, 1H), 7.20 δ (d, J=7, 1H), 7.35-7.70 δ (m, 4H), 8.23 δ (br d, J=7, 8-isocarbostyril H), 11.28 δ (br s, 1H, NH).

The melt of isomer 26 was essentially pure 27. This accounts for the wide melting range of 26, which decomposed affording the higher melting 27. A short boiling (10 minutes) of the ethanolic solution of 26 afforded on cooling colourless crystals of 27. A solution of 26 (230 mg) in benzene (20 ml) was fairly stable for days. Addition of a crystal of p-toluenesulfonic acid caused cleavage to isocarbostyril and phenylglyoxylamide 28. After 1 hr the solvent was evaporated and the mixture was separated by column chromatography, yielding phenylglyoxylamide 28 (93%), colourless needles m.p. 78-80°C from diisopropyl ether; ν_{NH} 3390, 3220 and $\nu_{C=O}$ 1690, 1660 cm^{-1}; NMR: 5.7 δ (br s, NH), 7 δ (br s, NH), 7.4-7.7 δ (m, 3H), 8.2-8.4 δ (m, 2H). (Found: C, 64.35; H, 4.75; N, 9.44. $C_8H_7NO_2$ requires: C, 64.42; H, 4.73; N, 9.39%). Analytical and spectroscopic data correspond to those reported for phenylglyoxylamide, m.p. 80-1°C.[23]

Addition of triethylamine (0.1 ml) to a solution of isomer 26 (0.1 g) in benzene (20 ml) also caused a smooth cleavage. After 3 days evaporation of the solvent afforded a residue. Grinding with water gave isocarbostyril 27 and acidification of the aqueous solution precipitated benzoic acid.

Cycloreversion of cycloadduct 24 - A solution of cycloadduct 24 (0.14 g, 0.5 mmoles), norbornene (0.94 g, 10 mmoles) and triethylamine (0.1 ml) was kept at r.t. under nitrogen. After 1 month the yellow colour of the cycloadduct disappeared. Evaporation of the solvent left an oily mixture of isoquinoline and the BZNO cycloadduct to norbornene, 15, in a 1:1 ratio (NMR). Column chromatography afforded a sample of 15, m.p. 50-1°C, identical with the cycloadduct of BZNO to norbornene described above. Monitoring by TLC showed that cycloreversion takes place with a half-life of approximately 1 week at r.t.

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