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Morpholines-(I)
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ω-(N-aryl-chloracetamido)-acetophenones have been cyclized with triethylamine in warm benzene solution to the corresponding 1,4-oxazines. The reaction appears to be general for any N-arly substituent, as long as an overall electron-withdrawing substituent is present para or meta, in the aromatic nucleus of the acetophenone moiety. The predominant tautomeric form present is shown by IR spectroscopy to be the “keto” tautomer in every case. The structure of one morpholine is confirmed by mass spectral fragmentation analysis.

Description of the Experiments

All m.p.'s are uncorrected and were taken in open capillaries with a Gallenkamp apparatus. IR spectra were recorded on a Perkin Elmer Infracord. Mass spectra were taken on a 21-103C CEC mass spectrometer. The microanalysis of the compounds reported were carried out at the Central Drugs Research Institute, Lucknow, India, by Dr. NITYA NAND.

p-Nitro-phenacyl aniline (1a): 9.3 g aniline in 75 ml benzene were cooled to 10°C and to it was added, with stirring, 25 ml of a solution of 12.2 g p-nitro-phenacyl bromide. The solution was stirred for 12 hrs after gradually warming up to 25°C and filtered. The dry residue was washed with several ml portions of warm water, titrating each time before sucking dry, to yield 9.1 g (74%) 1a as an orange powder. Scarlet prisms m.p. 163—164°C (Ethyl Acetate).

C₁₅H₁₄N₂O₃ (256.0) Calculated C 65.7 H 4.69 N 10.94, Found C 66.0 H 4.72 N 10.78. IR (Nujol) [μ] 2.93 (N—H); 5.93 (C = 0, aromatic ketone).

p-Nitro-phenacyl-p-anisidine (1b): 12.3 g p-anisidine in 25 ml benzene gave with 12.2 g p-nitro-phenacyl bromide as above, 12.2 g (83%) 1b. Deep brownish orange plates, m.p. 126—127°C (Ethyl Acetate).

C₁₅H₁₄N₂O₃ (256.0) Calculated C 66.7 H 5.18 N 10.37, Found C 66.7 H 5.62 N 10.12.

IR (Nujol) [μ] 2.93 (N—H); 5.92 (C = 0, aromatic ketone).

p-Nitro-phenacyl-p-anisidine (1b) : 12.3 g p-anisidine in 25 ml benzene gave with 12.2 g p-nitro-phenacyl bromide when reacted as above, 12.2 g (83%) 1b. Deep brownish orange plates, m.p. 166—168°C (Benzene).

C₁₅H₁₄N₂O₃ (256.0) Calculated C 65.7 H 4.69 N 10.94, Found C 66.0 H 4.72 N 10.78.

IR (Nujol) [μ] 2.93 (N—H); 5.93 (C = 0, aromatic ketone).

*p-Nitro-phenacyl-p-acetyl-aniline (1c): 6.75 g p- amino-acetophenone and 6.10 g p-nitro-phenacyl bromide was stirred 12 hr. in 30 ml acetone, filtered, washed thoroughly with hot water and sucked dry to yield 7.43 g (50%) 1c as a yellow powder. Golden yellow needles m.p. 175—176°C (Acetone).

C₁₅H₁₄N₂O₃ (286.0) Calculated C 66.7 H 5.18 N 10.37, Found C 66.7 H 5.62 N 10.12.

IR (Nujol) [μ] 2.93 (N—H); 5.92 (C = 0, aromatic ketone).

m-Nitro-phenacyl-aniline (1f): 4.65 g aniline and 6.1 g m-nitro-phenacyl bromide were reacted as above in 25 ml acetone for 4 hr., filtered, washed with water dried and weighed to yield 5.1 g (46%) 1f as a yellowish-white powder. Pale yellow cubes m.p. 158—159°C (Acetone).

C₁₅H₁₄N₂O₃ (286.0) Calculated C 66.7 H 5.18 N 10.37, Found C 66.7 H 5.62 N 10.12.

IR (Nujol) [μ] 2.84 (N—H); 5.92 (C = 0). p-Nitro-phenacyl-p-toluidine (1g) 14: Yellow needles m.p. 166—168 (Benzene).

C₁₅H₁₄N₂O₃ (286.0) Calculated C 70.6 H 4.58 N 9.15, Found C 70.4 H 4.46 N 9.33.

*p-Nitro-phenacyl-p-acetyl-aniline (1c): 6.75 g p- amino-acetophenone and 6.10 g p-nitro-phenacyl bromide was stirred 12 hr. in 30 ml acetone, filtered, washed thoroughly with hot water and sucked dry to yield 7.43 g (50%) 1c as a yellow powder. Golden yellow needles m.p. 175—176°C (Acetone).

C₁₅H₁₄N₂O₃ (286.0) Calculated C 66.7 H 5.18 N 10.37, Found C 66.7 H 5.62 N 10.12.

IR (Nujol) [μ] 2.93 (N—H); 5.92 (C = 0, aromatic ketone).

m-Nitro-phenacyl-aniline (1f): 4.65 g aniline and 6.1 g m-nitro-phenacyl bromide were reacted as above in 25 ml acetone for 4 hr., filtered, washed with water dried and weighed to yield 5.1 g (46%) 1f as a yellowish-white powder. Pale yellow cubes m.p. 158—159°C (Acetone).

C₁₅H₁₄N₂O₃ (286.0) Calculated C 66.7 H 5.18 N 10.37, Found C 66.7 H 5.62 N 10.12.

IR (Nujol) [μ] 2.84 (N—H); 5.92 (C = 0).

m-Nitro-phenacyl-p-toluidine (1g) 14: Yellow needles m.p. 166—168 (Benzene).

13 C. ENGEL u. OSCAR ZIELKE, Ber. dtsch. chem. Ges. 22, 203 [1899]

14 Synthesized by H. P. S. CHAWLA in this laboratory, unreported.
IR (Nujol) $[\mu]$ 2.95 (N—H); 5.95 (C=O, aromatic ketone); 14.5 (mono-substituted phenyl).

$N$-Chloroacetyl-$p$-nitro-phenacyl aniline (2a): 4.0 g of 1a, 2.0 g chloroacetic acid and 3.0 ml PCl$_3$ were refluxed together in solution in 50 ml anhydrous chloroform for 4 hr. The solution was cooled, washed successively with cold water, sodium bicarbonate solution then again with water, dried (Na$_2$SO$_4$) and filtered (charcoal). Removal of the solvent on a water bath afforded 4.4 g (84%) 2a as a crystalline mass. White needles m.p. 155—156 °C (Benzene).

C$_{16}$H$_{13}$N$_2$O$_4$Cl (332.5)
Calculated C 57.75 H 3.92 N 8.43, Found C 58.30 H 4.21 N 8.34.

IR (Nujol) [\mu] 5.72 (C=O, aromatic ketone); 6.03 (C=O, amide).

$N$-Chloroacetyl-$p$-nitro-phenacyl-$p$-anisidine (2b): 4.0 g of 1b, 2.0 g chloroacetic acid and 3.0 ml PCl$_3$ in 100 ml benzene gave on refluxing for 4 hr. and working out as above, 3.4 g (67.5%) 2b as a white powder. White plates m.p. 108—109 °C (Ethyl Acetate/Petroleum (60—80)).

C$_{17}$H$_{15}$N$_2$O$_5$Cl (362.5)
Calculated C 56.30 H 4.14 N 7.73, Found C 56.26 H 4.38 N 7.62.

IR (Nujol) [\mu] 5.83 (C=O, aromatic ketone); 5.95 (C=O, amide).

$N$-Chloroacetyl-$p$-nitro-phenacyl-$o$-toluidine (2c): 4.0 g of 1c, 4.0 g chloroacetic acid and 2.0 ml PCl$_3$ gave on refluxing 4 hrs. in benzene in the usual manner 4.5 g (88%) 2c as off white crystals. White needles m.p. 182—183 °C (Benzene/Petroleum).

C$_{17}$H$_{15}$N$_2$O$_4$Cl (346.5)
Calculated C 58.8 H 4.33 N 8.09, Found C 59.0 H 4.37 N 8.18.

IR (Nujol) [\mu] 5.8 (C=O, aromatic ketone); 6.0 (C=O, amide).

$N$-Chloroacetyl-$p$-nitro-phenacyl-$\alpha$-naphthylamine (2d): 4.0 g of 1d, 4.0 g chloroacetic acid and 3.5 ml PCl$_3$ gave on refluxing 4 hr. with 50 ml benzene 4.05 g (80%) 2d as a white crystalline material, when worked out as above. White needles m.p. 136—137 °C (Ethanol).

C$_{20}$H$_{15}$N$_2$O$_4$Cl (382.5)

$N$-Chloroacetyl-$p$-nitro-phenacyl-$p$-acetyl-aniline (2e): 2.0 g of the purified compd. 1e and 3.0 ml of freshly synthesized chloroacetyl chloride were refluxed in a small capsule fitted with a vertical, narrow air condenser and moisture guard, at 100—110 °C for 2 hr. The reaction mixture was cooled, poured into cracked ice and titurated till solid. Yield 2.4 g (97%) 2e as a brownish white solid. x 2 recrystallizations from acetone/petroleum afforded impure 2e m.p. 168—171 °C. Could not be purified sufficiently for microanalysis.

Mass Spectral Fragmentation (m/e): 374.5 (parent p); 338.0 (p—HCl); 308.0 (p—HCl—NO); 134 (CH$_3$CO·C$_6$H$_4$·NH); 148 (CH$_3$CO·C$_6$H$_4$·NHCH$_3$); 150 (NO$_2$·C$_6$H$_4$·CO).

IR (Nujol) 5.9, 5.8 and 6.0 $\mu$ broad peak with shoulders, overlapping C=O (acetyl); C=O (aromatic ketone) and C=O (amide).

$N$-Chloroacetyl-$m$-nitro-phenacyl-aniline (2f): 3.0 g of 1f, 1.5 g chloroacetic acid, 3.0 ml PCl$_3$ and 30 ml CHCl$_3$ (anhydrous) on refluxing 6 hr. and working out gave 3.2 g (82%) 2f as off-white crystals. White needles m.p. 105—106 °C (Acetone/Petroleum).

C$_{16}$H$_{13}$N$_2$O$_5$Cl (332.5)
Calculated C 57.75 H 3.92 N 8.43, Found C 57.70 H 3.66 N 8.56.

IR (Nujol) [\mu] 5.81 (C=O, aromatic ketone); 6.0 (C=O, amide).

$N$-Chloroacetyl-$p$-phenyl-phenacyl-$p$-toluidine (2g): 1.5 g of 1g, 0.85 g chloroacetic acid, 2 ml PCl$_3$ and 30 ml CHCl$_3$ gave on refluxing 4 hr. and working out 1.4 g (78%) 2g as an off white oil which solidified under petroleum. White needles m.p. 130—131 °C (Benzene/Petroleum).

C$_{23}$H$_{20}$NO$_4$Cl (377.5)
Calculated C 73.11 H 5.29 N 3.70, Found C 72.70 H 4.32 N 3.70.

IR (Nujol) [\mu] 5.8 (as a shoulder, C=O, aromatic ketone); 5.9 (C=O, amide).

$N$-Phenyl-3-oxo-$\Delta^2$-6-(p-nitro-phenyl)1,4-oxazine (3a): 2.0 g of 2a was heated with 10 ml triethylamine in 20 ml

![Fig. 1. IR-spectrum (Nujol) of $N$-Phenyl-3-oxo-$\Delta^2$-6-(p-nitro-phenyl)1,4-oxazine (3a).](image-url)
benzene solution for 2 hrs. at 80 °C. Rapid filtration afforded triethylamine hydrochloride corresponding to 54% elimination. The reaction was completed by boiling the solution for a further 10 hr. Total wt. of triethylamine hydrochloride 0.8 g (96.5%). The filtrate was immediately transferred to a 100 ml round bottom flask and stripped on a water bath under reduced pressure to yield 1.1 g (62%) 3a (tituration with petroleum). Brownish yellow needles, m.p. 180—181 °C (Benzene).

\[ \text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_4 \] (296.0)

Calculated C 64.95 H 4.06 N 9.46,
Found C 65.20 H 4.36 N 9.27.

IR (Nujol) [\( \mu \)] 5.9 (C = O, 3-oxo group); see Fig. 1.

N-p-Methoxy-phenyl-3-oxo-A5-6-(p-nitro-phenyl)-1,4-oxazine (3b): 2.0 g 2b, 10 ml triethylamine and 20 ml benzene at 80 °C/2 hrs. gave on filtration triethylamine hydrochloride corresponding to 81.5% elimination. Working out as above, after completion of the reaction afforded a total of 0.76 g Et3NHCl (100%) and 1.29 g (72.5%) 3b as a deep yellow powder. Bright yellow needles m.p. 182—183 °C (Ethyl Acetate/Petroleum).

\[ \text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_4 \] (310.0)

Calculated C 62.51 H 4.29 N 8.59,
Found C 62.84 H 4.55 N 8.65.

IR (Nujol) [\( \mu \)] 5.93 (C = O, 3-oxo group); see Fig. 2.

N-o-Methyl-phenyl-3-oxo-A5-6-(p-nitro-phenyl)-1,4-oxazine (3c): 2.0 g 2c, 20 ml Et3N and 40 ml benzene refluxed for 24 hr. and filtered to afford 0.7 g (97%) Et3NHCl and 1.33 g (72%) 3c as a yellow powder. Yellow needles m.p. 170—171 °C (Benzene/Petroleum).

\[ \text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_4 \] (310.0)

Calculated C 65.75 H 4.52 N 9.04,
Found C 65.90 H 4.64 N 9.19.

IR (Nujol) [\( \mu \)] 5.93 (C = O, 3-oxo group); see Fig. 2.

N-o-Acetyl-phenyl-3-oxo-A5-6-(p-nitro-phenyl)-1,4-oxazine (3d): 1.0 g 2e, 10 ml Et3N and 40 ml benzene on refluxing afforded triethylamine hydrochloride along with some tarry material. The benzene was partially distilled out after 6 hr. and petroleum added when 200 mg (22%) 3e as a pale yellow powder which could not be recrystallized will, was deposited. Yellow powder m.p. 252—253 °C (Acetone/DMF).

Mass Spectral Fragmentation m/e: 338 (molecular ion p); 308 (p—NO); 231 (p—107); peaks at 148 and 150 present in both precursors are absent.

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Fig. 2. IR-spectrum (Nujol) of N-p-Methoxy-phenyl-3-oxo-A5-6-(p-nitrophenyl)1,4-oxazine (3b).

Fig. 3. IR-spectrum (Nujol) of N-o-Methyl-phenyl-3-oxo-A5-6-(p-nitrophenyl)1,4-oxazine (3d).
IR (Nujol) [μ] 5.75 (C=O, 3-oxo-group); 5.98 (C=O, acetyl); see Fig. 4.

N-Phenyl-3-oxo-15-6-(m-nitro-phenyl)-1,4-oxazine (3f): 1.0 g 2f, 5 ml Et₃N and 10 ml benzene on refluxing gave on working out 0.65 g (74%) 3f as yellow crystals. Deep yellow needles m.p. 192–193 °C (Ethanol/Acetone).

C₁₆H₁₂N₂O₄ (296.0) Calculated C 64.95 H 4.06 N 9.46, Found C 64.20 H 3.60 N 9.57.

IR (Nujol) [μ] 5.93 (C=O, 3-oxo-group); see Fig. 5.

N-p-Tolyl-3-oxo-15-6-(p-phenyl-phenyl)-1,4-oxazine (3g): 1.3 g 2g in 20 ml warm ethanol on treatment with 0.2 g KOH in ethanol (10 ml) gave 0.75 g (63%) 3g as a white precipitate. Long white needles m.p. 203–204 °C (Ethanol).

C₂₃H₁₉N₂O₂ (341.0) Calculated C 80.9 H 5.77, Found C 81.0 H 5.27.

IR (Nujol) [μ] 5.9 (C=O, 3-oxo-group); 14.4 (monosubstituted phenyl); see Fig. 6.

Discussion

The cyclization of chloracetanilido-acetophenone with KOH in ethanol to N-phenyl-2-oxo-4-benzoyl-azetidine was reported by CHATTERJEE and CHAWLA in 1967. The structure of the cyclized product was proved conclusively by them to be a beta-lactam (2-oxo-azetidine) by a combination of spectrogra-
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phic methods. Subsequently, the strong activating ef­
fects of electron withdrawing groups on the N-aryl substituent, were discovered by CHATTERJEE and ABDULLA in similar cyclizations with halogen-acet­
amino esters 2, 3.

In the continuing search for a system in which the eliminated hydrogen atom was activated by only one electron withdrawing group and which with weak base could be cyclized to a beta lactam, the compound 2a was chosen with a nitro-group para­
in the acetophenone moiety. The argument for this choice was that in this system the nitro-group would render the carbonyl function attached to the phenyl ring more “ketonic” in character, which would result in a sufficient increase in the acidity of the keto­methylen protons to effect cyclization with weak bases such as triethylamine, in benzene solution to afford a beta-lactam.

While 2a eliminated the elements of HCl, the product obtained (3a) did not show the spectrum expected of a beta-lactam.

In the IR spectrum of a beta-lactam obtained from a halogen acetamino ketone, two bands are a minimum requirement in the C = O absorption region (5.5 µ to 6.1 µ). On the other hand the compound 3a showed only one band in its IR spectrum in this region, at 5.92 µ. On this basis, and the quantitative elimination of HCl by 2a to give 3a, the conclusion was that somehow one of the two carbonyl groups of the amido-ketone 2a (C = O, amide 6.0 µ; C = O, ketone 5.73 µ) was involved in the elimination reaction and was destroyed in the process. At this stage, a tentative structure was proposed for 3a: N-phenyl-
3-oxo-4β, 6α-(p-nitro-phenyl)-1,4-oxazine.

The chemistry of 1,4-oxazines (morpholines) has attracted much attention 4-8 and a number of these compounds have been introduced in chemotherapy or are potential chemotherapeutic agents 7, 8. In several 1,4-oxazine derivatives, anti-tubercular activity 9 and anti-neoplastic activity 10 has been reported.

In view of this interest in the chemistry of morpholines, and with a desire to offer a mechanistic interpretation of the formation of the morpholine 3a, a detailed study was undertaken in which the generality of a new route to 1,4-oxazine derivatives has been established:

![Scheme 1](image)

The amino-ketones 1 that are listed in table 1 were synthesized by stirring the appropriate phenacyl bromide in benzene, toluene or acetone solution when they precipitated out along with hydrobromides of the parent amines.

These were chloroacetylated by refluxing them with chloroacetic acid and PCl₅ in benzene or chloro­form 11 to yield compounds 2 (Table 2).

The above halogen-acetamino-ketones 2, were cy­
clized with triethylamine solutions in warm solvent benzene with the exception of 2g for which alco­holic KOH was used. The 1,4-oxazines 3 synthesized in the study are listed in Table 3.

The investigation was organised to correlate the generality of the morpholine formation in relation to the N-aryl substituent and the substituents in the

phenacyl moiety and to establish a rational mechanism which would explain the formation of morpholine in preference to the beta-lactam.

Unlike the kinetic results obtained when beta-lactams are formed from halogen-acetamino esters, the rate of formation of the 1,4-oxazines 3a, 3b and 3c was found to increase in the order mentioned. It was this observation which first gave an insight into the mechanism of the reaction. It appears that the abstraction of proton by the weak base, from compounds 2, is a fast, non-rate-governing step. The carbanion 4 that is formed then is resonance stabilized and is a hybrid of the canons A, B and C.

\[
\text{Delocalized "Carbanion"-4}
\]

The initial delocalization of the negative charge of the carbanion (canon A) renders the orbitals capable of allowing a delocalization of the N-non-bonded electrons into the p-nitro-group substituted in the phenacyl moiety. This phenomenon must be
distinguished clearly from the reports that have appeared concerning the “enol forms of phenacyl-aminines”\textsuperscript{12}. The formation of morpholines is due to an important delocalization effect distinct from enolization, which brings into play the amide N lone pair, thereby imparting the resonance hybrid a very large degree of oxanion character, the canons B and C contributing significantly. The electron-rich position in the transition state 4 is therefore the oxygen atom of the collapsed ketonic function and not the carbon atom from which the proton was initially removed. This oxygen atom then commits a slow rate-governing, nucleophilic attack on the closely neighbouring carbon atom holding the halogen, to afford morpholine. This is why the rate of morpholine formation is increased with an increase in the amide N-lone-pair localization, brought about by electron-donating para-substituents in the N-Aryl ring or by the out-plane deformation of the N-aryl system and the three valences of the nitrogen, with bulky \textit{ortho}-substituents.

Attention was next turned to whether an electron-withdrawing substituent \textit{para}- on the N-aryl moiety would affect the course of morpholine synthesis. It was surprising that with a \textit{p}-acetyl function 2\textit{e} gave some 1,4-oxazine, along with polymeric material as the major reaction product. The 1,4-oxazine 3\textit{e} was confirmed beyond doubt by a mass-spectral fragmentation analysis and clearly established that even when \textit{R}\textsubscript{3} in the hybrid 4 was electron-withdrawing, the morpholine synthesis nevertheless occurred, although in poorer yield.

In the system 2\textit{f} the nitro group is in the \textit{meta}-position of the phenacyl ring. Here too cyclization results in a 1,4-oxazine (3\textit{f}), via a non-classical delocalization of the N-lone-pair into the electron-depleted \(\pi\) orbitals of the aromatic nucleus. The system 2\textit{g} with a \textit{p}-phenyl substituent in the phenacyl ring was the closest to the systems investigated by Chawla\textsuperscript{1}. The cyclization was effected with ethanolic KOH solution, when the morpholine precipitated out as a white crystalline compound.

It seems, therefore, that the initial report of the synthesis of beta-lactams from the chloroacetyl derivatives of phenacyl-anilines was an exception rather than a rule and that in general any substituent which is relatively more “electron-withdrawing” than a hydrogen atom (such as NO\textsubscript{2} or a phenyl group viz. \textit{sp}\textsuperscript{2} carbon) will, if \textit{para}- or \textit{meta}-substituted in the phenacyl ring, lead to 1,4-oxazine derivatives.

Theoretically, these 1,4-oxazines are capable of existing in two tautomeric forms 3 and 3\textsuperscript{'}, shown below:

\begin{center}
\begin{tikzpicture}
\node at (0,0) {3\text{(keto)}};
\node at (1.5,0) {3\text{'(enol)}};
\end{tikzpicture}
\end{center}

If the IR spectra shown overleaf are examined, it will be at once apparent that the morpholines that have been synthesized with triethylamine/benzene exist as the keto-form and not as the enol 3\textsuperscript{'} . With alcoholic KOH solution, the morpholines developed a strong red color but attempts to recover the morpholine in enol form failed. This is surprising, because in the enol, the central morpholine nucleus is fully conjugated. However, spectral evidence definitely established the exclusive existence of the keto form.

We wish to convey to Professor Ajay K. Bose of the Stevens Institute of Technology, our highest sense of gratitude and respect for his keen interest in this work, and for providing the IR and Mass spectra. We also wish to thank Professor Dr. Hermann Zahn, Redaktion “Chemische Berichte” for his cooperation in making available photocopies of early German Works on acetophenone derivatives appearing in his journal.