The Synthesis and Properties of Some 2-Substituted-3-oxo-4H-1,4-Oxazines

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1,4-Oxazines, -cyclic elimination-mechanism. -IR-NMR

A new synthesis has been developed for the hitherto unreported 2-substituted-3-oxo-4H-1,4-oxazines 3b–3j via the cyclodehydrohalogenation of N-aryl-N-dichloroacetyl-2-amino-4'-nitroacetophenones in dimethyl sulfoxide with potassium t-butoxide. The structures of all the oxazine derivatives have been verified by IR and NMR spectroscopy and correlations between the structures and spectrographic characteristics have been made. In every case the only tautomer present was the one in which the cyaninyl group in position 3 of the oxazine ring existed in the "keto" form. Attempts to extend these cyclic elimination reactions to the synthesis of oxazepines have failed.

Experimental

All melting points are uncorrected and were obtained in open capillaries on a Thomas-Hoover Unimelt apparatus. Infrared spectra were recorded on a Perkin-Elmer B 237 grating spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian A60-A spectrometer with tetramethylsilane as an internal reference. Some typical experimental procedures are reported below. Table III lists the microanalytical data for the compounds described in the work.

2-(N-[4-Ethoxycarbonylphenyl]-N-[2-bromoacryloyl])-amino-4'-nitroacetophenone (1 b): To a solution of 16.52 g (2-equivalents) of potassium t-butoxide dissolved in 100 ml of anhydrous dimethyl sulfoxide. The rate of addition was adjusted to 2—3 drops per minute so that the solution remained a pale golden yellow at the end of the addition. The solution was acidified with 2 ml of glacial acetic acid and the solvent was removed that the solution remained a pale golden yellow at the end of the addition.

White plates, m.p. 168—169 °C (ethyl acetate/isopropanol). IR (KBr): CO amide, 1715 cm

2-(N-[4-Ethyloxybenzylphenyl]-N-[2,3-dibromopropionyl])-amino-4'-nitroacetophenone (2 f): A mixture of 1.0 g of 1 b and 1.0 ml of 2,3-dibromopropionyl chloride was heated at 100 °C for 1 hour in a small glass capsule fitted with an air condenser. Cooling and trituration with ethanol gave 1.45 g (88%) of 2 f. White plates, m.p. 167—168 °C (ethanol).

IR (KBr): C = O ester, ketone, 1700 cm

2-Hydroxy-3-oxo-4H-N-phenyl-6-(p-nitrophenyl)-1,4-oxazine (3 b): To a solution of 1.0 g of the amide 2 b

Experimental.

(100%) of 3 b as a yellow powder. Yellow plates, m.p. 155—156 °C (cyclohexane/chloroform).

IR (KBr): C = O 3-oxo, 1690 cm

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2-(1-Aziridinyl)3-oxo-4H-N-phenyl-6-(p-nitrophenyl)-1,4-oxazine (3f): A solution of 0.18 g of the 2-chloromorpholine 3d in 15 ml of anhydrous benzene was treated with an anhydrous solution of a mixture of 0.5 ml of ethylenimine and 1.5 ml of triethylamine in 5 ml of benzene at 25 °C. At the end of 2 hours the reaction mixture was filtered and the filtrate was taken to dryness at below 30 °C, to give a brown gummy mass. Chromatography on silica gel (chloroform) gave a total of 0.07 g (40%) of the required product 3f. Yellow microcrystals m.p. 165 — 168 °C (ether/chloroform).

IR (KBr): C = O, 3-oxo-, 1675 cm⁻¹.

H^1NMR (CDCl₃): τ = 8.04 (s, 4H) aziridine ring protons; 3.22 (s, 1H) H₂; 2.7 (s, 1H) H₅; 2.54 (s, 5H) phenyl protons; 2.0 (q, 4H) 4-nitrophenyl protons.

2-(1-Piperidinyl)3-oxo-4H-N-phenyl-6-(p-nitrophenyl)-1,4-oxazine (3h): To a solution of 0.1 g of 3d in 10 ml of anhydrous benzene was added a solution of 0.1 g (4 equivalents) of piperidine in 5 ml of benzene and the solution was stirred for 2 hours. The reaction was followed by tlc and filtered after the high Rf spot (CHCl₃/silica gel) due to the 2-chloro compound had disappeared. Removal of solvent afforded 110 mg (95%) of 3h as a yellow powder. Yellow crystals m.p. 164 — 165 °C (cyclohexane/chloroform).

IR (KBr): C = O, 3-oxo-, 1675 cm⁻¹.

H^1NMR (CDCl₃): τ = 8.42, 7.09 (mc, 10H) piperidine ring protons; 4.64 (s, 1H) H₂; 3.39 (s, 1H) H₅; 2.55 (s, 5H) phenyl protons; 2.02 (q, 4H) 4-nitrophenyl protons.

Solvolysis of 3d in methanol to give 3j: When a solution of 0.1 g of the 2-chloromorpholine 3d in methanol was allowed to stand at 40 °C for 2 hours, removal of the solvent afforded 0.1 g (100%) of the 2-methoxy-oxazine 3j. Long yellow needles, m.p. 171 — 172 °C (methanol).

IR (KBr): C = O, 3-oxo-, 1690 cm⁻¹.

H^1NMR (CDCl₃): τ = 6.37 (s, 3H) OCH₃; 4.55 (s, 1H) H₂; 3.24 (s, 1H) H₅; 2.6 (s, 5H) phenyl protons; 2.06 (q, 4H) 4-nitrophenyl protons.

Discussion

We had earlier reported the syntheses of a number of N-aryl-3-oxo-4H-1,4-oxazine derivatives, 3a, by the base catalyzed cyclodehydrohalogenation of appropriate N-aryl-N-monochloroacetylphenacylamines, 2a. It was shown that the reported isolation of some 2-oxoazetidines (β-lactams) from certain chloroacetanilidoacetophenones represented a case of departure from a general synthesis of N-aryl-3-oxo-4H-1,4-oxazine derivatives. In recent years the 1,4-oxazines and their isosteres have attracted the attention of several groups. With a view to further elaborating our new and general synthesis of 3-oxo-1,4-oxazines, and in order to study their chemical and physical characteristics, it was decided to attempt the synthesis of the hitherto unreported 2-substituted 1,4-oxazines 3b—3j.

The dichloroacetamides 2b and 2c needed for the proposed synthesis (Scheme 1) were prepared by refluxing the N-aryl-2-amino-4’-nitroacetophenones 1a and 1b respectively, with dichloroacetic acid in the presence of thionyl chloride in benzene solution for 4 to 6 hours.
Cyclization of 2b and 2c was achieved in 50% yield using 2-equivalents of potassium t-butoxide, in aqueous dimethyl sulfoxide solution, to give the 2-hydroxy-3-oxo-4//-1,4-ozazines 3b and 3c respectively. This cyclization reaction was very sensitive to the reaction conditions and could be achieved only in dilute solutions with the dropwise addition of base over a period of several hours. The use of concentrated solutions or anhydrous conditions led to the formation of highly colored gummy substances of unknown structure. Bases such as KOH in ethanol, triethylamine in benzene or sodium ethoxide in ethanol were unsuccessful as cyclization catalysts. It appears probable that the cyclization of the dichloroacetamides (for example 2b) involves a mechanism different to that operating in the cyclization of monochloroacetamides (for example 2a), which proceeds via the intermediacy of a carbanion. While it is possible that the inability of triethylamine to cyclize 2b could arise from the deactivation of alkyl halide displacement reactions by additional halogen atoms present on the same carbon atom, a model dichloroacetamide we had studied, 2d, was cyclized by the weak base triethylamine in benzene at room temperature (Scheme 2).

However, both the dichloroacetamides 2b and 2c could be recovered unchanged after refluxing them with triethylamine in benzene for several hours. It seems therefore that the effect of deactivation of elimination of one halogen by another is not responsible for the inertness of the dichloroacetamides 2b or 2c towards cyclic elimination of HCl in the presence of weak bases. The difference in reactivity between 2a and 2b (or 2c) may be explained by the changed acidities of the α-acetamido protons in 2b (and 2c) relative to the α' -ketomethylene protons. In 2a the acidity of the α'-ketomethylene protons is higher than that of the α-chloroacetyl protons and bases abstracted the more acidic proton generating a carbanion (Scheme 3). Cyclization proceeded through the stabilized enolate anion 5, giving the oxazine 3a.

With 2b (or 2c) the proton abstracted by bases is the α-acetamido proton indicated in Scheme 3.
straction of a second proton. The driving force for either mechanism would be the formation of the $C_3-C_6$ double bond in the transition state leading to the oxazine 3b. Though the epoxide 8 has not yet been isolated (presumably because it reacts immediately under the experimental conditions) the mechanism we have invoked, involving the carbene 7, is supported by precedents in the literature on the synthesis of carbonyl carbenes by the action of t-BuOK on dihalomethyl ketones and on the reactions of carbenes with electronegatively substituted carbonyl compounds to give epoxides.

Owing to the specific nature of the cyclization step we were able only to isolate the 2-hydroxymorpholines 3b and 3c which were then converted to the corresponding 2-chloro compounds 3d and 3e in excellent yields by refluxing them with thionyl chloride in benzene solution for 1 hour. The chloro substituent in 3d and 3e was very reactive and could be readily displaced by nucleophiles such as piperidine, pyrrolidine, ethylenimine and even methanol, to afford crystalline, readily characterised halogen-displaced oxazines 3f to 3j (Scheme 4). Though compounds 3b–3j were either cyclic hemiacetals, hemiaminals or acetals, they were all stable under ordinary conditions both in the solid state as well as in aprotic solvents.

The success of our 3-oxo-1,4-oxazine synthesis encouraged us to attempt an extension to higher Xo. 2-Subst. & 2-Substituent & N-Substituent & $\tilde{v}_{\text{c}=0}$ (KBr) \\
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3b & OH (OD) & Ph & 1690 \\
e & OH & 4-EtOOC$\text{C}_6$H$_4$ & 1705 \\
d & Cl & Ph & 1700 \\
e & Cl & 4-EtOOC$\text{C}_6$H$_4$ & 1715 \\
f & N & & 1675 \\
g & N & & 1700 \\
h & N & Ph & 1675 \\
i & N & Ph & 1675 \\
j & OCH$_3$ & Ph & 1690 \\
k & (CH$_3$)$_2$ & Ph & 1670 \\

ring compounds such as the oxazepines. However, the treatment of dibromopropionamides 2e and 2f with either weak or strong bases led only to the formation of the acyclic $\alpha,\beta$-unsaturated amides 10a and 10b respectively. Chromatography of the re-
action mixture failed to reveal the presence of any cyclisation product. The loss of the a-proton and the /5-bromine atom from \( 2 \) and \( 2f \) was established by calculating the coupling constants expected for \( \text{trans} \) and \( \text{cis} \) vicinal coupling and for geminal coupling in similarly substituted ethylenes. Agreement between calculated and measured values (2.3 Hz for 10a or 10b) was observed only when geminal coupling was assumed. The absence of any 2-bromomethyloxazines or oxazepines in the reaction product indicates that elimination of \( \text{Br}^- \) from the carbanion is much faster than any cyclization process.

**Infrared Spectra**

The 3-oxo-carbonyl absorption maxima for the compounds 3b, 3k, and 3l have been summarised in Table I. Correlations are apparent between the 3-oxo-carbonyl absorption frequencies and the electronegativity of the 2-substituent. For a given aroynyl substituent (e.g. Ph, 3d, 3f, 3h-3k), the CO...O frequency increases as the electronegativity of the 2-substituent increases. For the 2-chloro-substituent, the CO...O reaches a maximum of 1700 cm\(^{-1} \) (3d). The 2-hydroxy substituent in 3b lowers the CO...O by 10 cm\(^{-1} \) due to the lower electron affinity of oxygen relative to chlorine. The 2-methoxy-substituted morpholine 3j absorbs at the same frequency as 3b. The three oxazines 3f, 3h, and 3l, which have a nitrogen atom substituted at C1, have identical carbonyl absorptions at 1675 cm\(^{-1} \). The size of the ring in which the nitrogen substituent is incorporated has no effect on the 3-oxo-carbonyl absorption. The geminally substituted morpholine 3k absorbs at the lowest frequency of 1670 cm\(^{-1} \) owing to the electron donating effects of the two methyl substituents on C2.

Electron sinks on the N4-aryl substituent (3c, 3e, and 3g) cause an increase in the frequency of the C=O absorption. The incorporation of the N4-phenyl substituent on C2 in the 3-CO...O absorption by decreasing the frequency of the C=O...O substituent on C2 in the 3-CO...O absorption. The incorporation of the N4-phenyl substituent on C2 in the 3-CO...O absorption by decreasing the frequency of the C=O...O substituent on C2 in the 3-CO...O absorption. The incorporation of the N4-phenyl substituent on C2 in the 3-CO...O absorption by decreasing the frequency of the C=O...O substituent on C2 in the 3-CO...O absorption.
Proton Resonance Spectra

Table II lists the chemical shifts of the C2 and C5 protons (H2 and H5 respectively) of the oxazines 3b-3k. The C5 proton in all of the cases absorbs as a singlet integrating to 1 proton between 2.5 and 3.5 τ. The only correlation possible was the effect of the N-aryl substituent on the position of the H5 chemical shift. Electron sinks on the N-aryl substituent caused a downfield shift in the H5 absorption. In identically 2-substituted oxazines 3d and 3e (2-chloro-substitution) the 4-carbethoxyphenyl substituent in 3e caused a downfield shift of 0.06 τ for H5 relative to the N-phenyl substituted oxazine 3d (Table II). Similar downfield shifts may be detected for 3g relative to 3f.

The N-aryl substituent appears to have no effect on the chemical shifts of the C2 protons (H2), which are governed mainly by the nature of the 2-substituent. Thus in the pair of morpholines 3d and 3e (2-chloro substitution) the chemical shifts of H2 are 3.39 τ and 3.37 τ respectively. Both signals integrate to one proton indicating an absence of any enol tautomer. Similarly in the pair of morpholines 3f and 3g (2-1-aziridinyl substitution) the chemical shifts of H2 are 3.22 τ and 3.27 τ respectively. In contrast, when the 2-substituent is changed there is a great difference in the chemical shift of H2. In a given series (e.g. N-aryl substituent = Phenyl), the order of increasing (upfield) shifts are as follows:

2- (1-aziridinyl) - (3f) - 3.22 τ; 2-chloro- (3d) - 3.39 τ; 2-(1-pyrrolidinyl)-(3i) - 4.5 τ; 2-methoxy-(3j) - 4.55 τ; and 2-(1-piperidinyl)- (3h) - 4.64 τ. These chemical shift differences are easy to reconcile with the electronegativity of the 2-substituent and with the size of the ring in which it is incorporated.

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1. For the preceding publication see R. F. Abdulla and A. N. Bannerji, Z. Naturforsch. 26 b, 1140 [1971].