Morpholines-(IV)

Riaz F. Abdulla

Frick Chemical Laboratory, Princeton University, Princeton, New Jersey 08540, U.S.A.

and

Alok N. Bannerji

Department of Chemistry, Indian Institute of Technology, Kharagpur, W. Bengal, India

(Z. Naturforsch. 26 b, 1140—1143 [1971]; received May 28, 1971, revised July 7, 1971)

Cyclohydrohalogenation-beta-Lactams-Morpholin-3-ones-H-NMR Spectroscopy

N-Aryl-N-chloroacetyl-2-chlorophenacylamines (2) give morpholiones 3, or beta-lactams 4, depending upon the N-aryl-substituent. N-Phenyl-N-(2,3-dibromo-3-phenylpropionyl)-4-nitrophencyclamide did not undergo base-catalysed cyclization but gave, instead, the a-unsaturated, open-chain amide 5. N-Aryl-N-chloroacetyl-aminomethyl-2-naphthylketones afford only beta-lactams. The first attempt at the synthesis of a 2-chloro-3-oxo-morpholine resulted in the isolation of the 2-hydroxy-derivative. The H-NMR spectra of some more 3-oxo-morpholines have been recorded.

Experimental

All melting points are uncorrected and were obtained using a Thomas-Hoover Unimelt. IR Spectra were recorded on a Perkin-Elmer 237 B grating spectrophotometer. H-NMR Spectra were recorded on an A-60A Varian Spectrophotometer. Microanalyses were done by Professor Nitya Nand of the Central Drug Research Institute, Lucknow, India, and by Professor Franz Scheidt of Hoffmann-La Roche, Nutley, New Jersey, and agreed to within 0.5% of the calculated values.

Some typical experimental procedures are described below:

N-(2,3-dibromo-dihydrocinnamoyl)-N-phenyl-4-nitrophencyclamide 2f: 2.0 g of dihydrodibromocinnamic acid (prepared by the bromination of trans-2,3-benzoylacrylic acid) was refluxed with 4 ml of SOCl2 in 45 ml of dry chloroform for 1 hr. The chloroform together with excess thionyl chloride was distilled out and to the solid acid chloride remaining as residue was added 1.5 g of 4-nitrophencyclamide and 45 ml of chloroform. The mixture was refluxed for 6 hrs, cooled and filtered from some solid which had separated and the filtrate washed successively with 2 N HCl, 10% NaHC03 and passed through a short column of silica gel. Remo-

IR (CDCl3): CO, ketone, 1717; CO, amide, 1645/cm. 

H-NMR (CDCl3) (60 MHz): δ = 1.7 (q), 4-nitrophencycl protons (4H); 2.29, N-phenyl protons (5H); 4.47 (q), -CH2-; J = 12 Hz (1H); 4.77 (q), -CH3; J = 12 Hz (1H). 

(Decyl) (100 MHz), δ = 46% of the amide 5.

Dehydrohalogenation of 2f to 5: 1.0 g of 2f in 30 ml of benzene was boiled under reflux for 8 hrs with 10 ml of triethylamine and filtered to give 0.39 g of 4-nitrophenyl protons (46%) triethylamine hydrobromide. The filtrate was freed of excess triethylamine with 5 N HCl and worked out to afford a gummy mass weighing 0.84 g. This was dissolved in 25 ml of cyclohexane/benzene (5:1) and passed through a short column of silica gel. Removal of the solvent afforded 0.39 g (46%) of the amide 5.

Two crystallizations afforded the analytical sample in colorless needles, m.p. 137—139°C (Cyclohexane/benzene). The compound was homogeneous on tlc (MeOH/EtOAc, 1:9).

IR (CDCl3): CO, ketone, 1717; CO, amide, 1645/cm.

H-NMR (CDCl3) (60 MHz): δ = 1.5—2 (q), p-nitrophencycl protons (4H); 2.8—3 (two singlets), phenyl protons (10H); 3.25 (s) vinyl proton (1H); 4.95 (s) methane protons (2H).

N-Phenyl-2-hydroxy-3-oxo-3H-6-(4-nitrophencycl)-morpholine (3e): 1.0 g of the amide 2e was dissolved in 50 ml of commercially available DMSO (0.05% H2O) and to it was added a solution of 0.31 g (1 eq.) of potassium tertiary butoxide in 50 ml of dimethyl sulfoxide, dropwise, with vigorous stirring (magnetic stirr-

2 Research Scholar, Indian Institute of Technology, Kharagpur.
3 Visiting Fellow, supported by a Post Doctoral Fellowship from the Damon Runyon Memorial Fund for Cancer Research Inc., N. Y.

Requests for reprints should be sent to Dr. R. F. Abdulla, Frick Chemical Laboratory, Princeton University, Princeton, New Jersey 08540, U.S.A.
rer) over a period of 1 hr. A transient violet coloration was produced with the addition of each drop, which was rapidly discharged with stirring. The solution turned a deep orange-brown. At the end of 1 hr, the DMSO was removed on a rotary evaporator at 50°C and the residue taken up in benzene, washed with water, dried (MgSO₄) and the solvent removed to give an orange colored residue. Thin layer chromatography (Silicagel PF-254+366, 2 mm layer, ethyl acetate/chloroform 50+50) separated the product (lower \( R_f \) component) from unreacted amide. Recovery of the product from the plate gave 100 mg (ca. 10%) of the pure morpholine as a yellow powder. Yellow needles, m.p. 195–196°C (Cyclohexane/benzene).

IR (KBr) 3300/cm (O–H); 1685/cm (3-oxo-carbonyl).

H²-NMR (d₆-DMSO) \( \tau = 1.5–2 \) (O–H, doublet and nitrophenyl protons) (5H); 2.6 (s), phenyl protons (5H); 2.7 (s), \( C_5 \) proton (1H); 4.33 (d), \( C_2 \) proton (1H), \( J = 7 \) Hz.

\[ +D_2O: \] Coalescence of H₂ signal and disappearance of O–H doublet.

<table>
<thead>
<tr>
<th>Nr.</th>
<th>R</th>
<th>R²</th>
<th>X</th>
<th>Recryst. Solv.</th>
<th>yield</th>
<th>Analysed For</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>C₆H₅</td>
<td>-</td>
<td>-</td>
<td>MeOH/pet-ether</td>
<td>29</td>
<td>C₁₄H₁₃ClNClO₂ (245.5)</td>
</tr>
<tr>
<td>1b</td>
<td>4-ClC₆H₄</td>
<td>4-CIC₆H₄</td>
<td>-</td>
<td>Cyclohexane/Benzene</td>
<td>44</td>
<td>C₁₄H₁₂Cl₃NClO₂ (280.0)</td>
</tr>
<tr>
<td>1c</td>
<td>4-ClC₆H₄</td>
<td>4-ClC₆H₄</td>
<td>-</td>
<td>Cyclohexane/Benzene</td>
<td>74</td>
<td>C₁₃H₁₂Cl₃NClO₂ (275.6)</td>
</tr>
<tr>
<td>1d</td>
<td>4-MeOC₆H₄</td>
<td>2-naphthyl</td>
<td>-</td>
<td>Aceton/InP-ClOH</td>
<td>60</td>
<td>C₁₃H₁₇NO₂Cl (291.4)</td>
</tr>
<tr>
<td>1e</td>
<td>C₆H₅</td>
<td>4-0₂NC₆H₄</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2a</td>
<td>C₆H₅</td>
<td>4-ClC₆H₄</td>
<td>Cl</td>
<td>Cyclohexane</td>
<td>89</td>
<td>C₁₃H₁₂Cl₃NClO₂ (322.0)</td>
</tr>
<tr>
<td>2b</td>
<td>4-ClC₆H₄</td>
<td>4-ClC₆H₄</td>
<td>Cl</td>
<td>Cyclohexane/Isopropanol</td>
<td>90</td>
<td>C₁₃H₁₂Cl₃NClO₂ (356.5)</td>
</tr>
<tr>
<td>2c</td>
<td>4-MeOC₆H₄</td>
<td>4-MeOC₆H₄</td>
<td>Cl</td>
<td>Cyclohexane/Isopropanol</td>
<td>73</td>
<td>C₁₃H₁₂Cl₃NClO₂ (352.0)</td>
</tr>
<tr>
<td>2d</td>
<td>4-MeOC₆H₄</td>
<td>2-naphthyl</td>
<td>Cl</td>
<td>Cyclohexane/Isopropanol</td>
<td>69</td>
<td>C₁₃H₁₁Cl₃NClO₂ (367.6)</td>
</tr>
<tr>
<td>2e</td>
<td>C₆H₅</td>
<td>4-0₂NC₆H₄</td>
<td>Cl</td>
<td>Isopropanol</td>
<td>85</td>
<td>C₁₃H₁₂Cl₃N₂O₄ (367.2)</td>
</tr>
<tr>
<td>2f</td>
<td>C₆H₅</td>
<td>4-0₂NC₆H₄</td>
<td>Br (CH₂Br)</td>
<td>pet-ether/EtOH</td>
<td>40</td>
<td>C₂₂H₁₉Br₂N₂O₄ (546.0)</td>
</tr>
<tr>
<td>3a</td>
<td>C₆H₅</td>
<td>4-ClC₆H₄</td>
<td>-</td>
<td>Isopropanol</td>
<td>147–148</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>4-ClC₆H₄</td>
<td>4-ClC₆H₄</td>
<td>-</td>
<td>Cyclohexane/Isopropanol</td>
<td>101–102</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>4-ClC₆H₄</td>
<td>4-ClC₆H₄</td>
<td>-</td>
<td>Methanol</td>
<td>116–117</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>4-MeOC₆H₄</td>
<td>2-naphthyl</td>
<td>-</td>
<td>Cyclohexane/Isopropanol</td>
<td>138–139</td>
<td></td>
</tr>
<tr>
<td>3e</td>
<td>C₆H₅</td>
<td>4-0₂NC₆H₄</td>
<td>-</td>
<td>Benzene/Cyclohexane</td>
<td>195–196</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>137–139</td>
<td>Cyclohexane/Benzene</td>
<td>-46</td>
<td>C₂₂H₁₇Br₂N₂O₄ (465.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tab. 1. Amines, amides and dehydrohalogenated products.

Discussion

Interest in recent years has developed around the synthesis of the derivatives of 1,4-oxazines and their isosteres, which exhibit a wide range of biochemical activity⁴–⁶. For these reasons we have continued our investigations with appropriate precursors which we expected would yield the required derivatives of 3-oxo-1,4-oxazines (3-oxo-morpholines) of potential biochemical interest. We have further elaborated systems of \( \alpha \)-halogeno-acylamino-methyl-ketones as precursors to corresponding morpholinones and documented exceptional systems which did not yield the six-membered rings but other cyclic and acyclic derivatives.

The hitherto unreported chloracetanilido-4-chloro-acetophenones (2) afforded both the 3-oxo-morpholine 3e as well as the beta-lactams 4a and 4b. A strongly electron-donating substituent on the

---

$N$-atom appears to be a prerequisite for morpholine formation. The isolation of $3c$ also fits in with our earlier formulation of $d^-$-acceptor resonance in heavier halogen substituents $^7$.

Another system of substituted methyl-ketones showed no tendency for cyclization to morpholines under the influence of bases. These are the ketones derived from aceto-2-naphthone. When the ketomethyl substituent was on a non-fused para-diphenyl system, morpholine formation had been reported $^3$. Thus $N$-chloro acetyl-$N$-(4-anisyl)-aminomethyl-2-naphthyl-ketone $2d$ gave only the corresponding beta-lactam $4d$ on treatment with ethanolic potassium hydroxide solution. This result is obtained, in contrast to morpholine formation with diphenylmethyl-ketone derived precursors, probably because of the far greater stabilization of the anionic transition state expected to lead to morpholine, in the latter case relative to the former. This is illustrated in Fig. 2.

The synthesis of 2-chloro-3-oxo-$N$-phenyl-$d^-$-6(4-nitrophenyl)-morpholine was attempted because of the reactivity of a halogen atom substituted vic to both an ether oxygen and a carbonyl group. Such a disposition exists at $C_2$ in the 3-oxo-morpholines. In fact the activity of the 2-chloro-compound was so high that it reacted with traces of moisture present in the reaction mixture to give the 2-hydroxy derivative in poor yields. The 2-hydroxy morpholine was identified by its IR spectrum and the fact that the $C_2$ proton was split into a doublet centered at 4.33 r. The hydroxyl group signal was overlapped by the nitrophenyl protons. Deuterium exchange reduced the $C_2$ doublet ($J = 7$ Hz) to a singlet and the down-field $\mathrm{O-H}$ doublet disappeared. The 2-hydroxy-3-oxo-morpholine was stable under conditions of handling and showed no evidence of decomposition into the glyoxylic acid-amide via ring-chain tautomerism.

---

Table 2. Some $^1$H-NMR spectra of 3-oxo-morpholines showing the signals for the protons on C$_2$ and C$_5$.

We now have accurate information about the $^1$H-NMR absorption of the morpholine ring protons. The H5 protons absorb as sharp singlets between approximately 2.5 – 3.6 $\tau$. As before, the H2 protons are geminally coupled only in case of the N-(1-naphthyl)-substituted morpholine.

The amide 2f has an interesting and exceptional PMR spectrum, in which the ketomethylene protons are geminally coupled. In several of the other amides which we have examined such coupling is not present, or cannot be detected under the conditions of measurement.

We are grateful to Professor Edward C. Taylor, A. Barton Hepburn Professor of Organic Chemistry for his generous support and for granting facilities. Dr. Trevor A. Crabb of Portsmouth Polytechnic is thanked for running some IR and NMR spectra. Dr. Nitya Anand, Assistant Director, Central Drug Research Institute, Lucknow, India, kindly supplied the microanalytical data on a number of samples.

* There was an error in reporting the H$_5$ absorptions in an earlier publication; these values are withdrawn. R.F.A.