Studies on Lactams

BASANTA G. CHATTERJEE and NOEL L. NYSS
Department of Chemistry, Indian Institute of Technology, Kharagpur, India

(Z. Naturforsch. 26 b, 395—399 [1971]; received September 28, 1970)

The intramolecular alkylation of haloamides 18 where there is similar opportunity for formation of four member as well as of six member rings, leads to the formation of /?-lactams rather than that of six member rings. The study further shows that when the activity on the methyne hydrogen is simultaneously afforded by an aliphatic carbonyl and phenyl substituents, cyclisation can be effected by the weak base triethylamine. The paper records the synthesis of two unique dumbell shaped /?-lactams 19.

Discussion

Due to the extreme susceptibility of the /?-lactam carbonyl to nucleophilic reagents novel methods have been introduced for the synthesis of this four member cyclic amide 1.

SHEEHAN and Bose 2, 3 have reported the synthesis of lactams 2 by the intramolecular alkylation of a-haloacetamides 1, using the weak base triethylamine.

Fig. 1.

BOSE, GHOSH MAZUMDAR and CHATTERJEE 4 later studied the ease of formation of lactams and have suggested a carbanion intermediate in the formation of lactams.

BOSE and MANHAS 5 have extended their studies to the intramolecular alkylation of dihaloamides 3 and 6 and have established that under competitive conditions /?-lactams 4 form in preference to /?-lactams 5, whereas, amides 6 give /?-lactams 7 in quantitative yields. They have further shown that /?-lactams 9 cannot be synthesised by this technique, as illustrated by the reaction scheme shown in Fig. 2.

The choice of haloamides by Bose and Manhas for their study are not free from criticism, since the nature of the leaving halogen atoms are not identical.

Reprints request to Dr. B. G. CHATTERJEE, Department of Chemistry, Indian Institute of Technology, Kharagpur, India.

1 J. C. SHEEHAN and E. J. COREY, Org. Reactions 9, 388 [1957].
2 J. C. SHEEHAN and A. K. BOSE, J. Amer. chem. Soc. 72, 5158 [1950].
3 J. C. SHEEHAN and A. K. BOSE, J. Amer. chem. Soc. 73, 1761 [1951].
Table 1. Physical characteristics of compounds 12 and 13.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>12 a phenyl</td>
<td>127–128</td>
<td>L</td>
</tr>
<tr>
<td>12 b 4-methylphenyl</td>
<td>158–159</td>
<td>M</td>
</tr>
<tr>
<td>12 c 2,4-dichlorophenyl</td>
<td>179–180</td>
<td>M</td>
</tr>
<tr>
<td>12 d 4-acetylphenyl</td>
<td>141–142</td>
<td>M</td>
</tr>
<tr>
<td>13 a phenyl</td>
<td>118–119</td>
<td>L</td>
</tr>
<tr>
<td>13 b 4-methylphenyl</td>
<td>86–87</td>
<td>N</td>
</tr>
<tr>
<td>13 c 2,4-dichlorophenyl</td>
<td>186–187</td>
<td>K</td>
</tr>
<tr>
<td>13 d 4-acetylphenyl</td>
<td>93–94</td>
<td>M</td>
</tr>
</tbody>
</table>

Amines 12 needed for the investigation were prepared by mixing an acetone solution of amine 11 with the halo ketone 10 and stirring at room temperature for 8 to 36 hours. Halo ketone 10 was prepared by the bromination of an ethereal solution of dibenzylketone in the presence of a trace quantity of aluminium chloride. Refluxing of a benzene solution of amines 12 with chloroacetyl chloride resulted in the formation of amides 13.

As can be seen amides 13 have two active hydrogen atoms H₆ and H₈, thereby, offering dual possibilities of β-lactam 14 or 2,5-diketopiperidine 15 formation. Further it was of interest to see whether triethylamine would be capable of effecting the intramolecular alkylation of amides 13 when the methylene hydrogen was simultaneously activated by a phenyl and an aliphatic ketone function.

Amides 13 a and 13 b when treated with triethylamine eliminated the elements of hydrogen halide to the extent of 50% at room temperature and the reaction in both cases was eventually taken to completion at the reflux temperature of benzene. The halogen free liquids 14 a and 14 b isolated resisted crystallisation even after prolonged standing in the ice box. The sharp peak in their I.R. spectra at 1775/cm (CO cyclic-amide) rules out the formation of any 2,5-diketopiperidine.

Amide 13 c eliminated halogen acid very slowly at room temperature and the reaction was eventually taken to completion at the reflux temperature of benzene. Amide 13 d eliminated the elements of HCl rapidly at room temperature, when treated with triethylamine, the reaction going to completion in 8 hours. The I.R. spectra of the liquids 14 c and 14 d thus isolated, here also are compatible with four member ring formation rather than that of 2,5-diketopiperidines.

Attempts at characterising the liquid β-lactams 14 a to 14 d as their 2,4-dinitrophenyl hydrozone derivatives were unsuccessful.

The differences in the rates of cyclisation of haloamides 13 are in accordance with the earlier observation 6–8 that the delocalisation of the nonbonded electrons of the amide nitrogen atom into the N-aryl nucleus plays an important role in the formation of β-lactams.

It may, however, be argued that in amides 13 the hydrogen atom H₆ as a result of an inductive pull due to the adjacent N-atom is rendered non-equivalent to hydrogen atom H₈.

This led to the synthesis of amides 18 by the route outlined in Fig. 5.

Amides 18 a and 18 b were characterised by I.R. and N.M.R. spectra as well as by elemental analysis and so were the precursor amines 17 and di-
haloketone 16 characterised by I.R. spectra and elemental analysis.

Both amides 18a and 18b in which the methylene hydrogen atoms H₅ and H₆ are now rendered equivalent, eliminated hydrogen halide to the extent of 50% at room temperature when treated with triethylamine and in both cases the reaction was taken to completion at the reflux temperature of benzene, to yield solid products.

The N.M.R. spectra of the product isolated by the reaction of 18b with triethylamine established the presence of three types of protons, having,
(i) a singlet at 7.75 p (— CH₃),
(ii) a quadruplet in the 6.4 — 6.6 p region (methylene),
(iii) a multiplet in the 2.6 — 3.05 p region (aryl protons).

The N.M.R. spectra of the final product showed two distinct peaks in the 1760 cm⁻¹ (CO alkyl ketone). This completion at the reflux temperature of benzene, to an open capillary using a Gallenkamp melting point apparatus. I.R. spectra were recorded by a Perkin Elmer Infracord spectrometer. N.M.R. spectra were recorded by a Varian spectrometer.

Experimental

All melting points are uncorrected and were taken in an open capillary using a Gallenkamp melting point apparatus. I.R. spectra were recorded by a Perkin Elmer Infracord spectrometer. N.M.R. spectra were recorded by a Varian spectrometer.

\[ \text{a-Bromo-dibenzyllketone (10): } 27.30 \text{ g of dibenzyl ketone in } 27.00 \text{ ml of anhydrous ether was cooled in an ice salt bath. To this was added } 0.30 \text{ g AlCl}_3 \text{ and } 6.65 \text{ ml of } \text{Br}_2 \text{ over a period of 10 minutes with continuous stirring. Immediately after the addition of } \text{Br}_2 \text{ was complete the ethereal solution was washed thoroughly to remove the dissolved HBr and dried. Removal of the ether afforded } 30.00 \text{ g of a viscous liquid 10.} \]

\[ \text{a-Anilino-dibenzyllketone (12a): } 13.6 \text{ g 10 in } 15.0 \text{ ml of acetone was cooled in ice water and to this was added } 9.0 \text{ ml of freshly distilled aniline in } 6.0 \text{ ml of acetone, with stirring. After 6 hours the cake was cooled in the ice box and then filtered. After washing the residue with } 2 \text{ N HCl and then water there resulted } 6.0 \text{ g (50%) 12a. The product recrystallised from iso-} \]

[31x582]propanol melted at 127 — 128 °C.

C₂₁H₁₉NO (301)

Calc. C 83.71 H 6.31 N 4.65,
Found C 82.90 H 6.35 N 4.17.

I.R.: NH, 3350, CO ketone (alkyl) 1740/cm.

\[ \text{N-Phenyl-N-(2-chloroacetyl)-2-amino-dibenzyllketone (13a): } 3.0 \text{ g 12a in } 40.0 \text{ ml of dry benzene was refluxed with } 3.0 \text{ ml chloroacetyl chloride for 4 hours. After cooling the solution was washed with water to remove the excess chloroacetyl chloride and dried over anhydrous Na₂SO₄. Removal of the solvent afforded } 3.2 \text{ g (84.8%) 13a melting at } 118 — 119 \text{ °C. Recrystallisation from isopropanol did not effect the melting point.} \]

C₂₃H₂₀ClNO₂ (377.5)
Calc. C 73.08 H 5.30 N 3.70,
Found C 72.90 H 5.36 N 3.38.

I.R.: CO ketone (alkyl) 1745, CO amide (alkyl) 1655/cm.

\[ \text{4-Oxo-1,2-diphenyl-2-phenylacetyl-azetidine (14a): } 3.00 \text{ g 13a in } 30.00 \text{ ml of benzene and } 5.00 \text{ ml of triethylamine allowed to stand for } 16 \text{ hours at room temperature. The triethylamine hydrochloride eliminated weighed } 0.52 \text{ g (49%). The reaction was eventually taken to completion by refluxing for 6 hours. After cooling the solution was washed with } 2 \text{ N HCl and water and then dried over anhydrous Na₂SO₄. Removal of the solvent afforded } 2.70 \text{ g (100%) 14a as a liquid which resisted crystallisation even after prolonged standing in the ice box.} \]


\[ \text{α-(4-Methylanilino)-dibenzyllketone (12b): } 13.6 \text{ g 10 in } 15.0 \text{ ml acetone was cooled in ice water and to this was added } 11.0 \text{ g 4-methylaniline in } 10.0 \text{ ml acetone, with stirring. Work up after 4 hours afforded } 7.0 \text{ g (44.4%) 12b, which on recrystallisation from isopropanol/DMF melted at } 158 — 159 \text{ °C.} \]

C₂₂H₂₁NO₂ (315)
Calc. C 83.81 H 6.98 N 4.44,
Found C 84.60 H 7.21 N 4.81.

N-(4-Methylphenyl)-N-(2-chloroacetyl)-2-amino-dibenzylketone (13 b):
Work up afforded 4.2 g (85.7%) 13 b melting at 80—82 °C. Recrystallisation from ether (60/80 °C) raised the melting point to 86—87 °C.

C₂₂H₂₁NO (315)
Calc. C 83.81 H 6.98 N 4.44,
Found C 84.60 H 7.21 N 4.81.

N-(4-Acetylphenyl)-N-(2-chloroacetyl)-2-amino-dibenzylketone (13 d):
Work up afforded 0.80 g (74.7%) 13 d. The product recrystallised from isopropanol melted at 93—94 °C.

C₂₂H₂₁N₂O₂ (343)
Calc. C 80.49 H 6.12 N 4.08,
Found C 80.80 H 6.33 N 4.00.
I.R.: NH 3350, CO ketone (alkyl) 1720, CO ketone (aryl) 1670/cms.

4-Oxo-1-(4-methylphenyl)-2-phenyl-2-phenylacetylazetidine (14 b):
Work up afforded 0.90 g 13 c in 10.00 ml benzene

a-(4-Acetylanilino)-dibenzylketone (12 d):
Work up afforded 71.5 g (98%) 16 melting at 80-81 °C. The product was recrystallised from pet.ether (60/80 °C)/iso-propanol (drops).

C₁₅H₁₅Br₂O (368)
Calc. C 48.91 H 3.26,
Found C 49.10 H 3.63.

a,a’-Dibromo-dibenzylketone (16):
To 42.0 g dibenzyl ketone (Aldrich) in 100.0 ml of solvent ether containing 0.5 g anhydrous AlCl₃ was added over a period of ten minutes 20.0 ml of Br₂ (keep immersed in ice water bath to prevent overheating and stir well). After the addition of Br₂ is complete an additional 150.0 ml of solvent ether is added and the solution washed with water to remove the dissolved HBr. Removal of ether affords 71.5 g (98%) 16 melting at 80—81 °C. The product was recrystallised from ether (60/80 °C)/iso-propanol (drops).

C₂₇H₂₆N₂O (392)
Calc. C 82.65 H 6.12 N 7.14,
Found C 82.70 H 6.22 N 7.11.
a,a'-Di-(a-chloroacetanilido)-dibenzylketone (18 a) : 
1.20 g 17 a in 50.00 ml benzene and 3.00 ml chloroacetyl chloride refluxed for 6 hours. Work up afforded 1.67 g (100%) 18 a. The product recrystallised from isopropanol/benzene melted at 192 °C.

C<sub>31</sub>H<sub>26</sub>C<sub>12</sub>N<sub>2</sub>O<sub>3</sub> (545)  
Calc. C 68.26 H 4.77 N 5.14,  
Found C 67.85 H 4.93 N 5.53.

I.R.: CO ketone (alkyl) 1730, CO amide (split) 1680-1690/cm.

N.M.R.: 2.8-3.3 r multiplet (aryl protons), 3.7 r singlet (methyne protons), 6.10 — 6.2 r multiplet (methylene protons).

2,2'-Bis-(4-oxo-1,2-diphenyl-azetidinyl)-ketone (19a): 
1.00 g 18 a in 10.00 ml benzene and 3.00 ml triethylamine stirred at room temperature for 24 hours. Elimination of triethylamine hydrochloride was 0.25 g (50%). The reaction was taken to near completion in 24 hours at reflux temperature. Work up afforded 0.76 g (90%) 19 a as a semi-solid. Titurating and recrystallisation from pet. ether (60/80 °C)/isopropanol gave 0.60 g 19 a melting at 115 — 118 °C.

C<sub>31</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub> (472)  
Calc. C 78.39 H 5.08 N 5.93,  
Found C 78.61 H 5.24 N 5.67.

I.R.: CO /Mactam 1770, CO ketone (alkyl) 1725/cms (slight contamination).

a,a'-Di-(4-methyl-a-chloroacetanilido)-dibenzylketone (18 b): 
1.40 g 17 b in 50.00 ml benzene and 3.00 ml chloroacetyl chloride refluxed for 6 hours. Work up afforded 1.64 g (86.4%) 18 b. The product recrystallised from isopropanol melted at 185 — 186 °C.

C<sub>33</sub>H<sub>30</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub> (573)  
Calc. C 69.11 H 5.23 N 4.88,  
Found C 68.90 H 5.33 N 4.92.


N.M.R.: 2.7-3.3 r multiplet (aryl protons), 3.7 r singlet (methylene protons), 6.1 — 6.2 r multiplet (methylene protons), 7.7 r singlet (methyl protons).

2,2'-Bis-{4-oxo-1-phenyl-2-(4-methylphenyl)-azetidinyl}-ketone (19 b): 0.82 g 18 b in 6.00 ml benzene and 4.00 ml triethylamine allowed to stand at room temperature for 24 hours. The triethylamine hydrochloride eliminated weighed 0.20 g (50%). The reaction was taken to completion at reflux temperature of benzene in 24 hours. Work up afforded 0.64 g (90%) 19 b. The produce recrystallised from isopropanol/pet. ether (60/80 °C) melted at 223 — 224 °C.

C<sub>33</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub> (500)  
Calc. C 79.20 H 5.60 N 5.60,  
Found C 79.05 H 5.32 N 5.72.


N.M.R.: 2.6-3.05 t multiplet (aryl protons), 6.4 — 6.6 r quadruplet (methylene protons), 7.75 r singlet (methyl protons).

The authors wish to thank Dr. A. K. Bose of Stevens Institute of Technology, Hoboken, New Jersey, U.S.A., for his valuable suggestions and for supplying spectral facilities. Further, the authors express their gratitude to Dr. NITYA NAND of Central Drugs Research Institute, India, for supplying the analysis data. Dr. RIAZ F. ABDULLA of IIT Kharagpur is thanked for providing the interpretation of the nmr data.