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STUDIES ON LACTAMS—XXVII[a]

SYNTHESIS AND REACTIONS OF 4-CARBOXY-β-LACTAM

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Abstract—Reaction of phenoxyacetyl chloride with α-carbomethoxybenzylidine-*p*-anisidine **1** in presence of triethylamine gave a mixture of E and Z 1-(*p*-anisyl)-4-carbomethoxy-3-phenoxy-4-phenyl-2-azetidinones **2** which upon hydrolysis with lithium iodide in refluxing pyridine produced the corresponding acids in the ratio of 3:1. A series of substituted β-lactams were prepared by transforming the carboxy group of the E-isomer into the acid chloride, amide, cyano, acid azide, isocyanate, urethane, urea, hydroxymethyl, aldehyde, acetoxy and methoxy groups.

INTRODUCTION

Variations in the structure of penicillins and cephalosporins engaged the attention of many medicinal chemists as soon as the structure and stereochemistry of these antibiotics became evident. We became interested in monocyclic β-lactams having a free carboxy group because of their potential biological activity and also because of their possible role as intermediates for polycyclic β-lactams.

RESULTS AND DISCUSSIONS

1-(*p*-Anisyl)-4-carbomethoxy-3-phenoxy-4-phenyl-2-azetidinone **2** was prepared from phenoxyacetyl chloride and α-carbomethoxybenzylidene-*p*-anisidene **1**, a Schiff base (obtained from methyl benzoylformate and *p*-anisidine), in presence of triethylamine. The NMR spectrum of **2** showed two singlets at δ 5·29 and 5·76 for C-3 proton, indicating a mixture of two stereoisomers. The singlet at higher field (δ 5·29) was assigned to the isomer with its C-3 proton *cis* to the phenyl group based upon ring current effect. Treatment of the crude β-lactam **2** with lithium iodide in refluxing pyridine[1] gave the corresponding acids **3** and **4** in the ratio of 3 to 1 as indicated by the NMR spectrum without fission of the β-lactam moiety. The pure carboxy-β-lactam **3** was isolated by fractional crystallization.

The acid-β-lactam **3** was converted to its acid chloride **5** with oxalyl chloride and catalytic amounts of N,N-dimethylformamide at 0°. Reaction of **5** with a large excess of ammonia with cooling gave the amide **6** in good yield. The NMR spectrum of **6** showing the C-3 proton at δ 5·97 indicated that no inversion of stereochemistry at C-3 had taken place in presence of ammonia. Among the various dehydrating agents, phosphorus oxychloride was found to be suitable for the conversion of the amido-β-lactam **6** to the nitrile **7** in fair yield.

Presence of a free carboxy group at C-4 in **3** provided us the opportunity to investigate the possibility of introducing an amide side chain at the β-position to the β-lactam carbonyl (*cf* penicillins and cephalosporins have amide chain α to the β-lactam carbonyl). Thus the mixed anhydride **8** was prepared *in situ* by treatment of **3** with isobutyl chloroformate in presence of triethylamine at 0°. Subsequent addition of aqueous sodium azide to **8** produced the acid azide-β-lactam **9** which upon refluxing in dry benzene underwent rearrangement to the isocyanate **10**. Treatment of **10** with ethanol generated the crystalline urethane **11** in good yield. An attempt to prepare β-amino-β-lactam **12** by reacting the isocyanate **10** with water resulted in an urea analog[2] **13**, the structure of which was assigned on the basis of spectroscopic and analytical data, high m.p. and low solubility.

Stability of the urethane **11** and the substituted urea **13** is noteworthy. It may be recalled that β-amino-β-lactams, in general, are unstable and are susceptible to hydrolytic conditions leading to the cleavage of C_4-N and $/C_4$-C_3 bonds.[3] Apparently the acylation of the C_4-amino function enhances the stability of these compounds.

The acid-β-lactam **3** was not reduced with LAH at room temperature. Attempts to reduce **3** in refluxing THF cleaved the β-lactam. Even sodium bis (2-methoxyethoxy)aluminium hydride in various solvents[4] failed to effect the reduction. Diborane reduction of **3** according to the conditions of Brown *et al*[5] gave the expected carbinol-β-lactam **14**. Alternatively, reduction of the acid-azide **9** with potassium borohydride[6] at 0° provided the same

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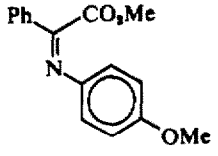
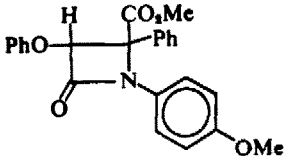
carbinol **14**. When β-lactam **14** was oxidized by pyridine trifluoroacetate and dicyclohexylcarbodiimide in DMSO at room temperature (Pfitzner-Moffatt oxidation[7]) the aldehyde **15** was obtained in moderate yield. However, reduction of the acid chloride-β-lactam **5** with lithium tri t-butoxy aluminiumhydride[8] at −75° produced the carbinol-β-lactam **14** instead of the aldehyde **15**. Decarbonylation of **15** was of special interest to us because it would provide a new route to the *cis*-β-lactam **16**. However, decarbonylation with rhodium complex[9] at higher temperature cleaved the β-lactam **15** while at lower temperature no change was observed. Halogenation with decarboxylation[10] was attempted on the acid-β-lactam **3** with lead tetraacetate and lithium chloride to obtain the corresponding chloro-β-lactam **17**, but a crystalline product was isolated whose spectroscopic and analytical data showed it to be the acetoxy-β-lactam **18**. This was also the sole product obtained when the reaction took place in the absence of any halide salt. The acetoxy-β-lactam **18** resisted hydrolysis with dilute hydrochloric acid in THF acetone. Also hydrolysis with ammonium hydroxide in benzene or potassium-t-butoxide solution was unsuccessful. Treatment of **18** with 30% trifluoroacetic acid generated the acyclic amide **20**, resulting from the cleavage of the expected hydroxy-β-lactam **19**. When ester-β-lactam **18** was shaken under hydrogen (40 psi) with Pd/C[11] in methanol, an ether **21** [NMR ($CDCl_3$): δ 3·73 (6H, -OMe); 5·19 (1H), 7·20 (14H) λ_{max}^{nujol} 1785 cm^{-1} (β-lactam C=O), *m/e* 375] instead of the expected structure **16** was produced: The same results were observed when



1



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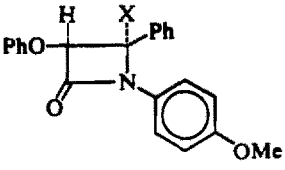
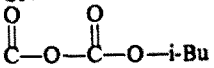
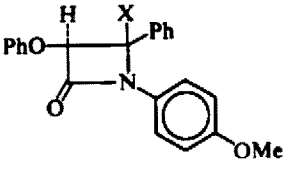
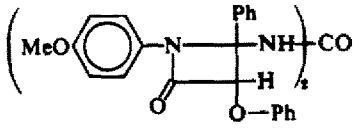


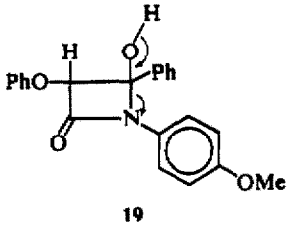
X =
3: CO_2H
5: COCl
6: $CONH_2$
7: CN
8: 
9: CON_3
10: N=C=O
11: $NHCO_2C_2H_5$
12: NH_2
14: CH_2OH
15: CHO
16: H
17: Cl
18: OAc
21a: OMe



4: X = CO_2H
12b: X = OMe



13

18 ⟶ 

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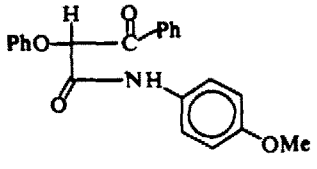
⟶ 

20

catalytic amount of hydrochloric acid was used in place of Pd/C. Furthermore, the crude product isolated from either reaction gave different C-3 proton resonance signals in the ratio of 4 to 1 (**21a**, **21b**); the major product **21a** (δ 5·19) was obtained through fractional crystallization. The product **21a** represents a result of inversion at the tertiary C atom but it is not yet clear whether a carbonium ion has been formed or an elimination of acetic acid has preceeded the addition of methanol. The same product **21** was also obtained when **18** was refluxed in methanol with a catalytic amount of anhydrous zinc chloride. The mechanism of the unusual conversion of acetoxy-β-lactam **18** to the corresponding methoxy-β-lactam **21** needs further study.

Previously[12] we have described methods for the synthesis of various α-substituted β-lactams by the acid chloride-imine reactions. A combination of these methods with the transformations described here for β-carboxy-β-lactams should lead to a wide variety of substituted β-lactams.

EXPERIMENTAL

All m.p. were determined on a "mel-temp" apparatus and were uncorrected. The NMR spectra were recorded on Varian A-60 A spectrometer using TMS as an internal standard. The chemical shifts are shown in δ value (ppm). IR spectra were taken on Perkin-Elmer 247 Grating spectrometer.

α-Carbomethoxybenzylidene-p-anisidine **1**. *p*-Amisidine (31 g, 0·252 mole), methyl benzoylformate (41 g, 0·250 mole) and *p*-toluenesulfonic acid (1 g) in dry benzene (250 ml) were refluxed using a Dean-Stark apparatus. Benzene was distilled off under vacuum and the crude product **1** crystallized from ether, yield 49 g (73%), m.p. 88–89°. (Found: C, 71·20; H, 5·60; N, 5·14. $C_{16}H_{15}NO_3$ required: C, 71·36; H, 5·61; N, 5·20%); IR cm^{-1} (nujol): 1620 (C=N), 1730 (C=O); NMR ($CDCl_3$): 3·55 (s, 3H), 3·65 (s, 3H), 6·80 (m, 3H), 7·35 (m, 4H), 7·78 (m, 2H).

1-(p-Anisyl)-4-carbomethoxy-3-phenoxy-4-phenyl-2-azetidinone **2**. Phenoxyacetyl chloride (19·7g, 0·115 mole in dry methylene chloride (100 ml) was added dropwise to a stirred soln of the Schiff base **1** (31 g, 0·115 mole), and triethylamine (11·5 g, 0·115 mole) in methylene chloride (300 ml) at 0° under an atmosphere of N_2. After stirring overnight at room temp, the product was poured into ice water, organic phase separated, washed successively with 5% $NaHCO_3$ aq, 5% HCl aq, water and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave **2**, yield 34 g (73%); m.p. 104–107 (chloroform-n-hexane); Mass spectrum *m/e*: 403, 269, 254, 210, 149, 134, IR CM^{-1} (nujol): 1725 (ester C=O), 1770 (β-lactam C=O), NMR ($CDCl_3$): 3·75 (s, 3H), 3·82 (s, 3H), 5·29 (s, ~ ½ H), 5·76 (s, ~ ½ H), 7·20 (m, 14 H).

E-1-(p-Anisyl)-4-carboxy-3-phenoxy-4-phenyl-2-azetidinone **3**. The ester-β-lactam **2** (25 g, 0·062 mole) and LiI (50 g) in dry pyridine (500 ml) were refluxed for 10 hr. The soln was cooled and poured cautiously into a mixture of chloroform (500 ml), crushed ice (500 g) and conc HCl (300 ml) with vigorous stirring. The organic layer was separated, washed with 5% HCl aq, water and dried over $MgSO_4$. Distillation of the solvent under vacuum afforded the acid 21 g (87%). Crystallization from chloroform–ether (1:3) gave the pure isomer **3**; yield 11 g (45%); m.p. 158–160°. (Found: C, 71·20; H, 5·22; N, 3·97. $C_{23}H_{19}NO_5$ requires: C, 70·94; H, 4·92; N, 3·60%); Mass spectrum m/e: 389, 255, 210, 149, 134; IR cm^{-1} (nujol): 1700 (acid C=O) and 1750 (β-lactam C=O); NMR (DMSO-d_6): 3·7 (s, 3 H), 5·85 (s, 1 H), 7·20 (m, 14 H).

E-4-Amido-1-(p-anisyl)-3-phenoxy-2-azetidinone **6**. Oxalyl chloride (1·3 ml) in dry benzene (10 ml) was added dropwise to a stirred soln of **3** (4·0 g, 1·03 mmoles) suspended in dry benzene (60 ml). Then 5 drops of N,N-dimethylformamide were added and the stirring continued for further 1 hr. Excess of oxalyl chloride and the solvent were removed under reduced pressure to obtain the thick oily acid chloride **5**. This acid chloride **5** dissolved in methylene chloride (60 ml) was added slowly into a methylene chloride (30 ml) soln containing anhyd ammonia (89 g) at 0° and stirred for 1 hr. The organic phase was separated and the aqueous phase extracted with methylene chloride. The combined extract was washed with water and dried over $MgSO_4$. Removal of the solvent gave the crude product **6** which was crystallized from chloroform–ether (1:1), yield 2·3 g (58%); m.p. 171–173°. (Found: C, 70·93; H, 5·09; N, 7·24. $C_{23}H_{20}N_2O_4$ requires: C, 71·12; H, 5·19; N, 7·21%); Mass spectrum *m/e*: 388, 344, 254, 222, 210, 149, 134; IR cm^{-1} (nujol): 1685 (amide C=O), 1760 (β-lactam C=O), 3165, 3385 (-NH_2); NMR (DMSO-d_6): 3·75 (s, 3 H), 5·97 (s, 1 H), 7·3 (m, 14 H).

E-1-(p-Anisyl)-4-cyano-3-phenoxy-4-phenyl-2-azetidinone **7**. Phosphorus oxychloride (6·5 ml) was added slowly into the amide **6** (1·4 g, 3·78 mmoles) in pyridine (25 ml) kept at an ice bath temp. After being stirred overnight at room temp, the mixture was cautiously poured over crushed ice and methylene chloride with vigorous stirring. The organic layer was washed with 1 N HCl, water, dried over $MgSO_4$ and solvent stripped off. Trituration with ether gave the solid product **7**, 0·8 g (61%), m.p. 116–118° (methylene chloride-ether). (Found: C, 74·76; H, 4·75, N, 7·61. $C_{23}H_{18}N_2O_3$ requires: C, 74·58; H, 4·80; N, 7·56%). Mass spectrum *m/e*: 370, 236, 221, 149, 135; IR cm^{-1} (nujol): 1780 (β-lactam C=O); NMR ($CDCl_3$): 3·70 (s, 3 H), 5·85 (s, 1 H), 7·2 (m, 14 H).

E-Ethyl 1-(p-anisyl)-3-phenoxy-4-phenyl-2-azetidinone-4-carbamate **11**. Isobutyl chloroformate (0·7 g, 5·1 mmoles) in THF (15 ml) was added slowly to **3** (2·0 g, 5·1 mmoles) and triethylamine (0·52 g, 5·2 mmoles) in THF (20 ml) at 0°. After stirring for 1 hr, sodium azide (0·5 g, 7·7 mmoles) in water (5 ml) was added and stirring continued for an additional 1 hr. The mixture was poured into ice water, extracted with ether and dried over $MgSO_4$. Removal of the solvent provided the oily acid-azide **9** which was dissolved in dry benzene (10 ml) and refluxed for 1 hr. Thereafter EtOH (1 ml) was added and refluxed for 10 min. The product was diluted with benzene, washed with water and dried. Removal of the solvent gave the solid product **11**, (750 mg, 38%); m.p. 150–151° (n-hexane-chloroform) (Found: N, 6·53. $C_{25}H_{24}N_2O_5$ requires: N, 6·48%); Mass spectrum *m/e*: 432, 386, 283, 237, 149, 134; IR cm^{-1} (nujol): 1675 (carbomate C=O), 1740 (β-lactam C=O), 3200 (-NH); NMR ($CDCl_3$): 1·1 (t, 3H), 3·66 (s, 3 H), 4·01 (q, 2 H), 6·18 (s, 1 H), 6·20 (s, 1 H), 7·0 (m, 14 H).

Z-1-(p-Anisyl)-4-hydroxymethyl-3-phenoxy-4-phenyl-2-azetidinone **14**

(a) Potassium borohydride (0·5 g, 10 mmoles) was added in small lots to the well stirred soln of **9** (pre-

pared from 2 g of **3** as described above) at 0° and stirred for 2 hr. AcOH was added from time to time to keep the pH between 6 and 8. Thereafter the mixture was quenched with MeOH (0·5 ml) and extracted with methylene chloride. The combined extract was dried over $MgSO_4$, removal of the solvent afforded 0·7 g (37%) of **14**, m.p. 166–167°. (Found: C, 73·75; H, 5·62; N, 4·13. $C_{23}H_{21}NO_4$ requires: C, 73·58; M, 5·64; N, 3·73%); Mass spectrum *m/e*: 375, 252, 241, 226, 222, 210, 195, 149, 134; IR cm^{-1} (nujol): 1730 (β-lactam C=O), 3400 (–OH); NMR (DMSO-d_6): 3·3 (s, 2 H), 3·7 (s, 3 H), 5·7 (s, 1 H), 7·15 (m, 14 H).

(b) A suspension of lithium tri-t-butoxyaluminum hydride (1·4 g) in diglyme (25 ml) was added over a period of 20 min to **5** (prepared from 2 g of **3** as described above) at −55°. After stirring for further 1 hr, it was poured into ice-water, extracted with methylene chloride, washed with water, dried and concentrated to dryness. Ether trituration gave the crude alcohol **14** which was crystallized from chloroform, m.p. 165–167°.

(c) Diborane (3 ml, 4 M) was added to **3** (1·3 g, 3·3 mmoles) in THF (10 ml) and stirred for 4 hr at room temp. Then EtOH (3 drops) was added and stirring continued for further 2 hr. Thereafter the product was poured into ice water containing 3 N HCl (1 ml), extracted with methylene chloride, washed with $NaHCO_3$ aq, dried over $MgSo_4$ and concentrated to the product **14**, m.p. 165–167°.

E-1-(p-*Anisyl*)-4-*formyl*-3-*phenoxy*-4-*phenyl*-2-*azetidinone* **15**

The alcohol **14** (3·2 g, 8·5 mmoles) was dissolved in dry benzene (30 ml) and DMSO (30 ml). Pyridine trifluoroacetate (800 mg, 4·2 mmoles) was added followed by dicyclohexylcarbodiimide (5·6 g, 16 mmoles) and stirred overnight. Thereafter methanolic solution of oxalic acid (1 ml) was added and the solid removed by filtration. The filtrate washed with water, dried over $MgSO_4$. The evaporation of solvent under reduced pressure gave **15** as an oil. Mass spectrum *m/e*: 373, 280, 252, 210, 149, 134; IR cm^{-1} (nujol): 1730 (—CHO), 1770 (β-lactam C=O); NMR ($CDCl_3$): 2·70 (s, 3H), 5·82 (s, 1H), 7·10 (m, 14H), 8·80 (s, 1H).

E-4-*Acetoxy*-1-(p-*anisyl*)-3-*phenoxy*-4-*phenyl*-2-*azetidinone* **18**

Lead tetraacetate (2·0 g, 4·5 mmoles) was added to a benzene (20 ml) soln of **3** (2g, 5·1 mmoles) and cupric acetate (100 mg) at 0° under N_2. Ice-bath was removed and the reaction was stirred for 1 hr at room temp. When evolution of the gas had ceased ethylene glycol (0·00 ml) was added to destroy excess lead tetraacetate. Benzene soln was decanted, washed with 5% $NaHCO_3$aq, dried and concentrated to dryness. Crystallization from benzene-ether yielded **18** 1·4 g (68%), m.p. 118–119°. (Found: C, 71·55; M, 5·13; N, 3·49. $C_{24}M_{21}NO_5$ requires: C, 71·45; N, 5·25; N, 3·47%); Mass spectrum: *m/e*: 403, 343, 266, 210, 135; IR cm^{-1} (nujol): 1740 (ester C=O), 1765 (β-lactam C=O); NMR ($CDCl_3$): 215 (s, 3H), 3·65 (s, 3H), 6·15 (s, 1H), 7·10 (m, 14H).

Z-1-(p-*Anisyl*)-4-*methoxy*-3-*phenoxy*-4-*phenyl*-2-*azetidenone* **21b**

(a) The ester-β-lactam **18** (1·18 g, 3 mmoles) in MeOH (80 ml) was refluxed with a catalylic amount of anhyd $ZnCl_2$ for 14 hr. Solvent was distilled off and the product taken in ether, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. Trituration with ether afforded **21b**; 0·6 g (51%): m.p. 127–128°. (Found: C, 73·72; H, 5·45; N, 3·56, $C_{23}H_{21}NO_4$ requires: C, 73·58; H, 5·64; N, 3·73%); Mass spectrum *m/e*: 375, 241, 226, 149, 134; IR cm^{-1} (nujol): 1785 (β-lactam C=O); NMR ($CDCl_3$): 3·73 (s, 6H), 5·19 (s, 1H), 7·20 (m, 14H).

(b) The ester β-lactam **18** (0·5 g, 1·2 mmoles) in MeOH (60 ml) and conc HCl (5 drops) was shaken under H_2 (40 psi) for 18 hr. Solvent was removed under vacuum and the product taken in methylene chloride, washed with 5% $NaHCO_3$aq, dried and concentrated to dryness. NMR indicated a mixture of isomers **21a,b**. Crystallization (benzene-ether) gave the pure Z-isomer **21b**, m.p. 128–129°.

Hydrolysis of isocyanate-β-lactam **10**. The isocyanate **10** (prepared from 1·0 g of **3** as described in the preparation of **11**) in dry benzene (40 ml) and 2N HCl (3 ml) was stirred overnight. Then the mixture was acidified cautiously and extracted with EtOAc. The aqueous layer was basified with NaOHaq, extracted with methylene chloride and dried over $MgSO_4$. Removal of the solvent provided the solid product, **20** m.p. 269–271°. (Found: C, 72·38; H, 5·09; N, 7·50. $C_{45}H_{38}N_4O_7$ requires: C, 72·27; H, 4·66; N, 7·20%); Mass spectrum *m/e*: 387, 237, 180, 165, 134; IR cm^{-1} (nujol): 1760 (β-lactam C=O) 1645 (amide, C=O).

Reaction of trifluoroacetic acid on 4-*acetoxy*-1-(p-*anisyl*)-3-*phenoxy*-4-*phenyl*-2-*azetidinone* **13**. The acetoxy-β-lactam **18** (560 mg) in THF (5 ml) was stirred with trifluoroacetic acid (15 ml; 50%) for 3 hr. Thereafter methylene chloride was added, the organic layer was washed with 5% $NaHCO_3$aq, dried over $MgSO_4$ and solvent removed under vacuum to obtain **13** as a solid product, m.p. 119–121°. (n-hexane + methylene chloride). (Found: C, 73·38; H, 5·47; N, 3·70. $C_{22}H_{19}NO_4$ requires: C, 73·13; H, 5·26; N, 3·88%); Mass spectrum *m/e*: 361, 256, 212, 149, 105; IR cm^{-1} (nujol): 1690 (C=O), 1625 (amide C=O); NMR ($CDCl_3$): 3·69 (s, 3H): 6·0 (s, 1H), 6·68–8·25 (m, 15H).

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