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SYNTHESIS OF SUBSTITUTED β-LACTAMS

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Abstract—Two new methods for β-lactam formation from various systems (type I) where the activating influence on the methine hydrogen is by groups other than two ester functions have been developed and several new β-lactams synthesized. These compounds together with the various intermediates have been characterized by analysis and in most cases by IR spectra.

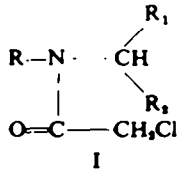
SEVERAL methods have been developed for the synthesis[1] of compounds containing the β-lactam moiety such as penicillins and cephalosporins.[2] The intramolecular alkylation of N-substituted α-chloracetamidomalonic esters[3] has been generally used.

A carbanion mechanism has been suggested for the intramolecular alkylation which can be brought about at room temperature in the presence of a weak base such as triethylamine, whereas, the intramolecular alkylation of an acetamidomalonic ester is carried out in the presence of a strong base such as sodium alkoxide.

It has been shown that the intramolecular alkylation of an α-haloacetamidomalonic ester can be effected by alcoholic potassium hydroxide in about 10 min and that saponification of the ester groups is not significant until the intramolecular alkylation is almost complete.

Two carbethoxy functions are necessary to activate the methine hydrogen for the intramolecular alkylation in the presence of triethylamine.[4] If the formation of a carbanion be a pre-requisite, the rate of intramolecular alkylation depends upon the rate of carbanion formation which in turn depends upon the activity of the electronegative groups attached to the methine carbon as well as on the strength of the base used.

Consequently, the intramolecular alkylation in compounds of the type I where the hydrogen under consideration is activated by groups other than two ester functions has been investigated in the presence of alcoholic potassium hydroxide.



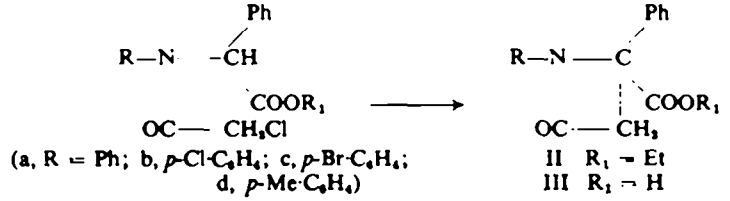
I

a R_1 = H; R_2 = COOEt
b R_1 = H; R_2 = Ph
c R_1 = Ph; R_2 = COOEt

[1] J. C. Sheehan and E. J. Corey, *Organic Reaction* (Edited by Roger Adams) Vol. IX, pp. 388. J. Wiley, New York, 1957.
[2] E. P. Abraham and G. G. F. Newton, *Biochem. J.* **58**, 103 (1954).
[3] J. C. Sheehan and A. K. Bose, *J. Amer. Chem. Soc.*, **73**, 1761 (1951).
[4] A. K. Bose, B. N. G. Mazumdar and B. G. Chatterjee, *J. Amer. Chem. Soc.* **82**, 3282 (1960).

When the activation is supplied by only an ester function or a phenyl substituent cyclization does not take place. It is interesting to note that (i) ethyl (N-*p*-chlorophenyl) α-chloracetamidoacetate (Ia) undergoes saponification at a faster rate at lower temperature than at 60° and that (ii) whereas no evidence of hydrogen chloride elimination was detected at room temperature or at 5°, the amide Ia eliminated hydrogen chloride to the extent of 30% at 60°.

Finally, compounds of the type Ic in which the activation is due to an ester group plus a phenyl substituent were prepared. These compounds Ic(R = Ph, *p*-Cl·C_6H_4, *p*-Br·C_6H_4 and *p*-CH_3·C_6H_4) undergo rapid cyclization in presence of potassium hydroxide. As in the malonic ester system, no product corresponding to a larger ring or linear polymerization could be isolated. The intramolecular alkylation is so fast compared to saponification that only high yields of β-lactams (II) were obtained on treatment of Ic with one equivalent of potassium hydroxide, but good yields of carboxy β-lactams (III) can be obtained if the amides (Ic) are allowed to stand overnight at room temperature with 2·2 moles of the base.



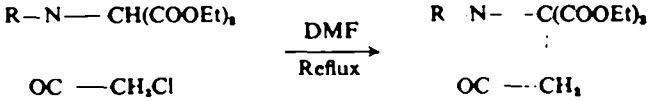
(a, R = Ph; b, *p*-Cl·C_6H_4; c, *p*-Br·C_6H_4; d, *p*-Me·C_6H_4)

II R_1 = Et
III R_1 = H

The β-lactams II and the acids III were characterized by IR spectra and elemental analysis.

The modified one-step operation developed[5] for the synthesis of β-lactams has been extended to the above systems with equal success and the products obtained were identical with authentic samples.

Since with the malonic ester system, the time required for the formation of β-lactams V in the presence of triethylamine is considerably reduced if the reaction is carried out at a higher temperature, the effect of temperature in the formation of β-lactams was investigated with various α-haloamides IV in dimethylformamide, the basicity of which is almost negligible and the b.p. is high (143–145°). The following β-lactams were prepared in almost quantitative yield by this method.



IV V

(a, R = Ph; b, *p*-Cl·C_6H_4; c, *p*-Br·C_6H_4; d, *p*-Me·C_6H_4; e, β-$C_{10}H_7$)

Similarly the amides Ic give high yields of the corresponding β-lactams on heating in dimethylformamide.

To further investigate whether temperature alone brought about the cyclization or whether a base was necessary for the removal of hydrogen halide, diethyl chloracetanilidomalonate was heated under reflux in toluene and xylene solutions for 6 hr without success. It was found that in the absence of a base, even in the presence of α-pinene which is a hydrogen chloride acceptor, no cyclization occurs.

When the amides Ia and Ib were similarly heated in dimethylformamide solution,

[5] B. G. Chatterjee, P. N. Moze and S. K. Roy, *J. Org. Chem.* **28**, 1418 (1963).

TABLE 1. SUBSTITUTED β-LACTAMS PREPARED BY ALCOHOLIC KOH METHOD[a]

Lactam	m.p.	Yield %	IR (μ) peaks	Formula	Found			Requires		
					C	H	N	C	H	N
IIIa	169–171°d	90[a]								
IIIb	181–182°d	80	5·65 5·85	$C_{16}H_{13}NO_3Cl$	63·60	4·65	3·97	63·68	3·98	4·64
IIIc	173–174°d	80	5·68 5·86	$C_{16}H_{13}NO_3Br$	55·01	3·96	3·94	55·49	3·46	4·04
IIId	193–194°d	89	5·72 5·90	$C_{17}H_{15}NO_3$	72·05	5·26	4·99	72·34	5·31	4·96

[a] Identical with an authentic sample.

hydrogen halide was eliminated to the extent of about 50% but the reaction products were intractable.

When the amides Ic or IV were heated with an equal weight of fused sodium acetate in an oil bath maintained at 140–150° for 1–3 hr, practically pure β-lactams were obtained in 90–95% yield.

This method, however, failed when the activating influence on the methine hydrogen is exercised by only a phenyl substituent or an ester group.

When N-benzylchloracetanilide (Ib) was heated with fused sodium acetate even to a temperature of 180°, no β-lactam was obtained. The solid reaction product (98%) was characterized by IR and NMR spectra and analysis as the open chain acetate.

Tables 1 and 2 summarize the β-lactams prepared by these methods.

TABLE 2. SUBSTITUTED β-LACTAMS PREPARED BY DIMETHYLFORMAMIDE AND FUSED SODIUM ACETATE METHODS

Lactam	m.p./n_D^{30}	Yield %
IIa	75–76°	90
IId	49–50°	90
Va	1·5161	98
Vb	1·5255	95–98
Vc	1·5390	95–97
Vd	88–90°	95–98
Ve	75–76°	95–98

EXPERIMENTAL[b]

N-(p-Chlorophenyl)glycine ester

A mixture of *p*-chloroaniline (12·8 g) and ethyl α-bromoacetate (8·4 g) in a round-bottomed flask fitted with a two-way stopcock and evacuated to 40 mm press was kept in an oven at 60–70° for 3 hr. The resulting solid cake was extracted with ether and filtered. The residue of *p*-chloroaniline hydrobromide (11 g) corresponded to 100% conversion. The filtrate was successively washed with 2N HCl and water, and dried ($MgSO_4$). Removal of the solvent afforded a pale yellow solid which recrystallized from a benzene–pet. ether (40–60°) mixture as yellow needles (9·0 g, 85%); m.p. 91–92°. IR: 2·85 μ (N—H stretching), 5·78 μ (ester CO). (Found C, 55·93; H, 5·52; N, 6·63. Calc. for $C_{10}H_{12}NO_2Cl$; C, 56·20; H, 5·62; N, 6·66%.)

[a] For other β-lactams prepared by this method and for the various intermediates, please refer to B. G. Chatterjee, V. Venkateswara Rao and B. N. Ghosh Mazumdar, *J. Org. Chem.* **30**, 4101 (1965).

[b] All m.ps are uncorrected.

Ethyl N-(p-*chlorophenyl*)-α-*chloracetamidoacetate* Ia

N-(*p*-chlorophenyl)glycine ester (5·0 g) and monochloroacetic acid (5·0 g) in dry benzene (75 ml) were heated under reflux with PCl_5 (2·5 ml) for 4 hr. The cooled benzene soln was decanted from the reaction mixture and washed thoroughly with water. The soln was dried (Na_2SO_4) and the solvent removed. The residue which solidified on scratching, recrystallized from ligroin as colourless crystals (6·0 g; 83%), m.p. 69–71°. IR: 5·75 μ (ester CO), 6·05 μ (open chain disubstituted amide function). (Found C, 49·65; H, 4·48; N, 4·80. Calc. for $C_{12}H_{13}NO_3Cl_2$: C, 49·65; H, 4·50; N, 4·82%.)

Attempted cyclization of ethyl N-(p-*chlorophenyl*)*chloracetamidoacetate*

To an EtOH soln of ethyl N-(*p*-chlorophenyl)chloracetamidoacetate (2·9 g) 10% alcoholic KOH (6·0 ml) was added and the mixture was allowed to stand at room temp. The shining crystalline material formed during ½ hr was removed by filtration and the filtrate acidified with glacial AcOH. The residue, on removal of the solvent, was taken up in benzene and washed with water. Removal of benzene afforded a gummy mass which could not be crystallized.

The shining crystalline material obtained above, was dissolved in water and acidified with dil. HNO_3. The oil that separated out solidified on scratching and was recrystallized from benzene (0·78 g; 30%), m.p. 135–137°.

The filtrate when treated with $AgNO_3$aq showed the presence of negligible amount of AgCl.

Since the acid could not be obtained analytically pure, methyl N-(*p*-chlorophenyl)chloracetamidoacetate was similarly prepared and saponified with alcoholic KOH. A comparison of the m.p. and mixture m.p. determination definitely established the acid as N-(*p*-chlorophenyl)chloracetamidoacetic acid.

N-*Benzylchloroacetanilide*(Ib)

This was obtained by chloracetylating benzylaniline (5·0 g) with monochloroacetic acid (5·0 g) and PCl_5 (2·5 ml) in dry benzene. The product on crystallization from benzene–pet. ether (40–60°) afforded colourless crystalline plates (5·7 g; 80%), m.p. 74–75°. IR: strong band at 6·0 μ (amide function).

Attempted cyclization of N-*benzylchloracetanilide*

An abs. EtOH soln of Ib (2·6 g) was treated with 10% alcoholic KOH (6·0 ml) at room temp. As there was no immediate separation of KCl the reaction mixture was allowed to stand for 12 hr before working up. The halide ion found was 30% based on AgCl. The viscous liquid residue afforded, after several extractions with pet. ether (60–80°), a few mg of a colourless solid, m.p. 52–53°. IR: 6·0 μ; halogen free.

A typical procedure for the synthesis of β-lactams II *and* III

(a) *Ethyl* α-(p-*chloroanilino*)*phenylacetate*. A mixture of *p*-chloroaniline (25·6 g) and ethyl α-bromophenylacetate (24·5 g) in a round-bottomed flask was evacuated to 40 mm press. After allowing the flask to stand at 60–70° in an oven for 8 hr the resulting solid cake was extracted with benzene and the *p*-chloroaniline hydrobromide (19·9 g; 95%) was filtered off. The filtrate after washing successively with 2N HCl and water was dried (Na_2SO_4). Removal of the solvent and crystallization of the crude material with benzene–pet. ether (40–60°) afforded colourless plates (27·5 g; 90%); m.p. 82–83°. IR: 2·85 μ (N—H band), 5·80 μ (ester CO). (Found C, 66·25; H, 5·65; N, 4·75. Calc. for $C_{16}H_{16}NO_3Cl$: C, 66·32; H, 5·52; N, 4·85%.)

(b) *Ethyl* N-(p-*chlorophenyl*) α-*chloracetamidophenylacetate* (Ic). This was obtained on chloracetylating ethyl α-(*p*-chloroanilino)-phenylacetate (5·0 g) with monochloroacetic acid (5·0 g) and PCl_5 (2·5 ml) in dry benzene. The product obtained on crystallization from benzene–pet. ether (40–60°) afforded colourless prisms (5·0 g; 82%); m.p. 76–77°. IR: 5·75 μ (ester CO), 5·95 μ (amide CO). This was found to be identical with an earlier sample.[6]

(c) 1-p-*Cholorophenyl*-4-*phenyl*-4′-*carbethoxyazetidin*-2-*one* (II). An EtOH soln of Ic (3·66 g) was treated with 10% alcoholic KOH (6·0 ml) and worked up after 15 min. The oily product obtained on evaporative distillation afforded a golden yellow liquid, η_D^{30} 1·5775, yield 80%. This was characterized after saponification.

(d) 1-p-*Chlorophenyl*-4-*phenyl*-4′-*carboxyazetidin*-2-*one* III. An EtOH soln of Ic (3·66 g) was

allowed to react with 10% alcoholic KOH (12·5 ml) for 12 hr. The acid obtained (2·45 g; 80%) was crystallized from acetone–benzene; m.p. 181–182° (dec). IR: 5·65 μ (β-lactam CO), 5·85 μ (carboxyl function). (Found C, 63·60; H, 4·65; N, 3·97. Calc. for $C_{16}H_{13}NO_3Cl$: C, 63·68; H, 3·98; N, 4·64%.)

A typical procedure for the one-step synthesis of the β-lactams II *and* III

1-p-*Tolyl-4-phenyl-4'-carbethoxyazetidin-2-one* (II). A mixture of 2·7 g of ethyl α-(*p*-toluidino)-phenylacetate and 1 ml of chloroacetyl chloride was heated for 4–5 min at 80° and then treated with 10 ml of abs. EtOH. After cooling the reaction mixture to room temp it was treated with 10% alcoholic KOH (15 ml) and was kept at room temp for 15 min. The reaction mixture was worked up in the usual way and the product obtained was crystallized from ligroin to afford 2·5 g (81%) of colourless prisms; m.p. 49–51°. The compd was identical with an authentic sample.

1-p-*Tolyl-4-phenyl-4'-carboxyazetidin-2-one* (III). After reacting 2·7 g of ethyl α-(*p*-toluidino) phenylacetate with 1 ml of chloroacetyl chloride for 5 min at 80° the mixture was first treated with 10 ml EtOH and then with 10% alcoholic KOH (21 ml) and kept at room temp (overnight). The reaction mixture was worked up in the usual way and the acid obtained (2·3 g; 81%) was crystallized from a mixture of benzene and acetone; m.p. 193–194° (dec). The compd was identical with an authentic sample.

Typical procedures for the synthesis of β-lactams using (a) *dimethylformamide and* (b) *fused* AcOH

(a) 1-p-*Tolyl-4, 4'-dicarbethoxyazetidin-2-one* V. A soln of 3·42 g of diethyl N-(*p*-tolyl)chloracetamidomalonate in 20 ml dimethylformamide was refluxed for 3 hr. The solvent was removed under red. press. and the residue taken up in benzene. The benzene soln was washed thrice with water. The combined aqueous washings on treatment with $AgNO_3$ after acidification with HNO_3 yielded 1·4 g (99%) of AgCl. The benzene soln was dried (Na_2SO_4), and the solvent distilled off. The crude product on crystallization from cyclohexane afforded colourless crystals; m.p. 88–90°. The compd was identical with an authentic sample.

(b) 1-*β-Naphthyl-4, 4'-dicarbethoxyazetidin-2-one* (V). An intimate mixture of diethyl N-(β-naphthyl) chloracetamidomalonate (1·9 g) and fused AcONa was heated at 140–145° in an oil bath for 1 hr. The reaction mixture was then poured into a large volume of distilled water. The product was collected by filtration and dried. The crude material (1·66 g; 98%) was crystallized from benzene–pet. ether (60–80°); m.p. 75–76°. IR: 5·65 μ (β-lactam), 5·75 μ (ester function). The compd was identical with an authentic sample.

Attempted cyclization of N-*benzylchloracetanilide* (Ib) *with* AcONa: *Isolation of* N-*benzyl-α-acetoxy-acetanilide*

A mixture of N-benzylchloracetanilide (2·6 g) and fused AcONa (2·6 g) was heated in an oil bath at 180° for 3 hr. The reaction mixture worked up in the above way when a colourless crystalline material was obtained. Crystallization of the product from benzene–pet. ether (60–80°) yielded colourless plates; m.p. 92–93°. IR: 5·75 μ (ester CO), 6·0 μ (amide CO). (Found C, 72·72; H, 6·39; N, 4·87. Calc. for $C_{17}H_{17}NO_3$: C, 72·08; H, 6·00; N, 4·59%.)

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