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SOME DERIVATIVES OF β-LACTAMS

B. G. CHATTERJEE, V. VENKATESWARA RAO and P. N. MOZA
Department of Applied Chemistry, Indian Institute of Technology, Kharagpur, India

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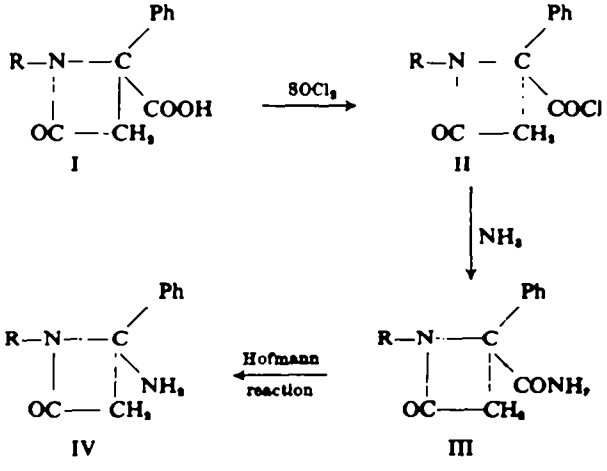
Abstract—Twelve new derivatives of β-lactams such as carboxamides salicylates, ureas and thioureas have been synthesized and characterized by analysis and IR or NMR spectra. It has been observed that sodium azide can bring about intramolecular alkylation of N-substituted α-haloacetamidomalonates.

SINCE penicillins and cephalosporins contain an acylamino group in position 3 of the β-lactam moiety, it was hoped that if 3-acylamino-β-lactams would be synthesized, they would possess antibacterial activity.

When 1-phenyl-3-chloro-4,4′-dicarbethoxyazetidin-2-one was reacted with sodium azide for a prolonged period, the product could not be obtained halogen free though the eliminated sodium chloride amounted to 70%.

ω-Chloro-ω′-azidoacetanilidomalonate was prepared by reacting diethyl-dichloroacetanilidomalonate with sodium azide at room temp but this did not cyclize when treated with alcoholic potassium hydroxide. At higher temp, sodium azide can bring about intramolecular alkylation of α-haloacetamidomalonates and this was verified by synthesizing a number of 1-aryl-4,4′-dicarbethoxyazetidin-2-ones in high yields from various α-haloamides by heating them with sodium azide in ethanol. These lactams were identical with authentic samples.[1]

Since all attempts to synthesize 3-amino-β-lactams failed, it was decided to concentrate on preparing 4-amino β-lactams by exploiting the carboxy group in β-lactams of type I.

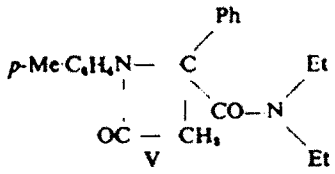


(a, R = *p*-Me·C₆H₄; b, *p*-Cl·C₆H₄)

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

Although the amides III were obtained in good yields, their conversion to the corresponding amino compounds IV by way of Hofmann reaction failed even when special conditions[2] for such a reaction were used.

Incidentally the β-lactam V was prepared and this was characterized by analysis, IR and NMR spectra.



The unsplit peak showing two protons at 6·43 τ can be easily attributed to the ring methylene protons.

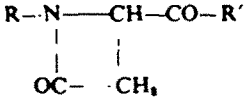
The four protons, two at 6·5 τ and two at 7·0 τ, are attributed to four methylene protons of the diethylamino group from the position as well as the splitting pattern.

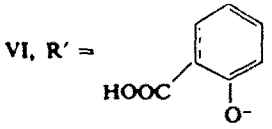
The six protons at 8·85 τ have been, for similar reasons, attributed to 6 methyl protons of the diethylamino group.

The single peak at 7·82 τ is attributed to the protons of the methyl group attached to aromatic nucleus.

Taking into consideration the above protons together with the aromatic protons at the usual place, we find that the NMR spectrum is consistent with the structure V.

As the azetidin-2-one-4-carbonyl chlorides can be easily prepared, it was thought of interest to utilize them for the synthesis of the compounds of the type VI, VII and VIII, since the salicylates,[3,4] and urea[5] and the β-lactam derivatives[6-8] are known to be physiologically active.





VII, R′ = —NH—CO—NH$_2$

VIII, R′ = —NH—CS—NH$_2$

(a, R = Ph; b, p-Cl-C$_6$H$_4$; c, p-Br-C$_6$H$_4$)

Salicylates VI were obtained in about 60% yield based on the acid chlorides. While the IR spectra of the acid chlorides had two peaks in the double bond region

[3] *Organic Reactions* (Edited by R. Adams) Vol. p. 267. J. Wiley, New York (1947).
[4] H. Dreser, *Pflugers Arch. ges. Physiol.* **76**, 306 (1899).
[5] J. Lehman, *Lancet*, **250**, 14 (1946).
[6] A. Burger, *Medicinal Chemistry* p. 371 Interscience (1960).
[7] Clarke, Johnson and Robinson, *The Chemistry of Penicillin*. Princeton Univ. Press, Princeton, New Jersey (1947).
[8] E. P. Abraham and G. G. F. Newton, *Biochem. J.* **58**, 103 (1954).
[9] E. Testa, L. Fontenella, G. F. Cristiani and F. Fava, *Liebigs, Ann.* **614**, 158 (1958).

(5·65 acyl CO; 5·75 β-lactam CO), the corresponding salicylates had an additional peak at 5·90 μ, evidently due to the CO of the carboxy function.

The three acyl ureas VII and the three acyl thioureas VIII have been characterized by analysis. As the IR spectra of urea and thiourea are complex, only some of the structural features have been correlated with the observed peaks, e.g., the N—H band at about 2·80 μ, β-lactam CO at 5·75 μ and the amide or the thioamide peak at 6·0 μ.

All the intermediates for the synthesis of the acid chlorides have already been reported.[9]

Table 1 summarizes the properties of the final products (VI, VII and VIII).

TABLE 1. SALICYLATES, UREA AND THIOUREA DERIVATIVES OF β-LACTAMS

Lactams	Crystallized from:	m.p.°	Found			Requires		
			C	H	N	C	H	N
VIa	Benzene	181–182	65·73	4·51	4·35	65·59	4·18	4·50
VIb	Benzene	168–169	59·32	3·72	4·38	59·04	3·47	4·05
VIc	Benzene	175–176	52·11	3·25	3·41	52·30	3·07	3·59
VIIa	EtOH–Acetone	245–247d	56·98	5·01	18·09	56·65	4·72	18·02
VIIb	EtOH-Acetone	245d	49·65	4·12	15·87	49·34	3·73	15·70
VIIc	EtOH-Acetone	243–244d	42·09	3·62	13·29	42·30	3·20	13·46
VIIIa	EtOH-Acetone	204d	53·37	4·81	17·02	53·01	4·41	16·86
VIIIb	EtOH-Acetone	212d	46·34	3·71	14·98	46·56	3·52	14·81
VIIIc	EtOH-Acetone	201d	40·51	3·37	12·65	40·24	3·04	12·80

EXPERIMENTAL[10]

Diethyl dichloroacetanilidomalonate

A mixture of diethyl anilomalonate (5·0 g), dichloroacetic acid (5·0 g) and PCl_5 (2·5 ml) in dry benzene (75 ml) was refluxed for 4 hr. The reaction mixture was worked up in the usual way and the product obtained (6·5 g, 91%) was crystallized from benzene–pet. ether (60–80°); m.p. 93–94°. IR: 5·75 μ (ester CO) and 5·95 μ (amide CO). (Found: N, 3·78. $C_{14}H_{17}NO_5Cl_2$ requires: N, 3·86%.)

Reaction with sodium azide

(a) *At reflux temp in* EtOH *soln.* When an EtOH soln of the above amide (3·62 g) was heated under reflux with NaN_3 (0·65 g) for 3 hr., the precipitated NaCl amounted to 97% of the theoretical value (based on AgCl). The reaction mixture was worked up in the usual way and the product obtained was a viscous liquid. The IR: 4·60 μ (azide function), 5·60 μ (β-lactam) and 5·70 μ (ester function), suggesting that cyclization had taken place in addition to the displacement reaction.

(b) *At room temp in* EtOH *soln.* An EtOH soln of the amide (1·81 g) and NaN_3 (0·33 g) was stirred for 6 hr by means of a magnetic stirrer at room temp. The product (1·65 g, 80%) obtained after working up the reaction mixture in the usual way was identified to be diethyl ω-chloro-ω'-azidoacetanilidomalonate by its IR spectrum: 4·60 μ (azide); 5·65 μ (ester function) and 5·90 μ (amide function). n_D^{20} 1·5178.

Attempted cyclization of diethyl ω-chloro-ω'-azido-acetanilidomalonate

Diethyl ω-chloro-ω'-azidoacetanilidomalonate (1·60 g) was dissolved in EtOH and 10% alcoholic KOH (3ml) was added. There was no precipitation of KCl even after allowing the reaction mixture to stand at room temp for ½ hr. The starting material was recovered almost quantitatively from the reaction mixture.

[9] B. G. Chatterjee and P. M. Moza, *J. Med. Chem.* **9**, 259 (1966).
[10] All m.ps are uncorrected.

1-Phenyl-3-chloro-4 4'-dicarbethoxyazetidin-2-one

An EtOH soln of diethyl dichloroacetanilidomalonate (3·62 g) was treated with 10% alcoholic KOH (6·0 ml) and the mixture was allowed to stand at room temp for 15 min. The product was worked up in the usual way. The viscous liquid on evaporative distillation afforded 2·6 g (83%) of a golden yellow liquid; n_D^{30} 1·5206 which agreed well with that of an authentic sample.

Reaction between 1-phenyl-3-chloro-4-4'-dicarbethoxyazetidin-2-one and sodium azide

To an EtOH solution of the above β-lactam (2·5 g) 0·5 g of NaN_3 was added and the mixture was refluxed for 6 hr on a steam bath. The viscous liquid residue obtained on working up the reaction mixture showed IR absorption peaks at 4·60 μ (azide group), 5·62 μ (β-lactam CO) and 5·75 μ (ester CO). The precipitated NaCl amounted to 0·74 g (70%). The product was not halogen free.

Intramolecular alkylation with NaN_3: *1-p-Tolyl-4,4'-dicarbethoxyazetidin-2-one*

An alcoholic solution of diethyl N-(*p*-tolyl)-chloracetamidomalonate (2·0 g) was heated under reflux with NaN_3 (0·41 g) for 3 hr. The reaction mixture was worked up in the usual way and the β-lactam crystallized from cyclohexane; m.p. 87–89°. The comp was identical with an authentic sample.

1-β-Naphthyl-4,4'-dicarbethoxyazetidin-2-one

This was obtained in a similar way from diethyl N-(β-naphthyl)chloracetamidomalonate (1·60 g) and NaN_3 (0·27 g). The product was crystallized from benzene–pet. ether (40–60°); m.p. 76–77°.

1-p-Tolyl-4-phenyl-4'-aminoazetidin-2-one (IVa)

(a) *1-p-Tolyl-4-phenylazetidin-2-one-4'-carbonyl-chloride* (IIa). A dry benzene soln of 2·3 g IVa was refluxed with freshly distilled $SOCl_2$ (2·5 ml) for 4 hr. The reaction mixture was worked up in the usual way and the acid chloride directly used for the next step.

(b) *1-p-Tolyl-4-phenyl-4'-carboxamidoazetidin-3-one* (IIIa). An ice cold soln of ammonia (sp.gr. 0·88, 5 ml) was gradually added to 2·0 g of the above acid chloride maintained at 0° in an ice bath. Care was taken not to allow the reaction temp to rise above 5°. The reaction mixture was allowed to stand for ½ hr and the product (1·9 g–99%) was collected by filtration. Recrystallization of the material from benzene–acetone afforded colourless prisms; m.p. 229–230°. IR: 2·86 μ (N—H bond), 5·65 μ (β-lactam CO) and 6·0 μ (amide function). (Found: C, 72·85; H, 5·71; N, 9·99. $C_{17}H_{16}N_2O_2$ requires: C, 72·01; H, 5·80; N, 9·85%.)

(c) *Attempted synthesis of 1-p-tolyl-4-phenyl-4'-aminoazetidin-2-one* (IVa). A soln of hypobromite was prepared at 0° by adding 0·5 ml of bromine to a NaOH soln (1·8 g in 20 ml of water). The amide (1·9 g) in a finely divided form was added and the mixture stirred at 0° for about 2 hr. The temp of the reaction mixture was then gradually raised and finally maintained at 70–75° for 15 min. On cooling the clear soln in an ice bath, the entire unchanged starting material crystallized out.

1-p-Chlorophenyl-4-phenyl-4'-carboxamidoazetidin-2-one (IIIb)

This was obtained when 1·0 g of 1-*p*-chlorophenyl-4-phenylazetidin-2-one-4'-carbonyl-chloride was treated with ammonia (5 ml). The crude product (0·9 g, 90%) was crystallized from chf.–benzene; m.p. 257–258°. IR: 2·88 μ (N—H bond), 5·68 μ (β-lactam) and 5·95 μ (amide CO). (Found: C 63·64; H, 4·31; N, 9·28. $C_{16}H_{13}N_2O_2Cl$ requires: C, 63·61; H, 4·92; N, 8·52%.)

1-p-Tolyl-4-phenyl-4'-N-(diethyl)carboxamidoazetidin-2-one (V)

This was obtained when the acid chloride IIa (1·2 g) was treated with 0·5 ml diethylamine in an ice bath. The crude product was crystallized from benzene–pet. ether (60–80°); m.p. 167–168°. IR: 5·65 μ (β-lactam) and 6·0 μ (amide function). (Found: C, 73·07; H, 7·69; N, 8·86. $C_{19}H_{24}O_2N_2$ requires; C, 73·88; H, 7·65; N, 8·12%.)

A typical procedure for the synthesis of VI, VII and VIII

1-p-Chlorophenylazetidin-2-one-4-carbonyl-chloride (A). A benzene soln of 2·0 g 1-*p*-chlorophenyl-4-carboxyazetidin-2-one was refluxed with 1·5 ml freshly distilled $SOCl_2$ for 4 hr. Excess of $SOCl_2$ was removed by repeated distillation with fresh quantities of dry benzene each time. Removal of the

solvent and crystallization of the crude material (2·0 g; 94%) from pet. ether (60–80°) afforded colourless needles; m.p. 102–104°. IR: 5·65 μ (β-lactam) and 5·75 μ (CO·Cl).

(A small portion (0·1 g) of this acid chloride was hydrolysed by alcoholic KOH (0·5 ml; 10%). The acid obtained melted at 143–144°. This was found to be identical with an authentic sample.)

1-p-*Chlorophenyl-4-(2'-carboxy) carbophenoxyazetidin-2-one* (VIb). A soln of A (0·43 g) and 0·25 g salicyclic acid in dry benzene was refluxed for 2 hr. On cooling the reaction mixture a white crystalline material settled down. This was removed by filtration and the filtrate evaporated. The crude material (0·35 g; 57%) on crystallization from benzene afforded colourless crystals, m.p. 168–169°). IR: 5·70 μ (β-lactam), 5·75 μ (ester CO) and 5·90 μ (carboxy function). (Found: C, 59·32; H, 3·72; N, 4·38. $C_{17}H_{12}NO_4Cl$ requires: C, 59·04; H, 3·47; N, 4·08%.)

1-p-*Chlorophenylazetidin-2-one-4-carbonyl urea* (VIIb). 0·32 g A was refluxed with 80 mg urea in dry benzene soln for 2 hr. The reaction mixture was left overnight at room temp. The white crystalline material obtained (0·2 g; 54%) was crystallized from acetone-EtOH; m.p. 245° (dec.) IR: 3·0 μ, 5·78 μ and 6·0 μ respectively for N—H, β-lactam and amide functions. (Found: C, 49·65; H, 4·12; N, 15·87. $C_{11}H_{10}N_3O_3Cl$ requires: C, 49·34; H, 3·73; N, 15·71%.)

1-p-*Chlorophenylazetidin-2-one-4-carbonyl thiourea* (VIIIb). 0·3 g A was refluxed with 0·1 g of thiourea in dry benzene soln for 2 hr. The reaction mixture was kept overnight at room temp. The solid that separated out was removed and the filtrate concentrated. The total solid material (0·23 g; 60·5%) was crystallized from acetone-EtOH; m.p. 212°(dec). IR spectrum showed the presence of β-lactam ring. (Found: C, 46·34; H, 3·71; N, 14·98. $C_{11}H_{10}N_3O_2SCl$ requires: C, 46·56; H, 3·52; N, 14·68%.)

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