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SYNTHESIS OF SUBSTITUTED β- AND γ-LACTAMS

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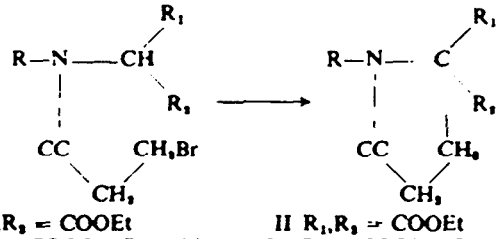
Abstract—The synthesis of substituted β-lactams has been successfully extended to substituted γ-lactams. Two new β-lactams have been obtained from a system where CO·Ph group alone supplies activation for the intramolecular alkylation. The β- and γ-lactams and the intermediates have been characterized by analysis and IR or NMR spectra.

The method employed for β-lactams[2] has been extended[3] to the synthesis of γ-lactams.

The N-substituted ω-bromopropionamidomalonates (I) can be cyclized to the corresponding γ-lactams (II) in a much shorter time if alcoholic potassium hydroxide is used instead of triethylamine. Even the amides III, which resists cyclization with



I R_1,R_2 = COOEt
III R_1 = COOEt; R_2 = Ph

II R_1,R_2 = COOEt
IV R_1 = COOEt; R_2 = Ph
V R_1 = COOEt; R_2 = COOH

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

triethylamine, are converted to the corresponding γ-lactams IV in high yields. This suggests that if the activating influence on the methine hydrogen is reduced, a stronger base is required.

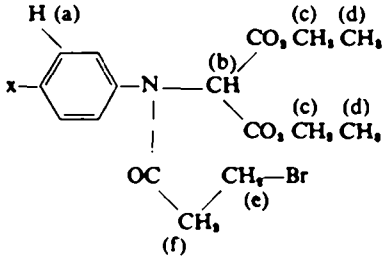
The rate of saponification becomes significant only after the amides I and III have been converted to the corresponding γ-lactams II and IV. These are obtained in high yields when equimolar proportions of the reactants are used, but in the presence of 2·2 moles alcholic potassium hydroxide, the corresponding γ-lactam acids V are obtained in good yield.

Reaction of the amides III with 2·2 moles alcoholic potassium hydroxide resulted in viscous liquids which could not be purified.

The intermediate amides of the type I and III, obtained from the various amino esters,[4] show in the IR spectra two distinct bands in the double bond region; one at 5·70 to 5·75 μ due to ester CO and the other at about 6·0 μ due to the CO of the open chain

[1] Synthesis of substituted β-lactams, B. G. Chatterjee and V. Venkateswara Rao, *Tetrahedron* **23**, 487 (1967).
[2] J. C. Sheehan and A. K. Bose, *J. Amer. Chem. Soc.* **72**, 5158 (1950).
[3] A. K. Bose, B. N. Ghoshmazumdar and B. G. Chatterjee, *J. Amer. Chem. Soc.* **82**, 3282 (1960).
[4] A. K. Bose, *J. Ind. Chem. Soc.* **31**, 108 (1954).

disubstituted amide function. The NMR spectra show the following pattern: four protons (a) at 2·55 τ (aromatic); one proton (b) at 4·49 τ (methine H); 4 protons (5·64, 5·75, 5·86 and 5·99 τ—the methylene protons (c) split by CH_3 (a)) two protons (6·30, 6·42 and 6·54 τ—the β-methylene protons (e) split by α-methylene protons (f)); 2 protons (7·15, 7·30 and 7·44 τ—the α-methylene protons (f) split by β-methylene protons (e); and 6 protons (8·67, 8·78 and 8·90 τ—the methyl protons (d) split by the methylene protons (c)). The IR and NMR spectra are, therefore, compatible with the formulation of the amide as:



Incidentally, compounds Ia and Id were reported earlier.[3]

The four γ-lactams (IIa–d) of the malonic ester system are liquids and after saponification to the acids (Va–d) were characterized by (i) IR spectra, (ii) m.m.p. determination with samples of the acids obtained on saponification of γ-lactams II prepared by the triethylamine method and (iii) by analysis.

The IR spectra of these γ-lactam acids show peaks at 5·70 to 5·75 μ (γ-lactam CO) and 5·80 to 5·85 μ (carboxyl function). The absence of a peak at 6·0 μ indicates that the ring remains intact during saponification.

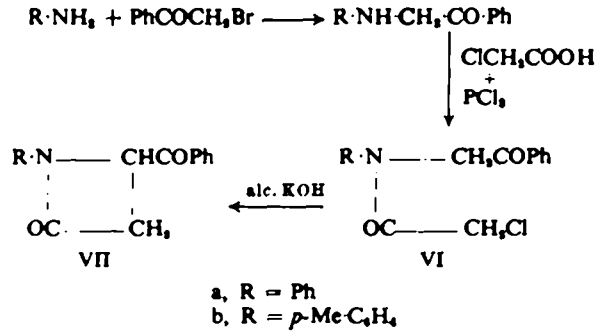
The γ-lactams IVa and IVc of the phenylacetic acid system were characterized by IR spectra and analysis. These lactams show absorption at 5·75 μ and 5·80 μ due to ester and lactam CO respectively.

The modified one-step operation for the synthesis of β-lactams[5] was applied to the synthesis of γ-lactams with equal success and the products were identical with authentic samples.

Dimethylformamide and fused sodium acetate used for the cyclization of N-substituted α-haloacetamidomalonic esters[1] were found equally effective for the cyclization of their homologues to the corresponding γ-lactams. Only two compounds, one from each set of amides I and III were cyclized and the γ-lactams obtained were identical with those prepared by other methods.

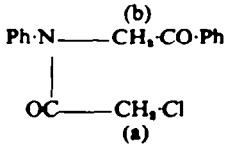
It has been observed[1,3] that if a single electronegative group is attached to the methine carbon no cyclization takes place. The acidity of the C—H bond in active methylene compounds is attributed to a combination of the inductive electron-withdrawing ability of the unsaturated substituent and the ability of these substituents to delocalize the negative charge after a proton has been removed. The effectiveness of a CO function as an activating group is much greater than an ester function or a phenyl substituent. It was, therefore, thought of interest to examine whether the CO·Ph group alone induces sufficient activation for the cyclization or not. Two amides VI were prepared as follows:

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



These amides undergo facile ring closure when treated with alcoholic potassium hydroxide. This system, however, fails to give the β-lactams VII in presence of triethylamine.

The intermediates VI and the β-lactams VII have been characterized by analysis, IR and NMR spectra. The IR spectra of the amides VI show peaks at 5·80 μ (ketonic CO) and 6·0 μ (amide CO). The NMR spectrum of VIa shows a peak at 6·02 τ (methylene protons a) and another at 4·85 τ (methylene protons b) in addition to the peaks due to aromatic protons. The IR and NMR spectra are consistent with the formulation of the amide VIa as:



The IR spectra of β-lactams VII show peaks at 5·70 μ (β-lactam CO) and 5·88 μ (ketonic CO). The NMR spectrum of VIIa shows two quadruplets (7·23, 7·16, 6·99, 6·93 τ and 6·70, 6·60, 6·45 and 6·35 τ) due to ring methylene protons and a quadruplet (4·70, 4·65, 4·60 and 4·55 τ) due to ring methine proton in addition to ten aromatic protons in the usual place.

These data establish that COPh group alone can supply enough activation for the cyclization of amides VI to the β-lactams VII in the presence of alcoholic potassium hydroxide.

Table 1 gives the properties of the amides III and Table 2 of the γ-lactams prepared by alcoholic potassium hydroxide method.

EXPERIMENTAL[a]

A typical procedure for the synthesis of γ-lactams II *and* V

1-Phenyl-5,5'-dicarbethoxy-pyrrolidin-2-one (II). To diethyl ω-bromopropionanilidomalonate (1·93 g) dissolved in EtOH, 10% alcoholic KOH (3·0 ml) was added. There was immediate separation of KBr (0·53 g; 90%) which was removed by filtration. The filtrate was neutralized with glacial AcOH and the solvent removed under red. press. The residue in benzene was washed with water and the soln was stripped after drying (Na_2SO_4). Evaporative distillation afforded a golden yellow liquid (0·97 g; 85%) n_D^{25} 1·5135. This refractive index agrees well with that of an authentic sample. The compd was further characterized after saponification.

1-Phenyl-5-carbethoxy-5'-carboxy pyrrolidin-2-one (V). Diethyl ω-bromopropionanilidomalonate (1·93 g) was dissolved in EtOH (15 ml) and 10% alcoholic KOH (6·0 ml) was added. The potassium

[a] All m.ps are uncorrected.

TABLE 1. PROPERTIES OF THE AMIDES OF TYPE III

Amide	M.p. (°C)	IR peaks (μ)	Formula	Found C	Found H	Found N	Requires C	Requires H	Requires N	Yield %
IIIa	94–95	5·75, 6·0	$C_{19}H_{20}NO_3Br$	58·71	5·19	3·30	58·46	5·12	3·58	80
IIIb	72–73	5·75, 6·0	$C_{19}H_{19}NO_3BrCl$	53·57	4·66	2·78	53·71	4·47	3·29	75
IIIc	92–93	5·70, 5·95	$C_{19}H_{19}NO_3Br_2$			2·61			2·99	75
IIId	51–52	5·75, 6·0	$C_{20}H_{23}NO_3Br$	58·84	5·58	3·13	59·65	5·44	3·46	78

salt precipitated by the addition of ether was taken up in water and acidified with dil HNO_3, yielding an oily substance. This was taken up in ether and washed with water and dried ($MgSO_4$). Removal of the solvent and crystallization of the product from benzene–pet. ether (40–60°) afforded colourless needles; m.p. 150–151°. IR: 5·75 μ (lactam CO) and 5·85 μ (carboxy function). The product was identical with an authentic sample.

A typical procedure for the synthesis of γ-lactams IV

(a) *Ethyl α-(ω-bromopropionanilido)phenylacetate* (IIIa). A mixture of ethyl α-anilinophenylacetate (5·0 g) and β-bromopropionic acid (5·0 g) was refluxed in dry benzene with PCl_3 (2·5 ml) for 4 hr. The benzene soln was washed thoroughly with water and dried (Na_2SO_4). The crude material (5 g, 85%) was crystallized from benzene–pet. ether (40–60°); m.p. 94–95° IR: 5·75 μ (ester CO) and 6·0 μ (amide function). (Found C, 58·71; H, 5·19; N, 3·30; $C_{19}H_{20}NO_3Br$ requires, C, 58·46; H, 5·12; N, 3·58%.)

(b) *1,5-Diphenyl-5'-carbethoxypyrrolidin-2-one* (IV). To an EtOH soln of 1·95 g of the above amide, 10% alcoholic KOH (3·0 ml) was added at room temp. The precipitated KBr was removed by filtration after 15 min and the solvent was removed under red. press. after acidification with glacial AcOH. The crude product (1·2 g; 85%) was crystallized from benzene–pet. ether (40–60°); m.p.

TABLE 2. SUBSTITUTED γ-LACTAMS PREPARED BY ALCOHOLIC KOH METHOD

Lactams	m.p./η_D^{30}	IR peaks (μ)	Yield %
IIa	1·5135		85[a]
Va	150–151°	5·75; 5·85	80[a]
IIb	1·5215		90[b]
Vb	170–171°[d]	5·69; 5·79	86[e]
IIc	1·5410		84[b]
Vc	183–185°[d]	5·77; 5·85	80[d]
IId	1·5245		80[b]
Vd	168–169°[d]	5·70; 5·75	80[e]
IVa	68–69°	5·75; 5·80	85[f]
IVb	Visc. liquid		80
IVc	65–66°	5·78; 5·80	80[g]
IVd	1·5578		80

[a] Known compound (Ref. 4).

[b] Characterized after saponification.

[c] Found C, 53·73; H, 4·59; N, 4·01; $C_{14}H_{14}NO_3Cl$ requires C, 53·61; H, 4·49; N, 4·49%.

[d] Found C, 46·42; Hm 4·14; Nm 3·61; $C_{14}H_{14}NO_3Br$ requires C, 47·19; H, 3·92; N, 3·92%.

[e] Found C, 61·19; H, 5·77; N, 5·19; $C_{18}H_{17}NO_3$ requires C, 61·85; H, 5·88; N, 4·81%.

[f] Found C, 73·82; H, 6·56; N, 4·25; $C_{19}H_{19}NO_3$ requires C, 73·78; H, 6·14; N, 4·53%.

[g] Found N, 3·70; $C_{19}H_{18}NO_3Br$ requires N, 3·60%.

68–69°. IR: 5·75 μ (ester) and 5·80 μ (γ-lactam CO). (Found C, 73·82; H, 6·56; N, 4·25: $C_{19}H_{19}NO_3$ requires C, 73·78; H, 6·14; N, 4·53%.)

A typical procedure for the one-step synthesis of γ-lactams II *and* V

1-*Phenyl-5,5'-dicarbethoxypyrrolidin-2-one* (II). A mixture of diethylanilinomalonate (2·51 g) and β-bromopropionyl chloride (1·5 ml) was heated at 80° for 5 min. About 10–15 ml of EtOH was then added and the soln cooled to room temp. The precipitate obtained on addition of 10% alcoholic KOH (15 ml) at room temp was removed by filtration after 15 min. On working up the reaction mixture in the usual way, the product was obtained as a viscous liquid which on evaporative distillation afforded a golden yellow liquid, n_D^{30} 1·5135. This was found to be identical with an authentic sample.

1-*Phenyl-5-carbethoxy-5'-carboxypyrrolidin-2-one* (V). After reacting 2·51 g of diethyl anilinomalonate with 1·5 ml of β-bromopropionylchloride for 5 min at 80°, the reaction mixture was first treated with 15 ml of EtOH and then with 10% alcoholic KOH (22 ml) for 1½ hr at room temp. The reaction mixture was worked up in the usual way and the product obtained (2·2 g; 80%) crystallized from benzene–pet. ether (40–60°); m.p. 150–151° (dec). The compd was identical with an authentic sample.

A typical procedure for the synthesis of γ-lactams using (a) *dimethylformamide and* (b) *fused* AcONa: 1-p-*Chlorophenyl-5,5'-dicarbethoxypyrrolidin-2-one* (IIb)

(a) *Using dimethylformamide*. A soln of 2·10 g of the amide Ib in 15 ml of dimethylformamide was refluxed for 3 hr. The solvent was removed under red. press. and the residue was 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, gave 0·88 g (95%) of AgBr. The benzene soln was distilled off to yield 1·52 g (90%) of a pale brown viscous liquid. The compd was characterized after saponification.

(b) *Using fused* AcONa. An intimate mixture of 2·1 g of the amide Ib and 2·1 g of AcONa was heated in a small round-bottomed flask fitted with an air condenser in an oil bath maintained at 145–150° for 1 hr. The reaction mixture was then poured into a large volume of water and the product was isolated by extraction with benzene. Removal of benzene afforded the γ-lactam which was characterized after saponification.

Anilinoacetophenone

A mixture of 10·0 g of phenacyl bromide and 10·0 g of aniline was taken in a 250-ml round-bottomed flask fitted with a two-way stopcock. The flask was kept in an ice bath and the inside pressure was gradually reduced to 20 mm, when the reaction started. The inside temp was not allowed to rise above 5°. A solid cake was obtained within about 20 min which was crushed and then extracted with ether. The aniline hydrobromide (8·4 g, 95%) was removed by filtration. The ether soln was washed with 2N HCl and finally with water. After drying ($MgSO_4$), the solvent was removed under red. press. The crude product (7·6 g, 85%) was recrystallized from ligroin; m.p. 89–90°. (Found: N, 6·70; $C_{14}H_{13}NO$ requires: N, 6·63%.)

N-*Phenyl-chloracetamidoacetophenone* (VIa)

This was obtained by treating the anilinoacetophenone (5·0 g) with monochloroacetic acid (5·0 g) and PCl_3 (2·5 ml) in the usual way. The crude material was recrystallized from ligroin (4·3 g, 63%), m.p. 114–115°. IR: a broad shoulder between 5·83 μ (ketonic CO) and 6·0 μ (amide CO). (Found: N, 4·95; $C_{16}H_{14}NO_2Cl$ requires: N, 4·87%.)

1-*Phenyl-4-benzoyl-azetidin-2-one* (VIIa)

To a soln of the above amide (2·5 g) in EtOH (15 ml), 10% alcoholic KOH (6·0 ml) was added. The reaction mixture was worked up in the usual way and the product crystallized from ligroin (1·5 g, 80%), m.p. 145–146°. IR: peaks at 5·70 μ (β-lactam CO) and 5·88 μ (ketonic CO). (Found: N, 5·50; $C_{16}H_{13}NO_2$ requires: N, 5·58%.)

p-*Toluidinoacetophenone*

This aminoketone was obtained on reacting 11·0 g of p-toluidine with 8·0 g of phenacyl chloride in the way described above. The crude product (7·3 g, 70%) was crystallized from ligroin; m.p. 121–123°. (Found: N, 6·20; $C_{15}H_{15}NO$ requires: N, 6·22%.)

N-(p-*Tolyl*)-*chloracetamidoacetophenone* (VIb)

The above aminoketone (5·0 g) when chloracetylated with 5·0 g of monochloroacetic acid and 2·5 ml of PCl_3 yielded the product as pink crystals (4·6 g, 70%). It was recrystallized from ligroin, m.p. 111–112°. IR: 5·83 μ (ketonic CO) and 5·95 μ (amide CO). (Found: N, 4·71. $C_{17}H_{16}NO_2Cl$ requires: N, 4·65%.)

1-p-*Tolyl*-4-*benzoyl*-*azetidin*-2-*one* (VIIb)

An EtOH soln of the above amide (2·75 g) was treated with 10% alcoholic KOH (6·0 ml) and the reaction mixture was worked up in the usual way after 15 min. The crude product (1·78 g, 75%), on recrystallization from ligroin, yielded colourless needles, m.p. 174–175°. IR: 5·70 μ (β-lactam CO) and 5·88 μ (ketonic CO). (Found: N, 4·20. $C_{17}H_{15}NO_2$ requires: N, 4·27%.)

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