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CYCLIZATION REACTIONS OF N-CARBAMOYL AND N-ACYL DERIVATIVES OF DL-HOMOSERINE

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Abstract—α-Carbamoylamino-γ-butyrolactone was synthesized and transformed into 5-(β-hydroxyethyl)- and 5-(β-bromoethyl)hydantoins. N-Carbamoyl- and N-acylhomoserine were found to undergo lactonization in preference to the formation of the corresponding hydantoin or azlactone respectively.

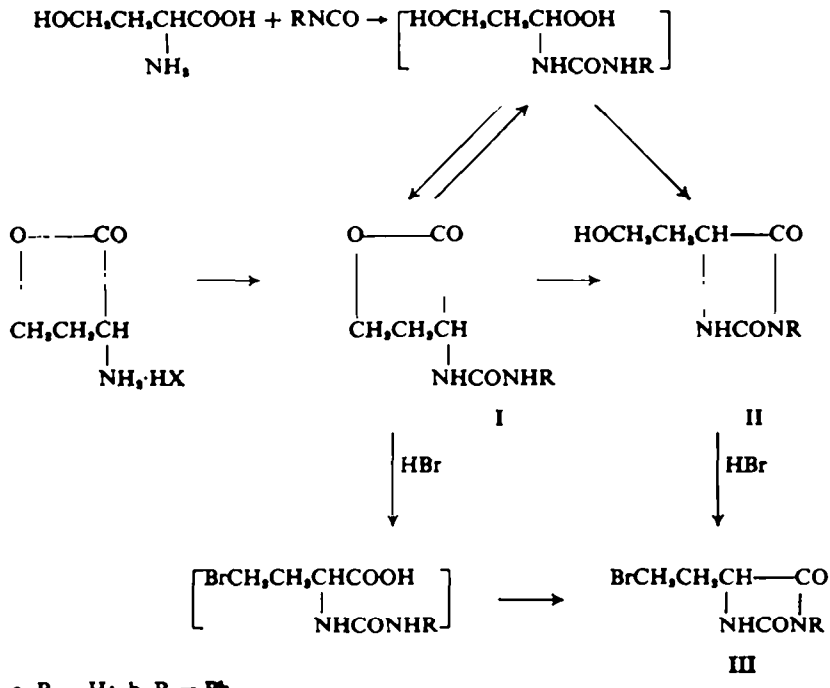
DURING work on a synthesis of methionine Livak *et al.*[1] treated homoserine with potassium cyanate and hydrobromic acid to obtain 5-(β-bromoethyl) hydantoin. They assumed that the reaction proceeds through α-carbamoylamino-γ-hydroxybutyric acid which undergoes direct cyclization to 5-(β-hydroxyethyl)hydantoin and subsequent substitution of the OH group by bromine to yield 5-(β-bromoethyl) hydantoin, a key substance in preparation of γ-functional-α-amino acids.[1,2] We elucidated the course of the reaction by the synthesis of α-carbamoylamino- and α-phenylcarbamoylamino-γ-butyrolactones (Ia, b). α-Carbamoylamino-γ-butyrolactone was cleaved by alkali to the α-carbamoylamino-γ-hydroxybutyric acid. The lactonization which occurred on acidification was detected by the hydroxamic acid test. On keeping this acidic solution for 24 hr the hydroxamic test became negative and 5-(β-hydroxyethyl) hydantoin (IIa) was isolated as the sole product.

Treatment of homoserine with phenyl isocyanate and alkali yielded the sodium salt of N-phenylcarbamoylhomoserine which on acidification underwent lactonization to N-phenylcarbamoylhomoserine lactone (Ib) in an almost quantitative yield. α-Phenylcarbamoylamino-γ-butyrolactone (Ib) was transformed to 3-phenyl-5-(β-hydroxyethyl)hydantoin (IIb) by short heating in water.

This behaviour indicates that lactonization is the kinetically preferred cyclization of α-carbamoylamino-γ-hydroxybutyric acid. Additional support for this preference was obtained by comparing the behaviour of α-carbamoylamino-γ-butyrolactone (Ia) and 5-(β-hydroxyethyl)hydantoin (IIa) on treatment with concentrated hydrobromic acid. We found that the lactone (Ia) was converted to 5-(β-bromoethyl) hydantoin (IIIa) much faster than the 5-(β-hydroxyethyl)hydantoin. In view of this finding the relatively easy conversion of the intermediary N-carbamoylhomoserine with concentrated hydrobromic acid, described by Livak,[1] can now be satisfactorily explained as proceeding via lactonization of α-carbamoylamino-γ-hydroxybutyric acid and subsequent formation of α-carbamoylamino-γ-bromobutyric acid.

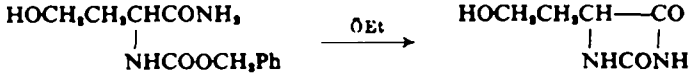
[1] J. E. Livak, E. C. Britton, J. C. Vander Weele and M. F. Murray, *J. Am. Chem. Soc.* **67**, 2218 (1945).
[2] D. D. Nyberg and B. E. Christensen, *J. Am. Chem. Soc.* **79**, 1222 (1957).

SCHEME A



a, R = H; b, R = Ph

In the transformation of α-carbamoylamino-γ-butyrolactone (Ia) to 5-(β-hydroxyethyl)hydantoin (IIa) the CO group of the internal ester reacted with the amidic NH_2 group of the α-carbamoylamine. This hydantoin derivative was also prepared by the cyclization of N-benzyloxycarbonylhomoseryl amide, through basic catalysis. However in this case the ureidic carbonyl group reacted with the amidic NH_2 group.



Substitution of the β-OH group by bromine occurred upon treatment of the hydroxyhydantoin (IIa) obtained, with concentrated hydrobromic acid. 5-(β-Bromoethyl)-hydantoin was also prepared by the cyclization of N-benzyloxycarbonylhomoseryl amide by basic catalysis, without isolation of the hydroxyhydantoin and subsequent treatment with hydrobromic acid. In the same way α-carbamoylamino-γ-butyrolactone gave a better yield of 5-(β-bromoethyl)hydantoin, even at room temperature.

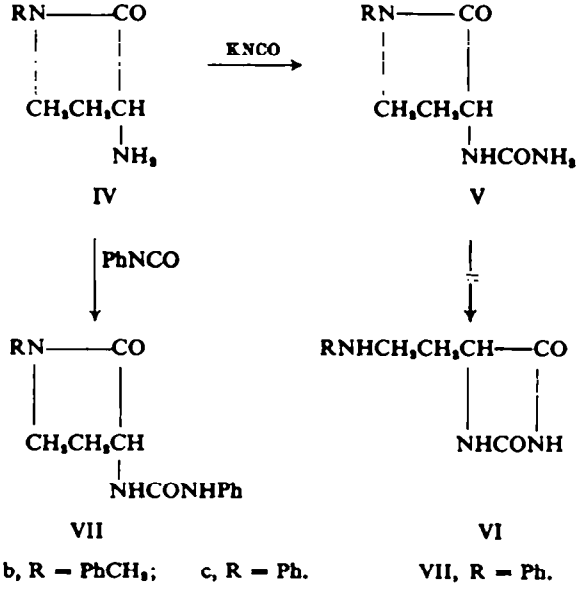
The greater stability of hydantoin, substituted at N-3 and C-5,[3] became evident by the rapid transformation of α-phenylcarbamoylamino-γ-butyrolactone (Ib) to 3-phenyl-5-(β-hydroxyethyl)hydantoin (IIb) even at room temperature. Thus treatment of homoserine lactone with phenyl isocyanate in dichloromethane at room temperature led directly to the hydantoin (IIb). On treatment of hydantoin (IIb) with 48% HBr 3-phenyl-5-(β-bromoethyl)hydantoin (IIIb) was obtained.

[3] E. Ware, *J. Am. Chem. Soc.* **60**, 2653 (1938).

Ring closure to γ-lactone was shown to be the preferred kinetic path even in the presence of amines (e.g. benzylamine or aniline); lactonization rather than amide formation occurred upon activation of the carboxylic group by N,N'-dicyclohexylcarbodiimide.

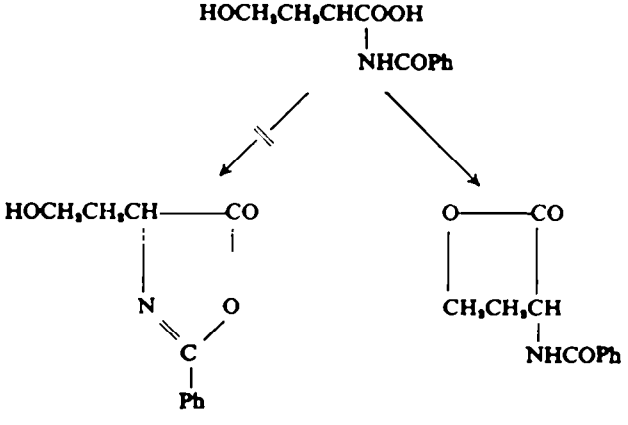
The inertness of α-carbamoylamino-γ-lactams (V) to conversion to 5-(β-aminoethyl) hydantoins (VI) was examined. 3-Carbamoylaminopyrrolidin-2-ones (V) were prepared from the corresponding 3-aminopyrrolidin-2-ones[4] (IV). α-Carbamoylamino-γ-lactams remained unaffected under conditions in which α-carbamoylamino- and α-N-phenylcarbamoylamino-γ-butyrolactones (Ia,b) were converted to the corresponding hydantoins (IIa,b).

SCHEME B



IV–V a, R = H; b, R = $PhCH_2$; c, R = Ph. VII, R = Ph.

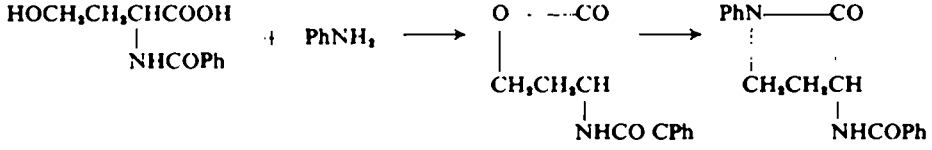
SCHEME C



[4] Y. Knobler, E. Bonni and T. Sheradsky, *J. Org. Chem.* **29**, 1229 (1964).

Intramolecular dehydration of α-benzamido-γ-hydroxybutyric acid might lead to α-benzamido-γ-butyrolactone or to 2-phenyl-5-(β-hydroxyethyl) isoxazolin-3-one; however, treatment with acetic anhydride[5] or with benzoyl chloride in pyridine[6] led exclusively to α-benzamido-γ-butyrolactone.

On heating N-benzoylhomoserine with aniline α-benzamido-N-phenyl-γ-butyrolactam was obtained via the γ-lactone.[4]



In the last reaction the tendency to lactonization rather than to other types of cyclization is further demonstrated.

EXPERIMENTAL

α-Carbamoylamino-γ-butyrolactone (Ia)

(a) α-Amino-γ-butyrolactone hydrochloride[7] (1·4 g, 0·01 mole) was added to a soln of KNCO (0·81 g, 0·01 mole) in water (2 ml). The soln was kept at room temp for 2 hr and then in the cold (0°) overnight. The precipitated product (Ia) was crystallized from a minimal quantity of water. The product (0·95 g, 66% yield), m.p. 158°; with $FeCl_3$ it gave a positive hydroxamic acid test.[8] (Found: C, 42·11; H, 5·51; N, 19·30. $C_5H_8N_2O_3$ requires: C, 41·67; H, 5·59; N, 19·44%.)

(b) α-Amino-γ-butyrolactone hydrochloride (2·06 g, 0·015 mole, KNCO (6·1 g, 0·075 mole), EtN_3 (1·5 g, 0·015 mole) and AcOH (1·5 g, 0·025 mole) were added to CH_2Cl_2 (250 ml). The reaction mixture was refluxed gently with stirring for 3 hr. The crude product and the excess of salts were filtered after cooling. The final product was obtained by several extractions of the solid with hot acetone and evaporation in the cold under reduced press. The mother-liquor yielded an additional crop of the product. The total yield was 2 g (93%), m.p. 156°. (Found: C, 41·45; H, 5·77; N, 19·30%.)

α-Phenylcarbamoylamino-γ-butyrolactone (Ib)

To a stirred soln of homoserine (11·9 g, 0·1 mole) in water (50 ml) were simultaneously added phenyl isocyanate (11 ml, 0·1 mole) and 1N NaOH (99 ml, 0·099 mole) during ½ hr. Additional 1N NaOH (50 ml, 0·05 mole) was added and the reaction mixture was stirred at room temp for another ½ hr. It was cooled, filtered and acidified to pH ≈ 1 with 18% HCl. After standing at room temp for 2 hr and in the cold (0°) overnight, the product precipitated (21 g, 95% yield), m.p. 156°. (Found: C, 60·07; H, 5·41; N, 12·50. $C_{11}H_{12}N_2O_3$ requires: C, 59·99; H, 5·49; N, 12·72%.)

Transformation of α-carbamoylamino-γ-butyrolactone (Ia) *to 5-(β-hydroxyethyl)hydantoin* (IIa)

(a) A soln of α-carbamoylamino-γ-butyrolactone (1·44 g, 0·01 mole) in 100 ml of AcOH–water (1:1) was heated at 90–100° for 4 hr and then left at room temp overnight. After evaporation of the soln *in vacuo* and crystallization of the residue from EtOH, 5-(β-hydroxyethyl)hydantoin (1·17 g, 81% yield) was obtained, m.p. 178°. (Found: C, 42·05; H, 6·03; N, 19·10. $C_5H_8N_2O_3$ requires: C, 41·67; H, 5·59; N, 19·44%.)

(b) The transformation of Ia to IIa was faster when Ia was dissolved in 12% HCl and treated as above. After 2 hr the hydroxamic acid test[8] was negative and 5-(β-hydroxyethyl)hydantoin (1·3 g, 90% yield) was obtained, m.p. 178°.

[4] H. E. Carter and C. M. Stevens, *J. Biol. Chem.* **133**, 117 (1940).
[5] H. E. Carter, P. Handler and C. M. Stevens, *J. Biol. Chem.* **138**, 619 (1940).
[7] M. Frankel, Y. Knobler and T. Sheradsky, *J. Chem. Soc.* 3642 (1959).
[8] A. I. Vogel *Practical Organic Chemistry* (3rd Edition) p. 1063. Longmans Green, New York, N.Y. (1956).

(c) When α-carbamoylamino-γ-butyrolactone was refluxed in EtOH, in acetone or in water for 4–5 hr, IIa was obtained in yields of 60%, 70% and 77% respectively.

Transformation of α-carbamoylamino-γ-hydroxybutyric acid to α-carbamoylamino-γ-butyrolactone Ia *and to 5-(β-hydroxyethyl)hydantoin* (IIb)

α-Carbamoylamino-γ-butyrolactone (0·144 g, 0·001 mole) was dissolved in 2N NaOH (1·5 ml). The hydroxamic acid test was negtive.[9] The cooled soln was acidified to pH = 1 with 18% HCl and left at room temp. After 2 hr a positive test for hydroxamic acid was obtained. After 24 hr the colour test was negative again and 5-(β-hydroxyethyl) hydantoin was obtained (0·1 g, 69·4% yield), m.p. 176°, identified by mixed m.p., IR spectrum and elemental analysis.

Transformation of α-phenylcarbamoylamino-γ-hydroxybutyric acid to α-phenylcarbamoylamino-γ-butyrolactone (Ib)

α-Phenylcarbamoylamino-γ-butyrolactone (0·45 g, 0·002 mole) was dissolved in 2N NaOH (1·5 ml). The cooled soln was acidified to pH = 1 with 18% HCl and left at room temp for 24 hr. The α-phenylcarbamoylamino-γ-butyrolactone (0·4 g, 90% yield) obtained ,m.p. 156°, gave a positive test for hydroxamic acid.[9] It was further identified by mixed m.p., IR spectrum and elemental analysis.

Transformation of α-phenylcarbamoylamino-γ-butyrolactone (Ib) *to 3-phenyl-5-(β-hydroxyethyl)-hydantoin* (IIb).

α-Phenylcarbamoylamino-γ-butyrolactone (1·4 g, 0·063 mole) in water (15 ml,) was refluxed for 10 min. Upon cooling, IIb was obtained (1·2 g, 86% yield), m.p. 110°. Found: N, 12·90. Calc. for $C_{11}H_{12}N_2O_3$: N, 12·72%.)

Transformation of α-carbamoylamino-γ-butyrolactone to 5-(β-bromoethyl)hydantoin (IIIa)

(a) α-Carbamoylamino-γ-butyrolactone (0·6 g, 0·00416 mole) was dissolved in 48% HBr (80 ml). The soln was heated for 2 hr at 90–100° (water-bath) and then evaporated to dryness *in vacuo*. The residue was crystallized twice from EtOH. 5-(β-Bromoethyl)hydantoin was obtained (0·6 g, 70% yield) m.p. 139–140°.[1] (Found: C, 29·60; H, 3·20; N, 13·60; Br, 38·40. Calc. for $C_5H_7BrN_2O_2$: C, 29·00; H, 3·40; N, 13·53; Br, 38·59%.)

(b) α-Carbamoylamino-γ-butyrolactone (0·5 g, 0·00346 mole) was dissolved in sat soln of HBr in AcOH (20 ml). The soln was left at room temp for 3 days and then evaporated to dryness at reduced press. The residue was crystallized twice from water and 5-(β-bromoethyl)hydantoin was obtained (0·39 g, 54·4% yield), m.p. 135°. (Found: N, 13·1; Br, 39·00%.)

Attempted transformation of 5-(β-hydroxyethyl)hydantoin (IIa) *to 5-(β-bromoethyl)hydantoin* (IIIa) *at* 100°

5-(β-Hydroxyethyl) hydantoin (0·4 g, 0·00277 mole) was dissolved in 48% HBr (60 ml) and treated as above. The starting compound, 5-(β-hydroxyethyl)hydantoin was recovered (0·2 g, 50% yield), m.p. 172°, and identified by mixed m.p., IR spectrum and elemental analysis.

5-(β-Bromoethyl)hydantoin (IIIa)

Compound IIa (1·44 g, 0·01 mole) was heated for 4 hr in refluxing 48% HBr (80 ml). The soln was evaporated to dryness at reduced press and the residue was twice crystallized from water and once again from EtOH. The IIIa thus obtained (0·12 g, 57% yield), melted at 138°.[1] (Found: N, 13·2; Br, 38·8. Calc. for $C_5H_7BrN_2O_2$: N, 13·53; Br, 38·59%.)

Treatment of α-benzyloxycarbonylamino-γ-hydroxybutyramide with ethanolic sodium ethoxide

α-Benzyloxycarbonylamino-γ-hydroxybutyramide[9] (5 g, 0·02 mole) was dissolved in abs EtOH (500 ml) in which Na (0·46 g, 0·02 mole) had been dissolved. The soln was heated under reflux for 50 hr and then divided into two equal parts:

(a) After concentration at reduced press the cold soln was acidified with conc HCl (Congo-red). After filtration of the inorganic salt, the soln was evaporated to dryness at reduced press and the

[9] T. Sheradsky, Y. Knobler and M. Frankel, *J. Org. Chem.* **26**, 1482 (1961).

residue was washed twice with EtOH and then crystallized from water. The product, 5-(β-hydroxyethyl) hydantoin (1·15 g, 80% yield) melted at 178°, (Found: C, 41·23; H, 6·20; N, 19·20. Calc. for $C_5H_8N_2O_3$: C, 41·67; H, 5·59; N, 19·44%.)

(b) The soln was evaporated to dryness at reduced press and the residue was dissolved in 48% HBr (50 ml). The soln was heated under reflux for 2 hr. The procedure was repeated after evaporation to dryness at reduced press. The residue was crystallized from water to obtain IIIa, (0·62 g, 30% yield) m.p. 137°.[1] (Found: N, 13·20; Br, 39·10. Calc. for $C_5H_7BrN_2O_3$: N, 13·53; Br, 38·59%.)

3-Phenyl-5-(β-hydroxyethyl)hydantoin (IIb)

To cold Chf (100 m,) were added with stirring, β-amino-γ-butyrolactone hydrochloride[7] (1·65 g, 0·012 mole); EtN_3 (1·2 g, 0·012 mole) and phenyl isocyanate (1·4 g, 0·012 mole). The stirred reaction mixture was left at room temp for 3 hr. After filtration of the ppt containing triethylamine hydrochloride and N,N'-diphenylurea, the chf soln was concentrated to 50 ml *in vacuo* and some impurities were filtered off, then evaporated to dryness and the residue was twice crystallized from AcOEt–pet ether and once again from water. The product (0·85 g, 32% yield), m.p. 110° gave a negative hydroxamic test.[8] The IR spectrum showed no absorption for γ-lactone at 5·65μ. (Found: C, 59·75; H, 5·44; N, 12·60. $C_{11}H_{12}N_2O_3$ requires: C, 59·98; H, 5·49; N, 12·72%.)

3-Phenyl-5-(β-bromoethyl)hydantoin (IIIb)

Compound IIb (0·2 g, 0·009 mole) was heated for 4 hr under reflux in 48% HBr (80 ml). After evaporation at reduced press, the residue was crystallized twice from EtOH. The product (0·15 g, 58·8% yield) melted at 108°. (Found: C, 47·33; H, 4·22; N, 9·90; Br, 27·65. $C_{11}H_{11}BrN_2O_3$ requires: C, 46·66; H, 3·91; N, 9·89; Br, 28·22%.)

3-Carbamoylaminopyrrolidin-2-one (Va)

α,γ-Diaminobutyric acid dihydrobromide[10] (5·51 g, 0·02 mole) was suspended in absolute EtOH (250 ml) and dry HBr was passed through the soln with gentle heating for 4 hr. The soln was left overnight at room temp and then concentrated at reduced press. The procedure was repeated twice. To the semisolid residue was added cold MeONa, prepared from Na (0·93 g) and MeOH (70 ml). After 15 min, excess of dry ether was added and the precipitated inorganic salt was filtered off.[11] The filtrate was concentrated at reduced press and the residue was dissolved in a small quantity of water. KNCO (2 g, 0·024 mole) in water (3 ml) was added and the soln was acidified with AcOH and left at room temp for 3 days. The soln was evaporated to dryness and the residue was twice crystallized from EtOH. Compound Va (0·45 g, 16% overall yield) was obtained, m.p. 220°. (Found: C, 41·23; H, 6·30; N, 28·95. $C_5H_9N_3O_2$ requires: C, 41·95; H, 6·34; N, 29·35%.)

1-Benzyl-3-carbamoylaminopyrrolidin-2-one (Vb)

1-Benzyl-3-benzamidopyrrolidin-2-one[9] (8·34 g, 0·0283 mole) was heated for 4 hr under reflux in 12% HCl (210 ml). After cooling, the precipitated benzoic acid was filtered off and the filtrate was extracted with ether and concentrated at reduced press. The semisolid residue was dissolved in abs EtOH (250 ml) and dry HCl was passed through the soln with gentle heating for 4 hr. The soln was concentrated and the procedure was repeated twice. To the semisolid residue a cold soln of EtONa was added (1·32 g, Na in abs EtOH (50 ml)). After 15 min, excess of dry ether was added and the precipitated inorganic salt was filtered off. The filtrate was concentrated at reduced press and the semisolid was dissolved in a small quantity of water. KNCO (2·43 g, 0·03 mole) in water (4 ml) was added and the soln was acidified with AcOH and left at room temp for 3 days. The soln was evaporated at reduced press and the residue was crystallized from EtOH. 1-Benzyl-3-carbamoylaminopyrrolidin-2-one thus obtained (3·12 g, 47% overall yield) melted at 212°. (Found: C, 61·37; H, 6·60; N, 17·10. $C_{12}H_{14}N_2O_2$ requires: C, 61·79; H, 6·48; N, 18·01%.)

1-Phenyl-3-phenylcarbamoylaminopyrrolidin-2-one (VII)

To a cold stirred soln of 1-phenyl-3-aminopyrrolidin-2-one hydrochloride[4] (3·2 g, 0·015 mole) in water (7·5 ml) 1N NaOH (15 ml, 0·015 mole) and phenyl isocyanate (1·8 ml, 0·016 mole) were added simultaneously. Additional 1N NaOH (7·5 ml, 0·0075 mole) was introduced and the reaction mixture

[10] Max Frankel, Y. Knobler and T. Sheradsky, *Bull. Res. Counc. Israel* 7A, 173 (1958).
[11] S. Wilkinson, *J. Chem. Soc.* 104 (1951).

was stirred for ½ hr, the ppt was filtered off and washed several times with hot AcOEt. The product (2·07 g, 46·7% yield) melted at 220°. (Found: C, 69·24; H, 5·50; N, 14·00. $C_{17}H_{17}N_3O_3$ requires: C, 69·14; H, 5·80; N, 14·23%.)

Reaction of α-benzamido-γ-hydroxybutyric acid with acetic anhydride

α-Benzamido-γ-hydroxybutyric acid[18] (3 g, 0·134 mole) was dissolved in Ac_2O (30 ml) and heated at 100° for ½ hr. After concentration at reduced press and addition of excess of petrol ether, α-benzamido-γ-butyrolactone was obtained (2·4 g, 87% yield), m.p. 142°.[18] (Found: N, 7·10. Calc. for $C_{11}H_{11}NO_3$: N, 6·83%.)

Reaction of α-benzamido-γ-hydroxybutyric acid and benzoyl chloride in pyridine

To a stirred cold soln of α-benzamido-γ-hydroxybutyric acid (2·23 g, 0·01 mole) in pyridine (20 ml), benzoyl chloride (1·4 g, 0·01 mole) was added gradually. The reaction mixture was brought to room temp, stirred at room temp for 15 min and poured on a mixture of ice-water and HCl (0·03 mole). The soln was extracted with ether. The combined ether extracts were dried with $MgSO_4$ and concentrated at reduced press. After addition of benzene–pet ether a semisolid was obtained and was crystallized twice from AcOEt–petroleum ether to yield α-benzamido-γ-butyrolactone (0·5 g, 24·4%), m.p. 145°.[18] (Found: N, 6·90. Calc. for $C_{11}H_{11}NO_3$: N, 6·83%.)

Reaction of α-benzamido-γ-hydroxybutyric acid with aniline

α-Benzamido-γ-hydroxybutyric acid (0·67 g, 0·003 mole) and aniline (2·4 g, 0·0257 mole) were heated under reflux for 1 hr. Aliquotes taken out after 10, 20 and 30 min showed the presence of γ-butyrolactone by the hydroxamic test. After an hr ether was added to the cooled reaction mixture and 1-phenyl-3-benzamidopyrrolidin-2-one (0·28 g, 33% yield) m.p. 210°,[4] precipitated. It was identified by mixed m.p., IR spectrum and elemental analysis. The filtrate was concentrated. Addition of pet. ether precipitated a mixture of the starting material and α-benzamido-γ-butyrolactone, as determined by IR spectrum. This ppt was washed several times with ether to yield α-benzamido-γ-butyrolactone (0·25 g, 40% yield) m.p. 143°.[18] (Found: N, 6·70. Calc. for $C_{11}H_{11}NO_3$: N, 6·83%.)

When α-benzamido-γ-hydroxybutyric acid (1·7 g, 0·0076 mole) and aniline (4·7 g, 0·0504 mole) were heated under reflux for 2 hr, and treated as above, 1-phenyl-3-benzamidopyrrolidin-2-one was obtained, (2·1 g, 98% yield), m.p. 210°,[4] and identified as above. (Found: N, 9·60. Calc. for $C_{17}H_{16}N_2O_2$: N, 10·00%.)

[18] E. Fischer and H. Blumenthal, *Ber. Dtsch. Chem. Ges.* **40**, 106 (1907).

[19] Max Frankel and Y. Knobler, *J. Am. Chem. Soc.* **80**, 3147 (1958); Y. Knobler and Max Frankel, *J. Chem. Soc.* 1629 (1958).