to the six-membered lactone. The ring closure of the monophenyl ester of succinic acid is 230 times as rapid as the glutaric ester,[11a] but this has been attributed to anchimeric assistance from the carboxylate anion.

Experimental

Lactones.—δ-Valerolactone was obtained by depolymerizing its commercially available polymer by distilling with red lead.[15] β-Methyl-δ-valerolactone was a commercial sample (Aldrich Chemical Co.). β,β-Dimethyl-δ-valerolactone was prepared by reduction of β,β-dimethylglutaric anhydride with sodium in ethanol.[16] δ,δ-Dimethyl-δ-valerolactone was prepared by reaction of glutaric anhydride with 2 equiv. of methylmagnesium iodide.[17] The physical constants of the valerolactones are given in Table III. The γ-butyrolactones were those used in a previous study.[2]

TABLE III

PHYSICAL CONSTANTS OF VALEROLACTONES[a]

Valerolactone	B.p., °C. (mm.)	$n^{25}D$
δ-	65 (3 mm.) [88 (4 mm.)][b]	1.4527 [1.4568[20]][b]
β-Methyl-	77 (8 mm.) [110–111 (15 mm.)][c]	1.4482 [1.4495][c]
δ-Methyl-	95 (9 mm.) [113 (20 mm.)][b]	1.4508 [1.4589[20]][d]
β,β-Dimethyl-	110 (10 mm.) [118–120 (20 mm.)][e]	1.4480
δ,δ-Dimethyl-	96 (5 mm.) [90 (3 mm.)][b]	1.4475 [1.4497[20]][b]

[a] Lit. values in brackets. [b] Ref. 18. [c] R. I. Longley, Jr., and W. S. Emerson, *Org. Syn.*, **35**, 87 (1955). [d] Ref. 19. [e] H. N. Rydon, *J. Chem. Soc.*, 594 (1936).

δ-Methyl-δ-valerolactone.—Ethyl acetoacetate (60 g.) was added to dry ethanol (200 ml.) containing sodium (6.5 g.), and ethyl β-bromopropionate (51 g.) in ethanol (50 ml.) then was added dropwise with stirring. The solution was heated to reflux for 4 hr. and worked up to give diethyl δ-acetoxyglutarate (25 g.), b.p. 138–142° (9 mm.), $n^{25}D$ 1.4361. The ester was refluxed with concentrated hydrochloric acid (250 ml.) for 6 hr. giving 5-ketohexanoic acid (25 g.), b.p. 125–130° (9 mm.), $n^{25}D$ 1.4367. The acid (10 g.) was dissolved in 5% sodium hydroxide (100 ml.) and treated with sodium borohydride (1 g.) in water (10 ml.). The solution was left at room temperature overnight, acidified with concentrated hydrochloric acid, saturated with salt, and extracted continuously with ether to give the lactone, b.p. 95° (9 mm.), $n^{25}D$ 1.4508 (lit. b.p. 113° at 20 mm.[18], $n^{20}D$ 1.4589[19]).

Equilibrium Constants.—The lactone (*ca.* 0.5 g.) was dissolved in 0.025 *M* hydrochloric acid (50 ml.) and immersed in a constant temperature bath at 25.0 ± 0.1° for up to 5 days. Aliquots were withdrawn, diluted with ice–water (20 ml.), and titrated with 0.02 *N* sodium hydroxide, using rapid magnetic stirring to avoid saponification of the lactone. Reproducible results were readily obtained.[20] Some samples were treated with an excess of sodium hydroxide, left at room temperature overnight, and back titrated with hydrochloric acid to determine the purity of the lactone.

Rate Constants.—The kinetic runs were carried out in the same manner by titrating aliquots at intervals of 10 to 60 min. Several aliquots were also left for 3 to 5 days to measure the equilibrium point. The pseudo first-order rate constants were determined from the slope of the linear plot of ln $(\chi_e - \chi)$ against time, using the kinetic relation,[21] $k't = (\chi_e/a) \ln [\chi_e/(\chi_e - \chi)]$, where a is the initial concentration of lactone, χ_e is the equilibrium concentration of liberated acid, and χ is the concentration of liberated acid at any time t. The rate constants (k_H) are expressed (Tables I and II) as second-order rate constants independent of the concentration of acid catalyst (see Table I; $k_H = k'_H/[H^+]$[18]).

Acknowledgment.—This work was financed in part by a grant from the National Science Foundation.

(15) H. K. Hall, Jr., M. K. Brandt, and R. M. Mason, *J. Am. Chem. Soc.*, **80**, 6420 (1958).

(16) S. S. G. Sicar, *J. Chem. Soc.*, 898 (1928); A. Burger and A. Hafstetter, *J. Org. Chem.*, **24**, 1290 (1959).

(17) G. Koppa and W. Rohrmann, *Ann.*, **509**, 259 (1934).

(18) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 580 (1933).

(19) M. Hudlicky, *Chem. Listy*, **45**, 380 (1952).

(20) *Cf.* F. A. Long, W. F. McDevit, and F. B. Dunkle, *J. Phys. Chem.*, **55**, 813 (1951).

(21) K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1950, p. 19.

Lactam Formation through Aminolysis of α-Amino-γ-butyrolactone. 2-Amino-4-hydroxybutyramides and 1-Aryl 3-Aminopyrrolidin-2-ones

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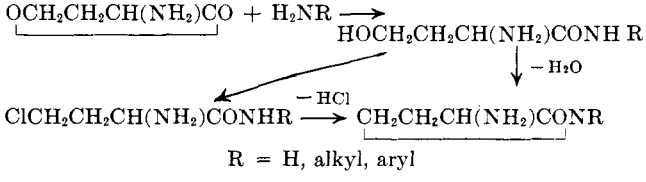
Reactions of α-amino- or α-benzamido-γ-butyrolactone with amines, leading to 1-aryl 3-amino- or 1-aryl 3-benzamidopyrrolidin-2-ones, or to α-benzamido-γ-hydroxybutyr-N-alkyl amides, are described. A mechanism is postulated for direct conversion of α-amino-γ-butyrolactone into 1-aryl 3-aminopyrrolidin-2-one, based on an unfavorable equilibrium for γ-hydroxybutyr-N-aryl amide formation and on irreversible oxygen–alkyl fission to α-amino-γ-arylaminobutyric acid, followed by direct γ-lactamization. Experiments using γ-butyrolactone and δ-valerolactone with aromatic amines demonstrate the dependence of reaction rate and of cyclization on the ring stability of starting and resulting compounds. Cyclization of γ-reactive butyr-N-alkyl amides to a lactonic, iminolactonic, or lactamic (γ-aminating) ring, determined by salt formation ability as well as by ring stability, is studied.

α-Amino-γ-butyrolactone (homoserine lactone) derivatives have been used for γ-amination by O-alkyl fission[1-3] or by γ-halogenation and appropriate subsequent amination.[1,3] In the present work, the application of homoseryl amides as possible intermediates in the γ-amination of α-amino-γ-butyrolactone was studied. Cyclization of such amides into α-amino-γ-butyrolactams in an intramolecular reaction or, indirectly, following γ-halogenation, was examined. The reactions in question might be formally postulated.

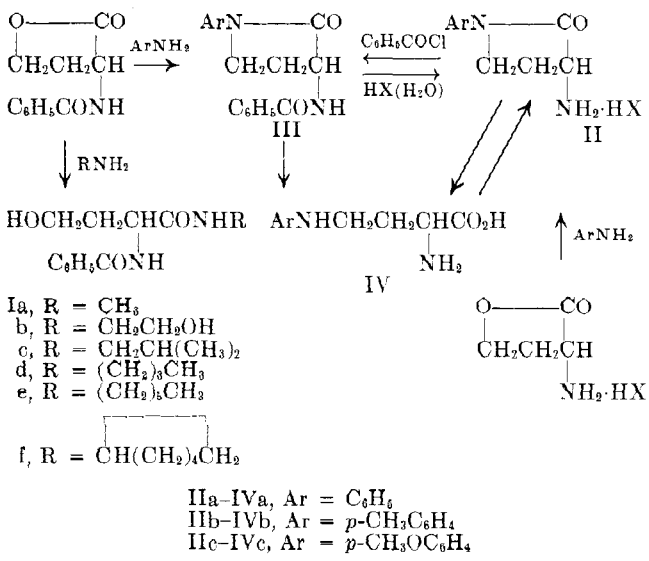


(1) M. Frankel, Y. Knobler, and T. Sheradsky, *Bull. Res. Council Israel*, **7A**, 173 (1958).

(2) G. Talbot, R. Gaudry, and L. Berlinguet, *Can. J. Chem.*, **36**, 593 (1958).

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

SCHEME I



α-Amino- and α-acylamido-γ-butyrolactone gave with primary aliphatic amines the expected homoseryl amides even at room temperature. With aromatic amines, no reaction was observed at room temperature, and the products obtained at the boiling point of the corresponding amine were 1-aryl 3-aminopyrrolidin-2-ones (IIa,b,c) and 1-aryl 3-benzamidopyrrolidin-2-ones (IIIa,b,c), respectively.

Benzoylation of the α-amino-γ-lactams (aminopyrrolidinones) II gave the formerly obtained α-benzamido-γ-lactams III, which also were debenzoylated to the aminolactams II by refluxing in 12% hydrochloric acid. In addition, the aminolactams II were characterized by their monopicrates and by their α-carbamido or α-phenylthiocarbamido derivatives.

Attempts to cleave the α-amino-γ-aryl butyrolactams (II) by heating in reflux concentrated hydrochloric, hydrobromic, or sulfuric acid, as well as in aqueous or alcoholic alkali, failed to yield the open α-amino-γ-arylaminobutyric acids, and the starting lactams were recovered. However, the ring fission of the lactams II and III to the acids IVa,b,c, was achieved by hydrolysis with barium hydroxide at 180-200° under a pressure of 12–15 atm. Monopicrates of the α-amino-γ-arylaminobutyric acids (IV) and their ethyl ester dihydrochlorides were prepared. (See Scheme I.)

The γ-N-arylated α,γ-diaminobutyric acids (IV) were cyclized to the α-amino-γ-N-aryl butyrolactams (II) by heating in the respective aromatic amine at reflux temperature without or in the presence of one equivalent of the amine hydrochloride, *i.e.*, under the same conditions as used during formation of the pyrrolidin-2-ones II.

The easy cyclization of the diamino acids IV suggests a formulation of the mechanism for the conversion of the lactones (a) into the lactams (d) *via* O-alkyl fission of the starting lactone (see Scheme II).

The course of the reaction of α-amino-γ-butyrolactone with a primary amine (and probably with other nucleophiles, too) depends upon the position of the equilibrium between the lactone (a) and the products of its O-acyl fission (b or b′). With the strongly basic aliphatic amines, the equilibrium lies far toward the γ-hydroxyamides (b), even at room temperature. On the other hand, with aromatic amines, presumably because of their low basicity and appreciable steric hindrance intensified by retarded C–N rotation, the lactone (a) is the favored side of the equilibrium. For example, α-amino-γ-butyrolactone as well as α-benzamido-γ-butyrolactone were recovered after heating in excess aniline (100°) for the same time period required for lactam formation at 170° (2 hr.). At reflux temperature an irreversible γ-aminolytic cleavage of the lactone (a) took place with aromatic amines, even though this reaction is considered to be slower and to need more drastic conditions[3] than the O-acyl fission. The intermediary α-amino- or α-benzamido-γ-arylaminobutyric acid (c′) is unstable at the reflux temperature of the aromatic amine, undergoing the easy cyclization of a γ-arylaminobutyric acid. This cyclization proved to proceed much faster than the O-alkyl fission, and only pyrrolidin-2-one (γ-lactam, d) appeared as the end product.

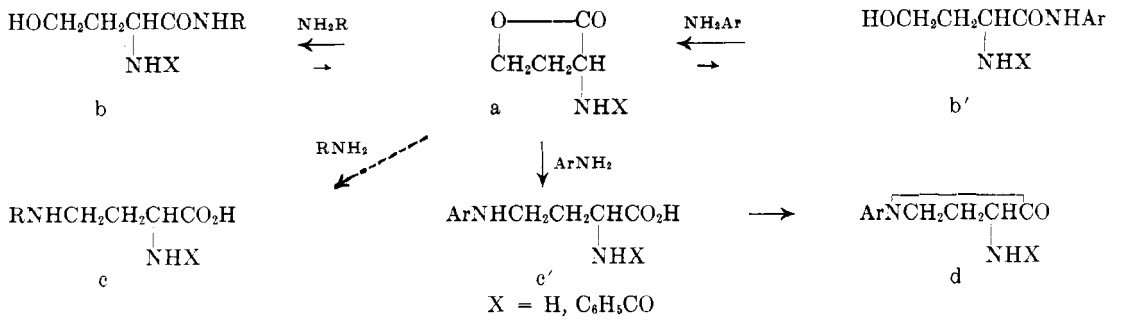
Additional evidence for the above postulated mechanism for γ-lactam formation through γ-aminolytic cleavage, and not through a γ-hydroxybutyr-N-aryl amide, is provided by cyclization of γ-hydroxybutyranilide. After heating in an excess of aniline for 2 hr. at reflux temperature, a small amount of the starting γ-hydroxybutyranilide and almost all of the amine, including that derived from the amide, was recovered; γ-butyrolactone was formed, but no 1-aryl pyrrolidin-2-one was detected.

That the difference in the course of the reaction depends on the alkylic or arylic character of the amine as well as on reaction time has not been considered previously. The formation of N-aryl pyrrolidin-2-ones could be assumed to proceed through γ-hydroxybutyr-N-aryl amides (and not by the γ-alkylic amination postulated above) because their preparation from γ-lactones and aromatic amines was performed under the extremely drastic conditions necessary for the cyclization of γ-hydroxy-N-alkyl amides, *i.e.*, at 215–300°[4,5] under pressure. The γ-hydroxy-N-alkyl amides have been isolated during the process of N-alkyl lactam formation. Thus, γ-lactamization may be considered to consist of dehydration achieved at highly elevated temperatures. However, γ-lactamization of γ-hydroxy-N-alkyl amides involves reversibility to γ-lactones (before irreversible O-alkyl fission); the drastic conditions in the presence of the aliphatic amine are required to force the thermal shift of the equilibrium back to the γ-lactone. The existence of this unfavored side of the equilibrium was demonstrated experimentally: α-carbobenzoxyamino-γ-butyrolactone was isolated after heating α-carbobenzoxyamino-γ-hydroxybutyr-N-benzylamide for several hours in boiling *o*-dichlorobenzene.

The γ-hydroxyamide–γ-butyrolactone equilibrium also was shown by heating α-benzamido-γ-hydroxybutyr-N-alkyl amides in boiling aniline. Fractions of the starting γ-hydroxyamide, of the intermediary α-benzamido-γ-butyrolactone, and of the resulting γ-lactam IIIa were isolated. Since γ-N-alkyl lactam could not be detected, direct lactamization of the γ-hydroxy-N-alkyl amide should not be considered. The formation of 1-phenyl-3-benzamidopyrrolidin-2-one

(4) E. Spaeth and J. Lintner, *Ber.*, **69**, 2727 (1936).
(5) W. Reppe, *Ann.*, **596**, 163 (1955).

SCHEME II



(IIIa) proceeds *via* lactonization and subsequent O-alkyl fission to the γ-arylamino acid.

Additional support for the interpretation of properties and reactions of γ-hydroxyamides and γ-lactams is provided by reference to δ-hydroxyvaleramide, δ-valerolactam, or δ-valerolactone equilibrium, as well as to the stability of homologous rings.

Easy preparation of δ-lactam from δ-hydroxyamide would be expected on the basis of gained stabilization energy contributed by nitrogen carbonyl interaction, giving rise to an *endo* double bond in the six-membered ring.[6] But δ-lactam formation, too, proceeds through an intermediary lactone and, subsequently, through a δ-aminovaleric acid. The δ-lactone–δ-hydroxyamide equilibrium, however, lies much more in favor of the hydroxyamide than the γ-lactone–γ-hydroxyamide one, in accordance with the known instability of δ-valerolactone (*exo* doubly bonded six-membered ring[6]). Therefore, enhanced O-acyl fission of once formed δ-lactone, facilitated by conversion of the trigonal atom of the six-membered ring to a tetrahedral one, might be expected through the intermediary addition compound with ammonia or amine, $\overline{OCH_2CH_2CH_2CH_2C(NH_2)OH}$. In fact, δ-valerolactone was obtained by Strojny, White, and Strojny[7] only by pyrolysis of δ-hydroxyvaleramide and removal of ammonia from the equilibrium.

γ-Butyrolactone is stable enough not to undergo effective O-acyl fission with aromatic amines even at reflux temperature; *e.g.*, after heating for 2 hr. in boiling aniline almost all of the amine and a small amount of the γ-lactam were isolated. By prolonged heating in aniline, γ-butyrolactone suffered slow irreversible γ-aminolytic cleavage to give N-phenylpyrrolidin-2-one. In contrast to that, δ-lactone–δ-hydroxyamide equilibrium lies in favor of the hydroxyamide even with aromatic amines. Heating δ-valerolactone with aniline, anisidine, or toluidine for 2 hr. at reflux temperature of the aromatic amine yielded the respective δ-hydroxy-N-aryl amide. Also, prolonged heating of δ-hydroxyvaler-N-aryl amides under the same conditions did not lead to detectable formation of N-aryl δ-lactam, and the δ-hydroxyamides were recovered. This fact emphasizes the importance of the stability of the intermediate lactone for the performance of subsequent aminolytic O-alkyl fission leading to γ-lactamization.

In addition to the stability of the γ-lactone intermediate (*exo* doubly bonded five-membered ring[6]), gain in stabilization may be expected by cyclization of the γ-arylamino acids to 1-aryl pyrrolidin-2-ones. Unsubstituted and N-alkylated γ-lactams are known to be less stable than the γ-aryl lactams owing to a strong nitrogen carbonyl interaction which gives rise to two adjacent trigonal atoms in the ring.[8] In the 1-aryl pyrrolidin-2-ones, however, nitrogen–aryl interaction should contribute to an exocyclic doubly bonded structure. This stabilization is reflected in the above-mentioned resistance of N-aryl pyrrolidin-2-ones to hydrolysis. Also, Bose and Manhas,[9] by utilizing N-ω-halogenoacylaminomalonic acid esters by the method of Sheehan and Bose,[10] showed that formation of five-membered N-phenyllactams tends to occur preferentially.

When α-amino-γ-butyrolactone hydrochloride and 2,4-dinitroaniline were used, no reaction occurred and both compounds were recovered. This base, as well as 4-nitroaniline, were too weak to react sufficiently to give the amide or the irreversible γ-aminobutyric intermediate. It was reported[11] that acidic catalysis facilitated the formation of some γ-dichlorophenylaminobutyr-N-dichloroanilide (14%) from γ-butyrolactone and 2,4-dichloroaniline. 1-Phenylpyrrolidin-2-one could also be obtained with a similar catalyst.[11]

The reaction of α-benzamido-γ-butyrolactone with a series of primary aliphatic amines was carried out at room temperature to yield the corresponding α-benzamido-γ-hydroxybutyr-N-alkyl amide (Ia–f), and these were not changed when heated at the boiling point of the amine for 2 hr.

Two possible cyclizations of γ-hydroxy-N-alkyl butyramide to γ-lactam or to γ-lactone may be considered. An attack on the slightly polarized γ-carbon atom by amidic or imidic nitrogen is quite unexpected, and no intramolecular dehydration could take place. Moreover, no effective stabilization energy can be gained with formation of the *endo* doubly bonded γ-lactam. The easier attack by γ-hydroxylic oxygen on the carbonylic or hydroxyimidic carbon would lead to expulsion of the amine and to formation of γ-lactone. The replacement of the more basic amine by γ-hydroxyl oxygen must, however, be readily reversible, and γ-hydroxyamide would be the kinetic product. Nevertheless, γ-lactone is the thermodynamically stable product, and its formation from a γ-hydroxyamide could be demonstrated as shown above, in a diluted solution. It was already mentioned that elevation of temperature to 250–300° should favor reversibility to γ-lactones and

(6) H. C. Brown, J. H. Brewster, and H. Schechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

(7) R. A. Strojny, H. C. White, and E. J. Strojny, *J. Org. Chem.*, **27**, 1241 (1962).

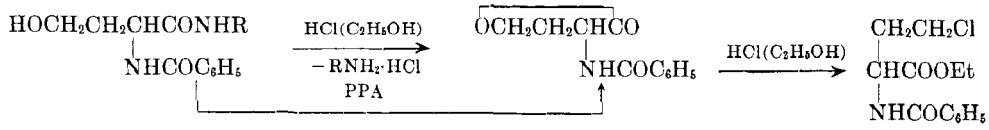
(8) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **80**, 6404 (1958).

(9) A. K. Bose and M. S. Manhas, *J. Org. Chem.*, **27**, 1244 (1962).

(10) J. C. Sheehan and A. K. Bose, *J. Am. Chem. Soc.*, **72**, 5158 (1950).

(11) H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, and J. Spille, *Ber.*, **89**, 2060 (1956).

SCHEME III



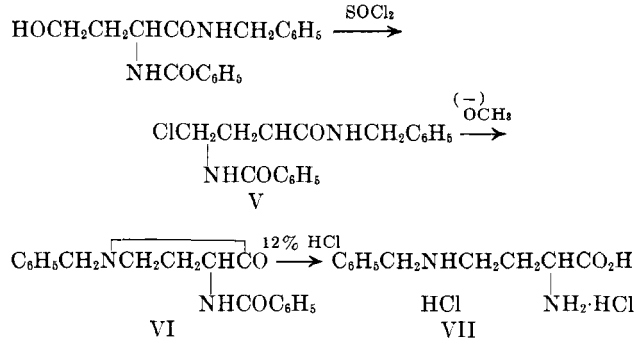
subsequent lactamization, but formation of γ-lactone was ascertained also below 200° even in the presence of excess aliphatic amine used as solvent. Since small amounts of γ-lactone are present, the irreversible γ-aminolytic cleavage proceeds slowly.

Heating of α-benzamido-γ-hydroxybutyr-N-benzylamide in a sevenfold excess of benzylamine under reflux for 35 hr. resulted in 1-benzyl-3-benzamidopyrrolidin-2-one (identical with the product obtained by the procedure described below). Heating of γ-butyrolactone in benzylamine as above leads at first to γ-hydroxybutyr-N-benzylamide (m.p. 72°), but very prolonged treatment (up to a week) yielded increasing amounts (up to 75%) of 1-benzyl-pyrrolidin-2-one (b.p. 148 at 5 mm.).

Reversible O-acyl fission of γ-lactone during cyclization of γ-hydroxyamide by the expelled aliphatic amine can be avoided by neutralization of the base. Lactonization of this kind is illustrated in reactions of γ-hydroxyamides (I) in ethanolic hydrogen chloride or in polyphosphoric acid (PPA). Saturation of an ethanolic solution of α-benzamido-γ-hydroxybutyr-N-alkyl amide (I) with hydrogen chloride under gentle refluxing (2 hr.) results in formation of α-benzamido-γ-halogenobutyric acid ethyl ester, the same product obtained from α-benzamido-γ-butyrolactone in ethanolic hydrogen chloride. α-Benzamido-γ-butyrolactone was obtained from γ-hydroxyamides by heating in polyphosphoric acid (100°).

Competing cyclization of lactamic or lactonic type can also be expected after γ-halogenation of γ-hydroxyamides (I). γ-Halogenobutyr-N-alkyl amides can cyclize to N-alkyl pyrrolidin-2-ones, and, here, iminolactone hydrochloride (2-alkyl iminotetrahydrofuran hydrochloride, $\overline{OCH_2CH_2CH_2C{=}NR}\cdot HCl$, prepared by Stirling[12]) is the competing product. Without addition of a base, the reaction should result in a preponderance of iminolactone due to increased stabilization by its *exo* double bond and to the thermodynamically favored salt formation. Laliberté and Berlinguet,[13] for example, isolated an N-alkyl imino-γ-lactone hydrochloride from an analogous γ-halogeno-α-alkylaminobutyr-N-alkyl amide. In the presence of a strong base, which promotes the reactivity of nitrogen by proton removal from the amidic group[14] and eliminates iminolactone salt formation, cyclization results to give N-alkyl pyrrolidin-2-one. The role of the strong base may be demonstrated in a reaction similar to those of Stirling,[12] *i.e.*, in the cyclization of γ-chlorobutyranilide. Heating in the presence of sodium carbonate (in ethanol–water) for 2 hr. results in two products, 1-phenylpyrrolidin-2-one and γ-hydroxybutyranilide; lactamization in the presence of the weaker base is slower and accompanied by γ-hydroxylation.

SCHEME IV



In practice, α-benzamido-γ-chlorobutyr-N-benzylamide (V) was prepared from γ-hydroxy-N-benzylamide[3] with thionyl chloride, and γ-lactamization to give 1-N-benzyl-3-benzamidopyrrolidin-2-one (VI) was carried out with the aid of sodium methoxide. The 1-N-benzylpyrrolidinone (VI) was used as a model substance because of its easily removable benzylic group. Hydrolysis of α-amino-γ-N-alkyl lactam (VI) with 12% hydrochloric acid yielded α-amino-γ-N-benzylaminobutyric acid dihydrochloride (VII).

Experimental

General Procedure for the Preparation of α-Benzamido-γ-hydroxybutyr-N-alkyl Amides (I, Listed in Table I).—α-Benzamido-γ-butyrolactone[15] (4.1 g., 0.02 mole) was dissolved with shaking in a fivefold excess of the respective amine. The mixture solidified within a few minutes. After standing at room temperature for 2–3 days, ether and petroleum ether (b.p. 40–60°) were added, and the precipitate was crystallized from ethanol.

1-Phenyl-3-aminopyrrolidin-2-one Hydrochloride (IIa).—α-Amino-γ-butyrolactone hydrochloride[16] (4.1 g., 0.03 mole) was heated in aniline (19.5 g., 0.21 mole) and kept under reflux for 2 hr. The solution was cooled, ether was added, and a crude product precipitated. Crystallization from absolute ethanol gave 6.2 g. (97%) of the γ-phenyllactam hydrochloride (IIa), m.p. 225°. The infrared spectrum showed no absorption in the 6.4–6.6-μ range (γ-lactam); λ_{max}^{Nujol} 5.95 (γ-lactam C=O), 3.03–3.13 (NH_3^+), 3.6–4.2 μ (NH_3^+).

Anal. Calcd. for $C_{10}H_{13}ClN_2O$: C, 56.5; H, 6.2; Cl, 16.7; N (Kj.),[17] 13.2; N (V. Sl.),[17] 6.6. Found: C, 55.8; H, 6.3; Cl, 16.9; N (Kj.), 13.15; N (V. Sl.), 6.5.

When the same reactants were heated as above for 0.5 hr. or for 1 hr., only a small amount of the resulting γ-lactam (IIa) could be obtained.

1-*p*-Tolyl-3-aminopyrrolidin-2-one Hydrochloride (IIb).—*p*-Toluidine (16.1 g., 0.15 mole) was heated to melting, α-amino-γ-butyrolactone hydrochloride (4.1 g., 0.03 mole) was added, and the solution was refluxed for 2 hr. The mixture solidified upon cooling. It was washed with many portions of ether in order to remove all the amine. The residue was crystallized twice from ethanol–ether yielding 5.65 g. (83%) of the γ-tolyllactam hydrochloride (IIb), m.p. 245°; λ_{max}^{Nujol} 3.00–3.28 (NH_3^+), 3.8–4.3 (NH_3^+), 5.75 μ (γ-lactam C=O), second amide band absent (γ-lactam).

(12) C. J. M. Stirling, *J. Chem. Soc.*, 255 (1960).
(13) R. Laliberté and L. Berlinguet, *Can. J. Chem.*, **40**, 1960 (1962).
(14) H. W. Heine, P. Love, and J. L. Bove, *J. Am. Chem. Soc.*, **77**, 5420 (1955).
(15) M. Frankel and Y. Knobler, *ibid.*, **80**, 3147 (1958); Y. Knobler and M. Frankel, *J. Chem. Soc.*, 1629 (1958).
(16) M. Frankel, Y. Knobler, and T. Sheradsky, *ibid.*, 3642 (1959).
(17) Kj. stands for Kjeldahl; V. Sl. for Van Slyke.

TABLE I

α-BENZAMIDO-γ-HYDROXYBUTYR-N-ALKYL AMIDES (I)

$HOCH_2CH_2CHCONHR$

$NHCOC_6H_5$

R	M.p., °C.	Yield, %	Formula	% C		% H		% N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3[a]	152	76	$C_{12}H_{16}N_2O_3$	61.0	61.2	6.8	6.9	11.8	11.7
CH_2CH_2OH	151	58	$C_{13}H_{18}N_2O_4$	58.7	58.3	6.8	7.1	10.5	10.4
$CH_2CH(CH_3)_2$	142	83	$C_{15}H_{22}N_2O_3$	65.0	64.1	7.9	7.8	10.1	10.1
$(CH_2)_3CH_3$	119	79	$C_{15}H_{22}N_2O_3$	65.0	64.3	7.9	7.6	10.1	9.9
$(CH_2)_5CH_3$	116	80	$C_{17}H_{26}N_2O_3$	66.6	66.3	8.5	8.4	9.1	9.2
$CH(CH_2)_4CH_2$	173	75	$C_{17}H_{24}N_2O_3$	67.1	66.8	7.9	7.9	9.2	9.0

[a] Aqueous methylamine (33%) was used.

TABLE II

1-ARYL 3-BENZAMIDOPYRROLIDIN-2-ONES (III)

$ArNCH_2CH_2CH(NHCOC_6H_5)C{=}O$

Ar	M.p., °C.	Yield, %	Formula	% C		% H		% N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
C_6H_5	209	57	$C_{17}H_{16}N_2O_2$	72.9	72.8	5.7	5.9	10.0	10.0
p-$CH_3C_6H_4$	211	78	$C_{18}H_{18}N_2O_2$	73.4	73.5	6.2	6.1	9.5	9.8
p-$CH_3OC_6H_4$	216	75	$C_{18}H_{18}N_2O_3$	69.6	69.1	5.8	5.7	9.0	8.9

TABLE III

1-ARYL 3-CARBAMOYLAMINOPYRROLIDIN-2-ONES

$ArNCH_2CH_2CH(NHCONH_2)C{=}O$

Ar	M.p., °C.	Yield, %	Formula	% C		% H		% N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
C_6H_5	310	56	$C_{11}H_{13}N_3O_2$	60.0	60.3	6.0	5.6	19.2	18.7
p-$CH_3C_6H_4$	312	43	$C_{12}H_{15}N_3O_2$	61.8	62.0	6.5	6.6	18.1	18.2
p-$CH_3OC_6H_4$	315	46	$C_{12}H_{15}N_3O_3$	57.8	57.3	6.1	6.1	16.9	16.4

Anal. Calcd. for $C_{11}H_{15}ClN_2O$: C, 58.3; H, 6.7; Cl, 15.6; N (Kj.), 12.4; N (V. Sl.), 6.2. Found: C, 55.6; H, 6.7; Cl, 15.8; N (Kj.), 11.9; N (V. Sl.), 5.9.

1-*p*-Tolyl-3-aminopyrrolidin-2-one hydrobromide was prepared as above, using α-amino-γ-butyrolactone hydrobromide[16] (5.4 g., 0.03 mole). The *p*-tolyl-γ-lactam hydrobromide, 4.9 g. (60%), melted at 230°.

Anal. Calcd. for $C_{11}H_{15}BrN_2O$: N, 10.3; Br, 29.5. Found: N, 9.7; Br, 30.6.

1-*p*-Anisyl-3-aminopyrrolidin-2-one hydrochloride (IIc) was prepared as described for IIb, using *p*-anisidine (18.4 g., 0.15 mole). *p*-Anisyllactam hydrochloride (IIc), 3.3 g. (45%), melted at 240°; λ_{max}^{Nujol} 2.8–3.0 (NH_3^+), 3.6–4.1 (NH_3^+), 5.9 μ (γ-lactam C=O), second amide band absent (γ-lactam).

Anal. Calcd. for $C_{11}H_{15}ClN_2O_2$: C, 54.4; H, 6.2; Cl, 14.6; N (Kj.), 11.5; N (V. Sl.), 5.7. Found: C, 54.5; H, 6.0; Cl, 14.6; N (Kj.), 11.8; N (V. Sl.), 5.6.

1-*p*-Anisyl-3-aminopyrrolidin-2-one hydrobromide was prepared as above, starting with α-amino-γ-butyrolactone hydrobromide (5.4 g., 0.03 mole); *p*-anisyllactam hydrobromide, 3.4 g. (40%), had m.p. 215°.

Anal. Calcd. for $C_{11}H_{15}BrN_2O_2$: N (Kj.), 9.7; N (V. Sl.), 4.8; Br, 27.8. Found: N (Kj.), 9.6; N (V. Sl.), 4.6; Br, 27.8.

General Procedure for the Preparation of 1-Aryl 3-Benzamidopyrrolidin-2-ones (III, Listed in Table II).—α-Benzamido-γ-butyrolactone[15] (4.1 g., 0.02 mole) was heated under reflux for 1 hr. in a fivefold excess of the respective aromatic amine. After cooling, ether and petroleum ether were added and the precipitate was crystallized from ethanol.

1-Aryl 3-Carbamoylaminopyrrolidin-2-ones.—The procedure below is general for the preparation of carbamoyl derivatives of 1-aryl 3-aminopyrrolidin-2-ones (II), listed in Table III.

1-Aryl 3-aminopyrrolidin-2-one hydrochloride (0.008 mole), potassium isocyanate (3.2 g., 0.04 mole), triethylamine (0.808 g., 0.008 mole), and glacial acetic acid (1.2 g., 0.02 mole) were added to 100 ml. of dry dichloromethane. The mixture was stirred at room temperature for 12 hr. Insoluble material was filtered, and the partially precipitated product was taken into ethanol and crystallized on concentration of the solution. Additional crops were obtained by concentration of the dichloromethane mother liquor.

1-Aryl 3-Phenylthiocarbamoylaminopyrrolidin-2-ones.—This procedure is general for the preparation of phenylthiocarbamoyl derivatives of 1-aryl 3-aminopyrrolidin-2-ones (II) listed in Table IV.

1-Aryl 3-aminopyrrolidin-2-one hydrochloride (II, 0.01 mole) was dissolved in 50 ml. of a pyridine–water mixture (1:1); the solution was brought to pH 9–10 by adding 2 *N* sodium hydroxide. Phenyl isothiocyanate (3 ml.) was added gradually with cooling (ice–salt bath), and after a few minutes a heavy precipitate separated. The crude product was washed with water and with petroleum ether and crystallized from benzene–petroleum ether.

Picrates of 1-Aryl 3-Aminopyrrolidin-2-ones (II).—A saturated solution of picric acid in ethanol was added to 1-aryl 3-aminopyrrolidin-2-one hydrochloride (II); the mixture was heated until dissolution and then for a few minutes more. After cooling, the precipitated picrate was collected and recrystallized from ethanol (see Table V).

Benzoylation of 1-Aryl 3-Aminopyrrolidin-2-one Hydrochlorides (II).—α-Amino-γ-lactam hydrochloride (IIa,b,c, 0.005 mole) was dissolved in 2 *N* sodium hydroxide (0.20 g., 0.005 mole) and, to the cooled solution, benzoyl chloride (2.1 g., 0.015 mole) was added in portions during 0.5 hr. The precipitate was washed with water and crystallized from ethyl acetate. These compounds, prepared from the aminolactams (II), were identical with the benzamidolactams (IIIa,b,c), as proved by mixture melting point, infrared spectrum, and elemental analysis.

Attempted Hydrolysis of 1-Aryl 3-Benzamidopyrrolidin-2-ones (II) with Mineral Acids.—α-Benzamido-γ-lactam (IIIa,b,c, 0.005 mole) was heated in refluxing 20% aqueous hydrochloric acid (20 ml.) for 2 hr. The mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue was washed with ether and crystallized from ethanol–ether. Its identity with aminolactam hydrochloride (IIa,b,c) was proved by mixture melting point, infrared spectrum, and elemental analysis.

The same products also were obtained after prolonged refluxing as above.

TABLE IV

1-ARYL 3-PHENYLTHIOCARBAMOYLAMINOPYRROLIDIN-2-ONES

$$ArNCH_2CH_2CH(NHCSNHC_6H_5)—C=O$$

Ar	M.p., °C.	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	% S Calcd.	% S Found
C_6H_5	192	98	$C_{17}H_{17}N_3OS$	65.6	65.8	5.5	5.7	13.5	12.9	10.3	10.3
p-$CH_3C_6H_4$	218	95	$C_{18}H_{19}N_3OS$	66.6	66.5	5.9	6.1	12.9	12.4	9.9	9.4
p-$CH_3OC_6H_4$	212	89	$C_{18}H_{19}N_3O_2S$	63.3	63.4	5.6	5.6	12.3	12.4	9.4	9.2

TABLE V

PICRATES OF 1-ARYL 3-AMINOPYRROLIDIN-2-ONES (II)

$$ArNCH_2CH_2CH[NH_2\cdot HOC_6H_2(NO_2)_3]C=O$$

Ar	M.p., °C.	Formula	% N Calcd.	% N Found
C_6H_5	243–245	$C_{16}H_{15}N_5O_{11}$	15.5	15.6
p-$CH_3C_6H_4$	250–255	$C_{17}H_{17}N_5O_{11}$	15.0	15.2
p-$CH_3OC_6H_4$	238–240	$C_{17}H_{17}N_5O_{12}$	14.5	14.5

2-Amino-4-arylaminobutyric Acids (IV).—General procedure for the barium hydroxide hydrolytic cleavage of 1-aryl 3-amino- and of 1-aryl 3-benzamido-pyrrolidin-2-ones (II and III) to yield the respective 2-amino-4-arylaminobutyric acids.

1-Aryl 3-aminopyrrolidin-2-one hydrochloride (II, 0.01 mole) or 1-aryl 3-benzamidopyrrolidin-2-one (III, 0.01 mole) and $Ba(OH)_2\cdot 8H_2O$ (10 g., 0.03 mole) were shaken in 100 ml. of water in an autoclave at 200° (12–15 atm.) for 0.5 hr. Shaking was continued for an additional hour without heating. Barium hydroxide and barium carbonate were filtered off and ammonium carbonate (4.5 g.) was added to the filtrate. Precipitated barium carbonate was removed by filtration and the filtrate was concentrated *in vacuo* until partial precipitation of the acid took place. Additional crops separated upon cooling. The 2-amino-4-arylaminobutyric acids (IV) were crystallized from concentrated hot aqueous solutions. Melting points and analytical values are listed in Table VI.

Cyclization of 2-Amino-4-arylaminobutyric Acids (IV). 1-Phenyl-3-aminopyrrolidin-2-one Hydrochloride (IIa).—2-Amino-4-phenylaminobutyric acid (IVa, 0.3 g., 0.0015 mole) was heated in aniline (6.5 g., 0.07 mole) for 0.5 hr. at reflux temperature. One equivalent of aniline hydrochloride (0.19 g., 0.0015 mole) was added, followed by an excess of ether. The crude product was crystallized from ethanol–ether. The 1-phenyl-3-aminopyrrolidin-2-one (IIa) obtained, 0.23 g. (72%), melted at 225°. None of the starting 2-amino-4-arylaminobutyric acid could be recovered.

Anal. Calcd. for $C_{10}H_{13}N_2O$: N (Kj.), 13.2. Found: N (Kj.), 12.9.

The corresponding γ-aryl amino-α-aminolactam hydrochlorides were obtained by a similar procedure from the parent acids, when heated in the respective amine. This aminolactam salt was identical with the 1-aryl 3-aminopyrrolidin-2-one hydrochloride prepared from α-amino-γ-butyrolactone hydrochloride and the aromatic amine (proved by mixture melting point and infrared analysis).

1-*p*-Tolyl-3-aminopyrrolidin-2-one hydrochloride (IIb) had m.p. 245°.

Anal. Calcd. for $C_{11}H_{15}ClN_2O$: N (Kj.), 12.4. Found: N (Kj.), 12.4.

TABLE VI

2-AMINO-4-ARYLAMINOBUTYRIC ACIDS (IV)

$$ArNHCH_2CH_2CH(NH_2)CO_2H$$

Starting lactam	Ar	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N (Kjeldahl) Calcd.	% N (Kjeldahl) Found	% N (Van Slyke) Calcd.	% N (Van Slyke) Found	M.p., °C.[a]	Yield, %	R_f[b]	Equiv. wt.[c] Calcd.	Equiv. wt.[c] Found
IIa	C_6H_5	$C_{10}H_{14}N_2O_2$	61.8	61.1	7.3	7.2	14.4	14.0	7.2	7.1	240	76.5	0.31	194.2	193.5
IIIa				61.7		7.6		13.8		7.0	245	72.0			
IIb	p-$CH_3C_6H_4$	$C_{11}H_{16}N_2O_2$	63.4	63.2	7.7	7.6	13.4	12.9	6.7	6.6	255	45.0	0.32	208.3	207.3
IIIb				63.5		7.5		13.1		6.9	255	50.0			
IIc	p-$CH_3OC_6H_4$	$C_{11}H_{16}N_2O_3$	58.9	58.2	7.2	7.5	12.5	12.0	6.2	5.9	225	40.0	0.33	224.3	225.0
IIIc				58.5		7.0		12.4		5.9	230	42.0			

[a] The acid melted with decomposition. [b] Butanol–water–acetic acid solution (4:1:1); spots detected by ninhydrin; t.l.c., Kieselgel G. Identical R_f values (±0.01) and equivalent weights (±0.1) were obtained for the acids IV, derived from α-amino-γ-lactams II or α-benzamido-γ-lactams III. [c] The determinations were carried out with a solution of 0.01 *N* $Ba(OH)_2\cdot 8H_2O$, by formol titration according to A. I. Vogel ["Quantitative Organic Analysis," Longmans, Green and Co., New York, N. Y., 1958, p. 409].

Picrates of 2-Amino-4-arylaminobutyric Acids (IV).—The picrates of the amino acids IV, listed in Table VII, were obtained as described for those of the aminolactams II.

TABLE VII

PICRATES OF 2-AMINO-4-ARYLAMINOBUTYRIC ACIDS (IV)

$$ArNHCH_2CH_2\underset{\displaystyle NH_2\cdot HOC_6H_2(NO_2)_3}{\overset{\displaystyle |}{C}}HCO_2H$$

Ar	M.p., °C.	Formula	% N Calcd.	% N Found
C_6H_5	238	$C_{16}H_{17}N_5O_{12}$	14.9	15.1
p-$CH_3C_6H_4$	246	$C_{17}H_{19}N_5O_{12}$	14.4	14.6
p-$CH_3OC_6H_4$	240	$C_{17}H_{19}N_5O_{13}$	14.0	14.0

2-Amino-4-arylaminobutyric Acid Ethyl Ester Dihydrochlorides.—2-Amino-4-arylaminobutyric acid (IV, 0.3 g.) was dissolved in a solution of 25% hydrogen chloride in ethanol (50 ml.) and left at room temperature for 24 hr. The solvent was evaporated *in vacuo*, and the residue was dissolved as above; this operation was repeated again. The residue was dissolved in ethanol, purified with charcoal, and precipitated by additon of dry ether. The products were crystallized twice from ethanol–ether. The ester dihydrochlorides of the acids (IV) thus obtained are listed in Table VIII.

1-*p*-Anisyl-3-aminopyrrolidin-2-one hydrochloride (IIc) had m.p. 240°.

Anal. Calcd. for $C_{11}H_{15}ClN_2O_2$: N (Kj.), 11.5. Found: N (Kj.), 11.5.

Attempted Reaction of α-Amino-γ-butyrolactone Hydrochloride with Aniline at 100°.—α-Amino-γ-butyrolactone hydrochloride (1.4 g., 0.01 mole) was heated with aniline (6.5 g., 0.07 mole) at 100° (water bath) for 2 hr. After cooling, ether was added and the starting material was recovered (1.2 g., 88%), m.p. 208°.

Anal. Calcd. for $C_4H_8ClNO_2$: N, 10.1. Found: N, 9.9.

The infrared spectrum was identical with that of the starting hydrochloride.

Likewise, α-benzamido-γ-butyrolactone was recovered after similar treatment by precipitation with petroleum ether.

Behavior of γ-Hydroxybutyranilide in Boiling Aniline.—γ-Hydroxybutyranilide (0.6 g., 0.0034 mole) was heated in aniline (1.86 g., 0.02 mole) for 2 hr. under reflux. After cooling, ether and petroleum ether were added; 0.1 g. (16%) of the recovered γ-hydroxyanilide crystallized in the cold overnight. The hydroxyamide was identified by melting point, infrared spectrum, and elemental analysis.

TABLE VIII

2-AMINO-4-ARYLAMINOBUTYRIC ACID ETHYL ESTER DIHYDROCHLORIDES

$ArNHCH_2CH_2CHCOOC_2H_5$
HCl $NH_2 \cdot HCl$

Ar	M.p., °C.	Yield, %	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	% Cl Calcd.	% Cl Found	% OC_2H_5 Calcd.	% OC_2H_5 Found
C_6H_5	158	56	$C_{12}H_{20}Cl_2N_2O_2$	48.8	48.8	6.8	6.9	9.5	8.9	24.0	24.1	15.3	15.5
p-$CH_3C_6H_4$	132	45	$C_{13}H_{22}Cl_2N_2O_2$	50.5	50.3	7.2	6.9	9.0	8.7	22.9	22.9	14.5	14.9
p-$CH_3OC_6H_4$	160	42	$C_{13}H_{22}Cl_2N_2O_3$	48.0	47.5	6.8	6.8	8.6	7.9	21.8	21.8	13.8	13.9[a]

[a] Additional value for the p-methoxyanisyl group. Calcd.: OCH_3, 9.5. Found: OCH_3, 9.4.

Hydrogen chloride was passed through the ether–petroleum ether solution, and aniline hydrochloride (2.75 g.) was isolated. The amount of the amine hydrochloride includes the starting aniline (0.02 mole) and the equivalent derived from the cleaved γ-hydroxyanilide (0.0028 mole). γ-Butyrolactone, which remained after evaporation of ether–petroleum ether, could be ascertained by hydroxamic acid test and by its refractive index.

Lactonization of α-Carbobenzoxyamino-γ-hydroxybutyr-N-benzylamide.—α-Carbobenzoxyamino-γ-hydroxybutyr-N-benzylamide[3] (0.5 g., 0.0145 mole) was heated in 50 ml. of *o*-dichlorobenzene for 12 hr. under reflux. After precipitation with petroleum ether, α-carbobenzoxyamino-γ-butyrolactone, 0.23 g. (67%), m.p. 110°,[15] was filtered off and showed λ_{max}^{Nujol} 5.65 μ (γ-lactone C=O).

Anal. Calcd. for $C_{12}H_{13}NO_4$: N, 6.0. Found: N, 6.2.

The starting γ-hydroxyamide could be recovered when heated only for 1 hr. in *o*-dichlorobenzene. After 6 hr., mixtures of γ-hydroxyamide and γ-lactone were obtained.

Treatment of α-Benzamido-γ-hydroxybutyr-N-alkyl Amide with Aniline.—γ-Hydroxy-N-methylamide (Ia, 0.7 g., 0.003 mole) was heated in boiling aniline (3 ml.) for 2 hr. After cooling, ether was added and a precipitate was filtered off. The solid, 0.25 g., (30%) was identical with 1-phenyl-3-benzamidopyrrolidin-2-one (IIIa), as proved by mixture melting point and infrared spectrum. By concentration and further crystallization from ether–petroleum ether, fractions of the starting γ-hydroxyamide (Ia) and of α-benzamido-γ-butyrolactone could be separated and identified as above.

With γ-hydroxy-N-hexylamide (Ie), lactonization was much slower and most of the starting amide was recovered. The first fraction (from ether–petroleum ether) contained a small amount of the γ-lactam (IIIa) and α-benzamido-γ-butyrolactone.

By heating the same γ-hydroxy-N-alkyl amides for 12–15 hr. in an excess of boiling aniline, the formation of γ-lactam (subsequently to γ-lactonization) was increased greatly with respect to both amides. N-Methylamide (Ia) afforded γ-lactam (IIIa) in almost quantitative yield, and the more inhibited N-hexylamide yielded 60% of the lactam (IIIa).

δ-Hydroxyvaler-N-*p*-anisidide.—δ-Valerolactone (5 g., 0.05 mole) and *p*-anisidine (30.8 g., 0.25 mole) were heated under reflux for 2 hr. The reaction mixture solidified upon cooling. Petroleum ether was added and the crude product was crystallized from benzene–petroleum ether. The *p*-anisidide, 10 g. (90%), melted at 105°.

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.6; H, 7.7; N, 6.3. Found: C, 64.3; H, 7.5; N, 6.4.

δ-Hydroxyvaler-N-*p*-toluidide was prepared like *p*-anisidide was from *p*-toluidine (5.4 g., 0.05 mole) and δ-valerolactone (1 g., 0.01 mole). The *p*-toluidide, 2 g. (96%), melted at 115°.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.5; H, 8.3; N, 6.8. Found: C, 69.5; H, 8.1; N, 7.1.

δ-Hydroxyvaler-*p*-toluidide did not change after heating in an excess of *p*-toluidine for 6–12 hr. at reflux temperature of the solvent.

δ-Hydroxyvaleranilide.—δ-Valerolactone (2.5 g., 0.025 mole) and aniline (11.6 g., 0.125 mole) were heated under reflux for 2 hr. The excess aniline was removed under reduced pressure and the residue was dissolved in ethyl acetate. The solution was clarified with charcoal and a semisolid was precipitated by addition of petroleum ether. It crystallized on storage in the cold for 2–3 days. The δ-hydroxyamide, 3.9 g. (80%), melted at 68–70°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8; N, 7.2. Found: C, 67.7; H, 7.8; N, 7.0.

δ-Hydroxyvaleranilide did not change after heating for 6–12 hr. in an excess of aniline under reflux.

The three δ-hydroxyvaler-N-aryl amides showed characteristic bands in the infrared spectrum indicating hydroxyl and monosubstituted aromatic amide groups: λ_{max}^{Nujol} 2.9–3.0, 9.4 (−OH); 6.0, 6.5 (CO–NH); 13.3, 14.4 μ (aromatic monosubstituted).

Reactions of γ-Butyrolactone and Aniline.—γ-Butyrolactone (25.8 g., 0.3 mole) and aniline (139.5 g., 1.5 mole) were heated under reflux (150–170°) for nearly 18 hr. with protection against moisture. Aniline and unchanged γ-butyrolactone were distilled under reduced pressure. The semisolid residue was crystallized from petroleum ether, yielding 1-phenylpyrrolidin-2-one, 3.85 g., (8.0%), m.p. 68°. Heating at 150–170° for 72 hr. yielded 35% of the γ-lactam, and for 100 hr., 80%. Heating of the same amounts of γ-butyrolactone and aniline for 120 hr. in the presence of excess water (6 ml.), at lower reflux temperature (120–130°) yielded 60% of the γ-lactam.

Anal. Calcd. for $C_{10}H_{11}NO$: N, 8.7. Found: N, 8.5.

Heating the same quantities of reactants for 2 hr. yielded minimal amounts of N-phenylpyrrolidin-2-one. Spaeth[4] obtained 55% yield at 215° (12 hr.); the high yield (85%) according to Meyer and Vaughan[18] is determined by prolongation of heating time and by elevation of temperature toward the end of the reaction.

Attempted Reaction of α-Amino-γ-butyrolactone Hydrochloride with *p*-Nitroaniline.—α-Amino-γ-butyrolactone hydrochloride (4.1 g., 0.03 mole) and *p*-nitroaniline (20.7 g., 0.15 mole) in 150 ml. of nitrobenzene were heated under reflux for 2 hr. After removal of nitrobenzene by steam distillation, *p*-nitroaniline (19.6 g., 95%), m.p. 148°, was recovered.

Reaction of α-Benzamido-γ-hydroxybutyr-N-alkyl Amide in Ethanolic Hydrogen Chloride. α-Benzamido-γ-chlorobutyric Acid Ethyl Ester.—α-Benzamido-γ-hydroxybutyr-N-hexylamide (Ie) (1.5 g., 0.005 mole) was dissolved in 60 ml. of ethanol, and dry hydrogen chloride was passed through the solution for 2 hr., the temperature being kept near boiling. The mixture was left overnight, a small quantity of inorganic material was filtered off, and the γ-chloro ester was precipitated from the cooled ethanolic solution by portionwise addition of water. The product (0.8 g., 60%) melted at 63°, lit.[19] m.p. 67°.

Anal. Calcd. for $C_{13}H_{16}ClNO_3$: N, 5.2; OC_2H_5, 16.7. Found: N, 5.8; OC_2H_5, 16.3.

The same γ-chloro ester (identified by mixture melting point and infrared spectrum) was obtained when α-benzamido-γ-hydroxybutyramide or N-methylamide (Ia) were heated as described above for N-hexylamide.

Lactonization of γ-Hydroxybutyr-N-alkyl Amide in Polyphosphoric Acid.—α-Benzamido-γ-hydroxybutyr-N-benzylamide (1.6 g., 0.005 mole) in 30 ml. of polyphosphoric acid (from British Drug Houses, 80% P_2O_5) was heated at 100° for 4 hr. The mixture was poured into 100 ml. of ice-water, and the water solution was extracted with chloroform. The chloroform extract was washed first with aqueous sodium bicarbonate and then with water, and dried over anhydrous sodium sulfate. The solution was concentrated and the residue crystallized from ethanol–ether yielding a product, 0.6 g. (58%), melting at 142°. The latter was identified as α-benzamido-γ-butyrolactone by mixture melting point and infrared spectrum.

The same results were obtained with α-benzamido-γ-hydroxybutyr-N-methylamide (Ia) and -N-hexylamide (Ie) with polyphosphoric acid.

γ-Chlorobutyranilide.—γ-Chlorobutyryl chloride (14.1 g., 0.1 mole) was added with stirring to a solution of aniline (9.3 g., 0.1 mole) in dioxane–water (4:1, 100 ml.), and the solution was neutralized with 5% sodium bicarbonate. The precipitated oil was crystallized from benzene–petroleum ether yielding 13.8 g. (70%) of the γ-chloroanilide, m.p. 68–70°.

(18) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 1554 (1957).
(19) E. P. Painter, *J. Am. Chem. Soc.*, **69**, 232 (1947).

Anal. Calcd. for $C_{10}H_{12}ClNO$: N, 7.1; Cl, 17.9. Found: N, 7.0; Cl, 17.6.

γ-Hydroxybutyranilide.—γ-Chlorobutyranilide (3.9 g., 0.02 mole) was heated in a solution of sodium carbonate (10.6 g., 0.01 mole) in 150 ml. of 33% ethanol until it dissolved. The solution was refluxed for 2 hr. with stirring and, after storage overnight in the cold (0°), sodium carbonate was filtered off and the filtrate was evaporated to dryness under reduced pressure. The solid residue was taken into hot benzene, and the benzene solution was concentrated to a semisolid. Petroleum ether was added, and the precipitate, obtained after storage in the cold (0°) overnight, was recrystallized from benzene–petroleum ether. The γ-hydroxybutyranilide thus obtained, 0.6 g. (17%), melted at 74–75°; λ_{max}^{Nujol} 3.0, 3.1, 3.15 (OH, NH-secondary amide); 6.0, 6.5 (CO–NH); 13.0–13.7, 14.4 μ (monosubstituted aromatic).

Anal. Calcd. for $C_{10}H_{13}NO_2$: N, 7.8. Found: N, 7.6.

Evaporation of the petroleum ether precipitation solvent left 1.1 g. (34%) of 1-phenylpyrrolidin-2-one, identified by mixture melting point and infrared spectrum.

α-Benzamido-γ-chlorobutyr-N-benzylamide (V).—α-Benzamido-γ-hydroxybutyr-N-benzylamide (3.2 g., 0.01 mole) was dissolved with cooling (ice–salt bath) in 10 ml. of thionyl chloride. The reaction mixture was stirred, brought to room temperature, and then heated to boiling. After cooling, ether and petroleum ether were added. The separated oil was washed with water and dissolved in ethanol. The product was precipitated by addition of water and crystallized from ethanol, yielding 2.8 g. (85%), m.p. 168°.

Anal. Calcd. for $C_{18}H_{19}ClN_2O_2$: C, 65.3; H, 5.8; N, 8.5; Cl, 10.7. Found: C, 65.5; H, 5.4; N, 8.5; Cl, 11.0.

α-Benzamido-γ-chlorobutyr-N-cyclohexylamide was prepared as above (52%), m.p. 195°.

Anal. Calcd. for $C_{17}H_{23}ClN_2O_2$: C, 63.3; H, 7.2; N, 8.7; Cl, 11.0. Found: C, 64.0; H, 6.8; N, 8.5; Cl, 10.6.

1-Benzyl-3-benzamidopyrrolidin-2-one (VI).—α-Benzamido-γ-chlorobutyr-N-benzylamide (1.6 g., 0.005 mole) was dissolved in 50 ml. of 1 *N* methanolic sodium methoxide and heated for 4 hr. at reflux. The solvent was evaporated, and the residue was washed with water and crystallized from ether–petroleum ether. The product, 1.2 g. (80%), m.p. 160°, was identified by mixture melting point and infrared spectrum.[3]

α-Amino-γ-N-benzylaminobutyric Acid Dihydrochloride (VII).—1-Benzyl-3-benzamidopyrrolidin-2-one (1 g., 0.0034 mole) was heated in 25 ml. of 20% aqueous hydrochloric acid. After cooling, benzoic acid was filtered, and the solution was washed with ether and evaporated. The semisolid residue was crystallized twice from ethanol–ether yielding the product, 0.5 g. (52%), m.p. 185–188°.

Anal. Calcd. for $C_{11}H_{18}Cl_2N_2O_2$: C, 47.0; H, 6.5; N (Kj.), 10.0; N (V. Sl.), 5.0. Found: C, 47.4; H, 6.5; N (Kj.), 10.1; N (V. Sl.), 5.3.

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Organic Polysulfides.[1] IV. Synthesis of Bis(triphenylmethyl) Polysulfides

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Bis(triphenylmethyl) penta-, hexa-, hepta-, and octasulfides were obtained in crystalline state by condensation of the triphenylmethyl hydrodi- or hydrotrisulfide with sulfur di- or monochloride, respectively. For comparison, the bis(triphenylmethyl) mono-, di-, tri-, and tetrasulfides were prepared also by the ordinary methods. The ultraviolet absorption spectra of a series of these polysulfides were measured. No anomaly was observed among the spectra as the number of sulfur atoms increased from one to eight.

In a previous paper,[2] dibenzyl and dibenzhydryl penta- and hexasulfides were prepared by condensation of the corresponding aralkyl hydrodisulfides with sulfur di- and monochloride, respectively.

$$2RSSH + SCl_2 \longrightarrow RSSSSSR \quad (1)$$

$$2RSSH + S_2Cl_2 \longrightarrow RSSSSSSR \quad (2)$$

The corresponding mono-, di-, tri-, and tetrasulfides were prepared also to compare some properties of each series of polysulfides from mono- to hexasulfide. All the results obtained there supported linear sulfur linkages of the polysulfides.

Alkyl hydrotrisulfides, RSSSH, were prepared by Böhme and Zinner[3] as indicated in eq. 3–5, where R represents methyl, ethyl, or benzyl group. In the present paper, this method was applied to prepare triphenylmethyl hydrotrisulfide. Bis(triphenylmethyl) hepta- and octasulfides were prepared by condensation of 2 moles of triphenylmethyl hydrotrisulfide and 1 mole of sulfur di- and monochlorides, respectively. The synthetic method is indicated in eq. 3–7, where R represents the triphenylmethyl group.

$$2CH_3COSH + 2Cl_2 \longrightarrow CH_3COSSCl + CH_3COCl + 2HCl \quad (3)[4]$$

$$CH_3COSSCl + RSH \longrightarrow CH_3COSSSR + HCl \quad (4)[4]$$

$$CH_3COSSSR + C_2H_5OH \longrightarrow RSSSH + CH_3COOC_2H_5 \quad (5)[3]$$

$$2RSSSH + SCl_2 \longrightarrow RSSSSSSSR + 2HCl \quad (6)$$

$$2RSSSH + S_2Cl_2 \longrightarrow RSSSSSSSSR + 2HCl \quad (7)$$

As reported in part I for dibenzyl and dibenzhydryl compounds, bis(triphenylmethyl) penta- and hexasulfides were prepared according to eq. 1 and 2, respectively. The bis(triphenylmethyl) mono-, di-, tri-, and tetrasulfides also were prepared to obtain a series of polysulfides from mono- to octasulfide. All of the polysulfides were obtained in the crystalline state, although dibenzyl and dibenzhydryl hexasulfides could not be obtained in the crystalline state but only in the oily state as reported in a previous paper.

Table I indicates melting points, color, yields, and analytical data of these compounds.

The ultraviolet absorption spectra (Fig. 1) were measured in chloroform solution between 240 and 380 mμ. The strong absorption band with a maximum between 240 and 250 mμ may be ascribed to triphenylmethyl group. The broad absorption band in the range of 290–330 mμ is probably due to linear S–S linkages in the polysulfides, because ultraviolet absorption spectra[2] of dibenzyl and dibenzhydryl polysulfides indicate the similar broad band in the same region. Figure 1 shows that, as the number of sulfur atoms in these polysulfides increases, the absorbance becomes

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