and 695 (Ph) cm^{-1}; λ_{max} 252, 257, 262, 264, 267, and 280 (shoulder) mμ (ε 577, 742, 738, 765, 644, and 300).

Anal. Calcd for $C_{43}H_{54}N_4O_{13}$ (834.9); C, 61.83; H, 6.52; N, 6.71. Found: C, 61.66; H, 6.68; N, 6.67.

The tetrapeptide was alternatively prepared from N,O-dibenzyloxycarbonyl-L-tyrosine, L-leucyl-β-*t*-butyl-L-aspartyl-L-serine methyl ester, and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (68%).

Registry No.—Glucagon, 35-25-6; IV, 5545-52-8; V, 7635-36-1; III, 7646-47-1; VI, 7646-48-2; VII, 7646-49-3; VIII, 7646-50-6; XVI, 7641-11-4; XVII, 7646-51-7; XVIII, 7646-52-8; X, 7646-53-9; XII, 7688-12-2; XX, 7646-54-0; XXII, 7688-13-3.

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Cyclization of ω-Haloamides to Lactams

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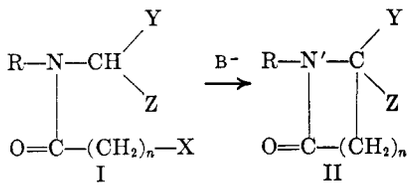
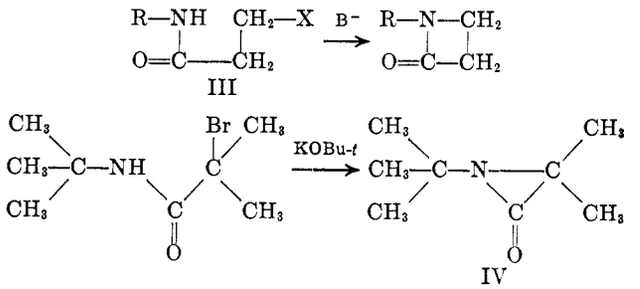
β-Lactams (n = 1) and γ-lactams (n = 2) of type II have been prepared in high yield by the cyclization of the intermediate I under the influence of a base[2-6] when Y and Z groups are electron-withdrawing groups, such as esters or nitriles.

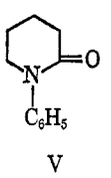


An interesting aspect of the cyclization of ω-haloacylaminomalonic esters (I, Y = Z = CO_2R) under the conditions used by Sheehan and Bose[2] is that it can yield only four- and five-membered lactams (n = 1 or 2). For reasons that are not clear neither the six- nor the seven-membered lactams (n = 3 or 4) can be prepared by this method.[3,6]

Another cyclization method that has been used for the synthesis of several β-lactams is that developed by Knunyants.[7] This involves the treatment of a β-haloamide of type III with a base, *e.g.*, sodium and liquid ammonia. That this method can be extended to three-membered heterocycles has been shown by Baumgarten[8] and Sheehan[9] in their syntheses of α-lactams (IV). Since no information can be found about the usefulness of this method for the synthesis of lactams of larger ring size we undertook a study on the cyclization of ω-haloamides (see Table I for pertinent data). We were particularly interested in finding out whether this cyclization had the same limitations as the cyclization of ω-haloacylaminomalonates.



In our study, sodium in liquid ammonia was used as the base for the cyclization of ω-haloamides. From Table II it will be seen that β-lactams could be prepared by this method in yields from 50 to 90%. The cyclization reaction was found to be equally successful for the synthesis of γ-lactams (48–79%). This method of lactam formation was also extended to the six-membered system[10] (V), but all attempts to cyclize ε-bromocaproic acid anilide under the Knunyants' conditions to get a seven-membered lactam failed and the starting amide was recovered.



V

We have also investigated the possibility of employing the readily available base, dimsyl anion, which is more convenient to work with than sodium in liquid ammonia. Corey[11] and others[12-14] have extensively used dimsyl anion ($CH_2^-SOCH_3$) as a base in various reactions. We have tested sodium hydride–dimethyl sulfoxide (DMSO) as well as potassium *t*-butoxide–DMSO as cyclization reagents for lactam synthesis from suitable haloamides. It was noticed that dimsyl anion could be used successfully to obtain four-, five-, and six-membered lactams. However, this base failed to product the seven-membered heterocyclic ring.

A comparative study on the use of various bases to effect the cyclization of β-bromopropionanilide was undertaken. Sodium in liquid ammonia, sodium hydride in DMSO, and potassium *t*-butoxide in DMSO were the bases examined. The best yield (95%) of 1-phenyl-2-azetidinone was obtained with sodium hydride in DMSO. Sodium in liquid ammonia and potassium *t*-butoxide in DMSO gave 68 and 70% of cyclized product, respectively. Since other haloamides

(1) Abstracted from the M.S. Thesis of S. J. Jeng, Stevens Institute of Technology, 1966.

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(7) I. L. Knunyants and N. P. Gambaryan, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1037 (1955), and subsequent papers in this series.

(8) (a) H. E. Baumgarten, R. L. Zey, and U. Krolls, *J. Am. Chem. Soc.*, **83**, 4469 (1961); (b) H. E. Baumgarten, *ibid.*, **84**, 4975 (1962); (c) H. E. Baumgarten, J. F. Fuerholzer, R. D. Clark, and R. D. Thompson, *ibid.*, **85**, 3303 (1963).

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(10) N-Phenyl-2-piperidone has been prepared before by a sequence of multiple steps or by special techniques, such as, electrolytic reduction using lead cathodes. See B. Sakuri, *Bull. Chem. Soc. Japan*, **13**, 482 (1938); F. Boyer, German Patent 943,228 (1938); O. V. Schickh, British Patent 914,404 (1963); M. A. Butt, J. A. Elvidge, and A. B. Foster, *J. Chem. Soc.*, 3068 (1963).

(11) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).

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(13) G. G. Price and M. C. Whiting, *ibid.*, 775 (1963).

(14) F. C. Chang and N. W. Wood, *Tetrahedron Letters*, 2969 (1964).

TABLE I
ω-HALOAMIDES

Compd (no.)	Mp, °C	Yield, %	Formula	Anal., % Found C	Found H	Found N	Calcd C	Calcd H	Calcd N
N-Phenyl-β-bromopropionamide[a] (1)	118–118.5	75.2							
N-o-Bromophenyl-3-bromopropionamide (2)	93–94.5	97	$C_9H_9Br_2NO$	35.10	2.65	4.65	35.21	2.96	4.56
N-o-Fluorophenyl-3-bromopropionamide (3)	84.5–85	92	C_9H_9BrFNO	44.00	3.84	5.71	43.92	3.69	5.79
N-p-Bromophenyl-3-bromopropionamide (4)	134	90	$C_9H_9Br_2NO$	35.56	2.76	4.50	35.40	2.96	4.56
N-p-Bromophenyl-2,2-dimethyl-3-chloropropionamide (5)	110–111	73	$C_{11}H_{13}BrClNO$	45.85	4.32	4.84	45.46	4.51	4.82
N-p-Chlorophenyl-3-bromopropionamide (6)	126–127	86	$C_9H_9BrClNO$	42.94	3.15	5.25	41.17	3.46	5.34
N-p-Iodophenyl-3-bromopropionamide (7)	157–158	80.3	C_9H_9BrINO	30.71	2.73	4.04	30.57	2.57	3.96
N-p-Methoxyphenyl-3-bromopropionamide (8)	111–112	58.6	$C_{10}H_{12}BrNO_2$						
N-Phenyl-4-bromobutyramide[b] (9)	69–71	81	$C_{10}H_{12}BrNO$						
N-o-Bromophenyl-4-bromobutyramide (10)	67–68.5	88	$C_{10}H_{11}Br_2NO$						
N-o-Fluorophenyl-4-bromobutyramide (11)	57–57.5	61	$C_{10}H_{11}BrFNO$	67.00	5.33	7.94	67.03	5.63	7.81
N-p-Bromophenyl-4-bromobutyramide (12)	110–111	88	$C_{10}H_{11}Br_2NO$						
N-p-Chlorophenyl-4-bromobutyramide (13)	92.5–93.5	84.2	$C_{10}H_{11}NrClNO$	33.11	3.03	3.59	32.63	3.01	3.81
N-p-Iodophenyl-4-bromobutyramide (14)	136.5–137.5	75	$C_{10}H_{11}BrINO$	44.12	4.16	5.10	43.42	4.01	5.06
N-Phenyl-5-bromovalaramide (15)	95.5–97	70.3	$C_{11}H_{14}BrNO$						
N-Phenyl-6-bromocaproamide (16)	79–81	65	$C_{12}H_{16}BrNO$						
N-3α-Cholestanyl-4-bromobutyramide (17)	201–202	95	$C_{31}H_{54}BrNO$	68.98	10.11		69.37	10.14	2.61

[a] E. H. Charlesworth and H. J. Anderson, *Can. J. Res.*, **28b**, 1 (1950). [b] H. W. Heine, P. Love, and J. L. Bove, *J. Am. Chem. Soc.*, **77**, 5420 (1955).

TABLE II
LACTAMS

Compd (no.)	Mp, °C	Yield, %	Method	Formula	Anal., % Found C	Found H	Found N	Calcd C	Calcd H	Calcd N
1-Phenyl-2-azetidinone (1)	77–78	68	A							
		95.6	B							
		70.3	C							
1-o-Bromophenyl-2-azetidinone (2)	53–54	71	B	C_9H_8BrNO	47.74	3.89	6.08	47.82	3.57	6.30
1-o-Fluorophenyl-2-azetidinone (3)	76.5–77	90.4	B	C_9H_8FNO						
1-p-Bromophenyl-2-azetidinone (4)	125–126.5	58	A	C_9H_8BrNO	47.66	3.54	6.06	47.82	3.57	5.20
1-p-Bromophenyl-3,3-dimethyl-2-azetidinone (5)	83–84	55	A	$C_{11}H_{12}BrNO$	52.04	4.69	6.09	51.99	4.76	5.51
1-p-Chlorophenyl-2-azetidinone (6)	131.5–132.5	73	B	C_9H_8ClNO	39.55	2.99	4.72	39.64	2.96	5.14
1-p-Iodophenyl-2-azetidinone (7)	157–159	80.6	B	C_9H_8INO	59.18	4.88	7.81	59.52	4.44	7.71
1-p-Methoxyphenyl-2-azetidinone (8)	98–99	50	A	$C_{10}H_{11}NO_2$	67.84	6.17	8.08	67.77	6.25	7.91
1-Phenyl-2-pyrrolidone[a] (9)	65–66	48	A	$C_{10}H_{11}NO$						
1-o-Bromophenyl-2-pyrrolidone (10)	54.5–55	50	B	$C_{10}H_{10}BrNO$	50.03	4.26	5.71	50.02	4.20	5.83
1-o-Fluorophenyl-2-pyrrolidone (11)	50–51	61	B	$C_{10}H_{10}FNO$	67.00	5.33	7.94	67.03	5.63	7.81
1-p-Bromophenyl-2-pyrrolidone (12)	97–98	67	A	$C_{10}H_{10}BrNO$	50.36	4.08	5.96	50.02	4.16	5.83
1-p-Chlorophenyl-2-pyrrolidone (13)	94–95	54	B	$C_{10}H_{10}ClNO$	42.21	3.84	4.34	41.83	3.51	4.85
1-p-Iodophenyl-2-pyrrolidone (14)	140.5–141.5	79	B	$C_{10}H_{10}INO$	60.95	5.06	6.71	61.38	5.15	7.16
1-Phenyl-2-piperidone[b] (15)	101–102	61.5	A	$C_{11}H_{13}NO$						
1-3α-Cholestanyl-2-pyrrolidone (16)	129–130	90	B	$C_{31}H_{53}NO$	81.38	11.36		81.69	11.72	3.07

[a] G. R. Proctor and R. H. Thomson, *J. Chem. Soc.*, 2302 (1957). [b] M. A. Butt, J. A. Elvidge, and A. B. Foster, *ibid.*, 3068 (1963).

were not studied under parallel conditions it will not be appropriate to generalize but from the point of view of high yield and ease of operation sodium hydride in DMSO can be recommended as a convenient base for this type of cyclization.

Experimental Section[15]

Representative experimental procedures are described below.

N-p-Bromophenyl-2,2-dimethyl-3-chloropropionamide.—A solution of p-bromoaniline (4.3 g), β-chloropivalic acid (3.44 g), and phosphorus trichloride (4 ml) in benzene was refluxed for 4 hr. The reaction mixture was washed with water, sodium bicarbonate solution, dilute hydrochloric acid, and water, respectively. The solvent from the benzene layer after drying over anhydrous magnesium sulfate was removed under reduced pressure. The residue was crystallized from benzene–petroleum ether (bp 38–52°) as colorless needles: mp 110–111°, λ_{max}^{Nujol} 3.02 (NH) and 6.02 μ (amide carbonyl).

N-Phenyl-β-bromopropionamide.[16]—A benzene solution (250 ml) of aniline (6.2 g) and β-bromopropionyl chloride (11.36 g) was refluxed for 3 hr. The reaction mixture was then treated as above to get the amide.

1-Phenyl-2-azetidinone.[17] **A. Using the Sodium in Liquid Ammonia Method.**—In a two-necked, round-bottom flask fitted with a nitrogen inlet and a calcium chloride tube, were placed about 30 ml of liquid ammonia and a few crystals of ferric nitrate. The flask was cooled in a Dry Ice–acetone bath. Small pieces of sodium metal (1.26 g) were added over a period of 10 min. The reaction mixture was stirred. Blue color developed on the addi-

(15) All melting points are uncorrected. Microanalyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck Institut, Mülheim (Ruhr), West Germany. The nmr spectra were recorded on a Varian A-60A spectrometer. The infrared spectra of the compounds were recorded on a Perkin-Elmer Infracord. Compounds **8**, **10**, **12**, **16** (Table I), and **3** (Table II) which have not been described previously gave the expected molecular ion and fragmentation pattern in their mass spectra recorded on a 21-103C CEC mass spectrometer.

(16) See Table I, footnote *a*.

(17) J. C. Sheehan and P. T. Izzo, *J. Am. Chem. Soc.*, **70**, 1985 (1948); **71**, 4059 (1949).

tion of sodium. After the blue color disappeared the N-phenyl-β-bromopropionamide (5.7 g) was added in small amounts. The mixture was then left at room temperature. When all the ammonia had evaporated the residue was extracted with benzene. The benzene extract was washed with water and dilute hydrochloric acid and dried over magnesium sulfate. Evaporation of the solvent afforded 2.6 g (68%) of the product which was crystallized from ethanol–water mixture, mp 77–78° (lit.[17] mp 78–79°), λ_{max}^{Nujol} 5.72 μ. The proton nmr spectrum showed multiplet at τ 2.79 (5 H, aromatic), triplet centered at 6.49 (CH_2N), and another triplet at 7.03 (CH_2CO).

B. Using the Sodium Hydride–DMSO Method.—In a flame-dried, two-necked flask, fitted with a nitrogen inlet and a dropping funnel, were placed DMSO (about 10 ml) and sodium hydride (0.6 g). The flask was warmed in the oil bath carefully below 75° under vigorous stirring until the evolution of hydrogen ceased. The color of the solution in the flask turned light brown. This solution was cooled to room temperature, and a methylene chloride solution (20 ml) of N-phenyl-β-bromopropionamide (4.6 g) was added dropwise. The reaction mixture was allowed to stand for 8 hr. Water was then added to the reaction mixture and extracted with benzene. The benzene extract was treated as usual to get the β-lactams (2.86 g, 95.6%).

C. Using the Potassium *t*-Butoxide–DMSO Method.—The procedure was essentially the same as in method B excepting that potassium *t*-butoxide was substituted for sodium hydride.

Registry No.—N-*p*-Bromophenyl-2,2-dimethyl-3-chloropropionamide, 7661-06-5; in Table I—**1**, 7661-07-6; **2**, 7661-08-7; **3**, 7661-09-8; **4**, 7661-10-1; **5**, 7661-06-5; **6**, 7661-12-3; **7**, 7661-13-4; **8**, 7661-14-5; **9**, 7661-15-6; **10**, 7661-16-7; **11**, 7661-17-8; **12**, 7634-72-2; **13**, 7661-18-9; **14**, 7661-19-0; **15**, 7661-20-3; **16**, 7661-21-4; **17**, 7661-22-5; in Table II—**1**, 4458-63-3; **2**, 7661-23-6; **3**, 7661-24-7; **4**, 7661-25-8; **5**, 7661-26-9; **6**, 7661-27-0; **7**, 7661-28-1; **8**, 7661-29-2; **9**, 4641-57-0; **10**, 7661-30-5; **11**, 7661-31-6; **12**, 7661-32-7; **13**, 7661-33-8; **14**, 7661-34-9; **15**, 4789-09-7; **16**, 7661-36-1.

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Aza Steroids. VII. 18-Nor-D-Homo-8-Aza Steroids

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In a continuing study[2] on the total synthesis of aza steroids, we have prepared, *via* a novel route, the 18-nor-D-homo-8-azaestrone derivative, I, previously described by Nelson,[3] *via* II. Our approach to I began with the tetrahydroisoquinoline, III, which condensed smoothly with 1,3-cyclohexanedione to give the enamino ketone alcohol IV, in good yield.[2] However, when the latter was treated with phosphorus tribromide, an oily bromide, V, was obtained which slowly crystallized, on standing, to a salt containing ionic bromine. The ultraviolet spectrum of salt possessed a maximum at 318 mμ (ε 33,400) and infrared bands typical of the conjugated iminium linkage. As previously reported,[2] the bromide V, when treated immediately after preparation with silver perchlorate in acetonitrile, gave an unstable iminium salt (VI, X = ClO_4), which was quickly neutralized with dilute base to give VII in high yield. The structure of the salt obtained by spontaneous cyclization of V was still uncertain, but further insight into its nature was obtained when this salt produced VII when cautiously neutralized with dilute base. Alternatively, VII, upon treatment with hydrogen bromide, gave VIII (see Scheme I). On the basis of this behavior the salt was assigned the structure, VIII, which is the O-protonated form of the enamino ketone VII.

When VIII and VI each were hydrogenated in the presence of platinum oxide, the amino alcohol IX, was obtained as the sole product in both cases. The stereochemistry of IX was assigned by both chemical and spectroscopic techniques. Considering the BC-ring junction initially, IX was completely devoid of Bohlmann bands[4] in the infrared; yet the nmr spectrum exhibited the C-9 proton (steroid numbering) at τ 6.4. The data obtained from these techniques proved to be contradictory since *trans*-quinolizidines have usually been found to possess Bohlmann bands and exhibit the C-9 proton above τ 6.2.[5] In order to clarify the discrepancy of the BC fusion, the alcohol IX was oxidized to the ketone I using the Jones method.[6] Examination of I clearly showed the Bohlmann absorption of the *trans*-quinolizidine (BC rings) and the C-9 proton at 6.3–6.4 (partially masked under the *methoxyl* singlet). A search of the literature provided other examples where Bohlmann bands appeared *not* to have been observed in systems known to possess the *trans*-quinolizidine moiety.[7] The possibility still remained, however, that the Jones oxidation proceeded with epimerization at C-9, resulting in the *trans*-BC junction. This possibility was discarded when the ketone I was reduced stereospecifically back to the starting alcohol IX, and the Bohlmann bands were once again absent. With the BC-ring stereochemistry firmly established, the stereochemistry at C-13, -14, and -17a was next investigated. The CD junction can be considered to be *trans* since no epimerization occurred when the ketone I was equilibrated with base. Nelson[3] has also assigned the *trans*-CD junction to ketone I, obtained by lithium aluminum hydride reduction of VII, as well as the *trans*-BC junction. The configuration of the 17a-hydroxyl group in IX was assigned an *axial* position based upon nmr chemical shifts of axial and equatorial cyclohexanols. Eliel has shown[8] that the carbinol proton in axial alcohols appear at 210–250 cps and at 180–190 cps for equatorial alcohols. The carbinol proton in IX appeared at 240–250 cps (τ 5.8–6.0).

(1) This study was supported by funds granted by the National Institutes of Health (NIGMS-06248-06).

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