[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY[1]]

Reactions of Lactams with Diazoalkanes[2]

JACK W. RALLS[3]

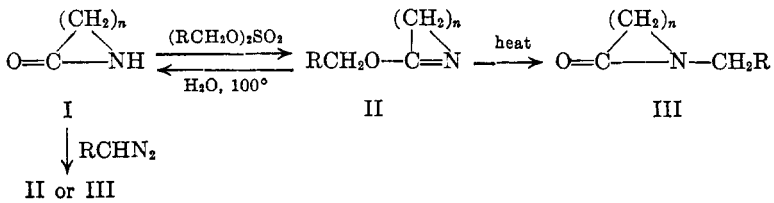
Received April 22, 1960

Five-, six-, and seven-membered lactams react sluggishly with diazomethane and diazoethane to produce *O*-alkyllactims or *N*-alkyllactams. Only traces of products are formed from lactams and diazoalkanes in pure ether solution. The reaction is promoted by alcohols. Caprolactam and valerolactam give *O*-alkyllactims with alcoholic, ethereal diazoalkane solutions. The *N*-alkylation of butyrolactam is catalyzed by fluoboric acid.

During a study of vegetable flavor, non-volatile acids were determined by gas chromatography of their ethyl esters.[4,5] In the preparation of reference standards for this determination, an anomalous reaction was observed between 5-pyrrolidone-2-carboxylic acid and diazoethane. A second product, $C_9H_{15}O_3N$, accompanied the expected ethyl ester; it appeared to be formed by ethylation of the lactam moiety. To obtain a better understanding of this result, an investigation of the reactions of monocyclic lactams with diazoalkanes was made.

A literature search through 1956 revealed no previous description of the reactions of monocyclic, monofunctional lactams with diazoalkanes. A number of more complex lactams have been treated with diazomethane and the products identified. While oxindole does not react,[6] the methylation of 3-hydroxymethyleneoxindole has been reported by several groups[7]; the products are 3-methoxymethyleneoxindole and 2-methoxy-3-formylindole. Benzoxazolinones produce *N*-alkylated products on treatment with diazomethane.[8] Dissolved 2-oxo-1,2-dihydrobenzo-1,3,4-triazine reacts to produce the *O*-alkylated product; treatment of the solid compound with ethereal diazomethane results in *N*-alkylation primarily.[9] The recorded information suggests that *N*-alkylation is the expected result of the reaction between lactams and diazoalkanes. *O*-alkylation would take place when the rare[10,11] lactim tautomer is favored.

The alkylation, hydrolysis, and thermal rearrangement of lactams are summarized in the following representation. The preparation of *O*-alkylcaprolactims (II. $n = 5$, R = CH_3, H) by the slow addition of an alkyl sulfate to a refluxing solution of caprolactam in benzene was described by Benson and Cairns.[12] Using the same conditions, it was found that valerolactam gave the *O*-alkyllactim (II. $n = 4$, R = H) and that butyrolactam gave only the *N*-alkyllactam (III. $n = 3$, R = CH_3).



Thermal rearrangement of the *O*-alkyllactims provided the *N*-alkyllactams.[12]

Analysis of the mixtures produced by the reactions of lactams with diazoalkanes was made using gas chromatography. The retention times of the compounds used in this study are tabulated in Table I.

The results of reactions of lactams with two equivalents of diazoalkane under various solvent conditions are shown in Table II. The extent of reaction is very low with alcohol-free, ethereal, solutions of diazoalkanes.

With the six- and seven-membered ring lactams,

(1) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Dept. of Agriculture.

(2) Presented in part before the Organic Chemistry Division, American Chemical Society, 137th National Meeting, Cleveland, Ohio, April 1960.

(3) Collaborator employed by the National Canners Association with which this work was conducted cooperatively.

(4) H. G. Walker, unpublished results, Western Regional Laboratory, 1956–57.

(5) L. D. Quin and M. E. Hobbs, *Anal. Chem.*, **30**, 1400 (1958).

(6) G. Heller, *Ber.*, **52**, 741 (1919).

(7) See. E. Wenkert, N. K. Bhattacharyya, T. L. Reid, and T. E. Stevens, *J. Am. Chem. Soc.*, **78**, 797 (1956) and references cited therein.

(8) H. Zinner and H. Herbig, *Chem. Ber.*, **88**, 1241 (1955).

(9) L. Ergener, *Rev. fac. sci. univ. Istanbul*, **A15**, 91 (1950); *Chem. Abstr.*, **44**, 10718h (1950).

(10) F. Arndt, *Rev. fac. sci. univ. Istanbul*, **A9**, 19 (1944); *Chem. Abstr.*, **40**, 1787[6] (1946).

(11) For an interesting lactam-lactim structure see W. S. Worrall, 136th Meeting of the American Chemical Society, Atlantic City, N. J., September 1959, Abstracts of Papers, p. 31P.

(12) R. E. Benson and T. L. Cairns, *J. Am. Chem. Soc.*, **70**, 2115 (1948).

TABLE I

RETENTION TIMES FOR LACTAMS AND ALKYLATED LACTAMS, MINUTES

Compound	Column Substrate: LAC 446 150°	LAC 446 202°	Apiezon 150°	DEGA 202°
N-Ethylbutyrolactam	—	—	12.3	—
Butyrolactam	—	—	18.4	—
O-Methylvalerolactim	1.6	—	4.5	—
N-Methylvalerolactam	15.0	—	—	—
Valerolactam	45.2	—	—	—
O-Methylcaprolactim	2.0	—	6.6	—
O-Ethylcaprolactim	2.3	—	9.0	—
N-Ethylcaprolactam	20.6	—	29.7	—
Caprolactam	54.2	11.3	—	—
Ethyl 1-ethyl-5-pyrrolidone-2-carboxylate	12.1	2.6	—	16.8
Ethyl 5-pyrrolidone-2-carboxylate	>150.0	32.9	—	42.8

TABLE II

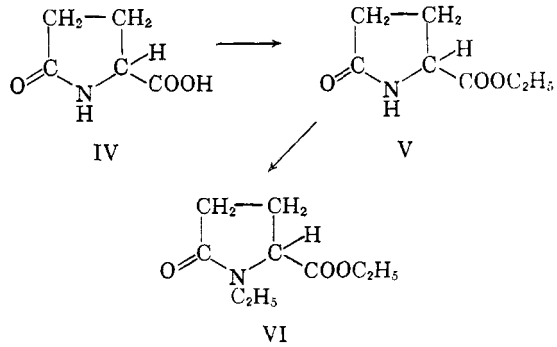
REACTIONS OF LACTAMS WITH DIAZOALKANES

Compound	Conditions[a]	Products, *O*-Alkyl	Ratio of GC Peak Areas: *N*-Alkyl	Lactam
Butyrolactam	C	0	0	98
	D	0	1	15
Valerolactam	A	1	0	63
	B	1	0	7.3
Caprolactam	A	1	0	86
	B	1	0	14
	C	1	0	10
Ethyl 5-pyrrolidone 2-carboxylate	C	0	1	29
5-Pyrrolidone-2-carboxylic acid	C	0	1	2
	E	0	1	1275

[a] A. Diazomethane in anhydrous ether. B. Diazomethane in ether-methanol. C. Diazoethane in ether-ethanol-1-propanol. D. Diazoethane in ether + 5 mole % fluoboric acid. E. Diazoethane in anhydrous ether.

the addition of alcohol promotes a slow reaction to form *O*-alkyllactims. No reaction takes place with the unsubstituted butyrolactam until the reaction is catalyzed with fluoboric acid[13,14] and the product is the *N*-alkyllactam.

The observation which motivated this study is apparently a special case of catalysis by the surface of the ether-insoluble 5-pyrrolidone-2-carboxylic acid (IV). The secondary product is ethyl 1-ethyl-5-pyrrolidone-2-carboxylate (VI); this conclusion follows from the empirical formula, infrared spectrum, and thermal and hydrolytic[12] stability. The observation that V gives about a 3% yield of VI under conditions where butyrolactam forms no *N*-ethylbutyrolactam may imply that a concerted intramolecular *trans*-ethylation is operating in the



pyrrolidonecarboxylic acid series. No further study of these reactions is planned.

The results reported here emphasize the importance of using alcohol-free diazoalkane solutions to avoid possible reaction with the lactam portion of a compound being treated. The reaction of lactams with diazoalkanes is so slow that in most uses of diazoalkanes other functional groups would react preferentially to the lactam portion. A recent example of this situation is the formation of the enol ether of methyl 3-azabenzocycloheptene-4,7-dione-6-carboxylate on reaction with excess diazomethane in ether-methanol.[15]

EXPERIMENTAL

Diazoalkane solutions. A. Diazomethane in absolute ether prepared from nitrosomethylurea by distillation with ether and drying over potassium hydroxide pellets.[16] B. Above preparation containing added methanol (2% by volume). C. Diazoethane in ether containing some ethanol and 1-propanol[17] prepared from nitrosoethylurethane by distillation with ether.[18] D. Diazoethane in anhydrous ether prepared from nitrosoethylurethane and a solution of sodium in ethylene glycol with nitrogen sweeping.[19] The yield was only 25% and considerable low boiling material was formed concurrently (shown by gas chromatography). E. Diazoethane in anhydrous ether prepared as for diazomethane[20] except that *N*-ethyl-*N*-nitroso-*p*-toluenesulfonamide[21] was used in place of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide; yield 35%. The content of diazoalkanes was determined by the benzoic acid assay method. The reactions of lactams with diazoalkane solutions were carried out by swirling at 0–4° for 1 hr. followed by standing at 22–26° for 16 hrs.

The gas chromatography unit was an Aerograph Model A-110 C instrument with a four filament thermal conductivity cell and a 1-mv., recorder. The 1/4 in. by 5 ft. columns used were LAC 446 (glycol-adipate polymer), Apiezon "M," or diethylene glycol–adipate polymer (DEGA) 30 parts on firebrick (30–60 mesh) 70 parts. The carrier gas was helium at a flow rate of 50 ml. per min. Temperature control was ±1°.

(13) M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, **6**, 36 (1959).

(14) E. Muller, H. Huber-Emden, and W. Rundel, *Ann.*, **623**, 34 (1959).

(15) T. A. Geissman and A. K. Cho, *J. Org. Chem.*, **24**, 41 (1959).

(16) *Org. Syntheses*, Coll. Vol. II, 165 (1943).

(17) J. van den Berghe, Ph.D. thesis, University of Wisconsin, 1952.

(18) A. L. Wilds and A. L. Meader, Jr., *J. Org. Chem.*, **13**, 763 (1948).

(19) H. Meerwein and W. Burneleit, *Ber.*, **61**, 1840 (1928).

(20) T. J. deBoer and H. J. Backer, *Rec. trav. chim.*, **73**, 229 (1954).

(21) D. H. Hey and T. J. deBoer, *Rec. trav. chim.*, **73**, 686 (1954).

Preparation of the reference compounds followed literature directions. *O*-ethylcaprolactim[12] (infrared: 3.4, 5.95, 6.90, 7.26, 7.45, 7.98, 8.37, 9.17, 9.52 μ), *N*-ethylcaprolactam[12] (infrared: 3.42, 6.12, 6.74, 6.96, 7.25, 8.34 μ), *N*-methylvalerolactam[22] [infrared: 2.9 (hygroscopic), 3.4, 6.14, 6.64, 7.38 μ]. *O-Methylvalerolactim* was prepared using the method described for *O*-methylcaprolactim.[23] The fraction b.p. 56°/32 mm. was collected, yield 48%, n_D^{25} 1.4538. Infrared: 3.4, 5.96, 6.96, 7.35, 7.45, 8.22, 9.83 μ.

Anal. Calcd. for $C_6H_{11}ON$ (113.15): C, 63.68; H, 9.80; N, 12.38. Found: C, 63.4; H, 9.65; N, 12.3.

Attempted *O*-alkylation[23] of 2-pyrrolidone (butyrolactam) gave, as the only product, *N*-ethylbutyrolactam,[24] b.p. 90–92°/15 mm., n_D^{25} 1.4624 in 38% yield.

Treatment of ethyl D,L-5-pyrrolidone-2-carboxylate under the same conditions[23] with ethyl sulfate resulted in a partial reaction (ethyl sulfate recovered) and a poor yield of ethyl 1-ethyl 5-pyrrolidone-2-carboxylate.

The following method for preparation of the known[25] ethyl D,L-5-pyrrolidone-2-carboxylate was used: A suspension of 15 g. of D,L-5-pyrrolidone-2-carboxylic acid[26] in 150 ml. of ethanol was mixed with 1.5 g. of *p*-toluenesulfonic acid monohydrate and heated under reflux. The solution was treated with 50 ml. of benzene and slowly distilled using a Vigreux column over a period of 0.5 hr. During another 4.5 hr., addition of a mixture of 75 ml. of benzene and 19 ml. of ethanol was made to keep the volume of the reaction mixture essentially constant. The cooled reaction mixture was treated with 0.42 g. of anhydrous sodium carbonate, filtered, and the ethanol and benzene removed at reduced pressure. The residue was distilled. The fraction boiling at 136–138°/0.5 mm. was collected. The liquid product (15.9 g., 87% yield) solidified after long standing, m.p. 49–51°; infrared: 3.05, 3.32, 5.75, 5.85, 8.28 μ.

Anal. Calcd. for $C_7H_{11}O_3N$ (157.17): C, 53.49; H, 7.06; N, 8.91. Found: C, 53.4; H, 6.99; N, 8.80.

Ethyl 1-ethyl-5-pyrrolidone-2-carboxylate. The reaction of 3 g. of D,L-5-pyrrolidone-2-carboxylic acid with two equivalents of diazoethane[18] gave a liquid product. Distillation produced 0.8 g. of liquid, b.p. 83–85°/2 mm., n_D^{25} 1.4496, and 1.8 g. of ethyl 5-pyrrolidone-2-carboxylate. The first fraction was not homogenous as shown by gas chromatography. The purified sample was isolated from the effluent helium stream of the gas chromatography unit, n_D^{25} 1.4596, infrared: 3.36, 5.74, 5.88, 6.85, 7.03, 7.80, 8.34 μ.

Anal. Calcd. for $C_9H_{15}O_3N$ (185.22): C, 58.36; H, 8.16; N, 7.56. Found: C, 57.6; H, 8.15; N, 7.45.

The product was stable at 180–220° and also was recovered after heating in boiling water for 5 hr.[12,27]

Acknowledgments. The author is indebted to H. G. Walker, J. W. Corse, and L. A. Goldblatt for gifts of reagents and for discussions of the problem. The analyses were made by L. M. White and G. E. Secor. The 2-pyrrolidone was a gift from Antara Chemicals, New York.

ALBANY, CALIF.

(22) L. Ruzicka, *Helv. Chim. Acta*, 4, 472 (1921).

(23) *Org. Syntheses*, 31, 72 (1951).

(24) N. J. Leonard and A. B. Simon, *J. Org. Chem.*, 17, 1262 (1952).

(25) E. Abderhalden and E. Wurm, *Z. Physiol. Chem.*, 82, 160 (1912).

(26) A. F. Beecham, *J. Am. Chem. Soc.*, 76, 4613 (1954).

(27) Mention of specific products does not imply endorsement by the Department of Agriculture over others of a similar nature not mentioned.

[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN & PHARMACEUTICAL CORP.]

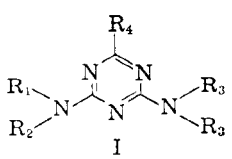
Guanamines. V. Chloromethylguanamines

SEYMOUR L. SHAPIRO, ELAINE S. ISAACS, VINCENT A. PARRINO AND LOUIS FREEDMAN

Received May 19, 1960

A series of chloromethylguanamines (I) have been prepared. The reduction of I, R_4 = —CH_2Cl to I, R_4 = —CH_3 with acetone-sodium iodide-acetic acid has been effected in a wide variety of I, and a mechanism for this reaction proposed.

As intermediate reactants for preparation of aminomethylguanamines[1] and allied derivatives, halomethylguanimines of the type I were required.



I

R_1 = alkyl, aralkyl, aryl
R_2 = hydrogen, alkyl
R_1R_2N = heterocyclic rings
R_3 = hydrogen, methyl
R_4 = —CH_2Cl, —$CHCH_3Cl$

The compounds were obtained from the R_1-R_2—N^1—, R_3R_3—N^5— substituted biguanide upon reaction with the appropriate ester, $R_4COOC_2H_5$, or acid chloride, R_4COCl, as previously described[2] (Table I).

As reactions of the halogen in chloromethylguanamines have been only briefly evaluated,[3–5] it was of interest to study this in further detail.

Heating typical compounds wherein I, R_4 = —CH_2Cl (or even —CH_2I), —$CHCH_3Cl$ in alcoholic silver nitrate gave no precipitate of silver halide. Treatment of such compounds with sodium iodide in acetone, with warming, yielded rapid precipitation of sodium chloride. Employment of acetone–sodium iodide–acetic acid reagent[3] (ASA reagent) resulted in rapid oxidation of iodide to iodine. Upon treatment of the reaction mixture with aqueous sodium bisulfite, a variety of I,

(1) S. L. Shapiro, E. S. Isaacs, and L. Freedman, *Guanamines. VI, J. Org. Chem.*, 26, 74 (1961).

(2) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, 81, 3996 (1959).

(3) S. L. Shapiro and C. G. Overberger, *J. Am. Chem. Soc.*, 76, 97 (1954).

(4) V. Ettel and J. Nosek, *Chem. Listy.*, 46, 289 (1952) [*Chem. Abstr.*, 47, 4344 (1953)].

(5) W. H. Schuller, U. S. Patents 2,848,413, 2,848,451, 2,848,452 (Aug. 19, 1958).