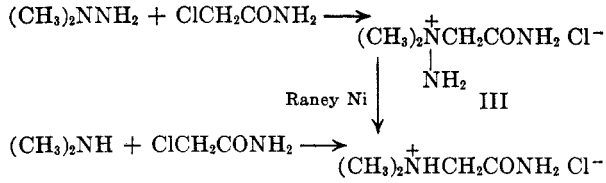
In another attempt to prepare II, an aqueous solution of compound I was refluxed with excess acrylonitrile for 36 hours, but the starting materials were recovered.

The failure of *unsym*-dimethylhydrazine to undergo double cyanoethylation can be compared to the difficulty with which methylamine and ethylamine react with a second mole of acrylonitrile.[1] The amines do yield dicyanoethylated products, however, under conditions in which only monocyanoethylation of *unsym*-dimethylhydrazine occurs.

Although it is known that alkylhydrazines undergo alkylation on the nitrogen which already bears an alkyl group,[2,3] the reaction of chloroacetamide and *unsym*-dimethylhydrazine was examined as a possible route to the desired acetic acid derivative.



The product isolated was 1-carbamylmethyl-1,1-dimethylhydrazinium chloride (III) as shown by the following observations. Hydrogenolysis of the nitrogen-nitrogen bond with Raney nickel in ethanol[4] produced a crystalline solid which did not depress the melting point of an authentic specimen of N,N-dimethylaminoacetamide hydrochloride. The latter compound was prepared by passing dimethylamine into a solution of monochloroacetamide in dioxane.

Although no attempt was made to hydrolyze III, the hydrolysis of I was tried using the barium hydroxide method which has been employed in the hydrolysis of β-aminopropionitrile to β-alanine.[5] No identifiable material was isolated. Hydrolysis with concentrated hydrochloric acid was also unsuccessful. From an attempt to convert the nitrile to the corresponding amide using polyphosphoric acid[6] only resinous materials were isolated. An attempt was also made to convert I directly to the ester by refluxing with an ethanolic solution of hydrogen chloride, but again only tars were obtained.

EXPERIMENTAL[7]

1,1-Dimethyl-2-(β-cyanoethyl)hydrazine. Acrylonitrile (17.5 g., 0.33 mole) was added slowly to a refluxing solution of 30 g. (38 ml., 0.5 mole) of *unsym*-dimethylhydrazine in 40 ml. of water. After an additional two hours of heating the reaction mixture was distilled under reduced pressure. The principal fraction distilled at 80–90° (3 mm.) and weighed 33 g. (87%). The product was a colorless, odorless oil, n_D^{25} 1.441, d_4^{20} 0.92, which slowly turned red on standing.

1,1-Dimethyl-2-(β-cyanoethyl)-4-phenylthiosemicarbazide. Equal amounts of 1,1-dimethyl-2-(β-cyanoethyl)hydrazine and phenyl isothiocyanate were heated together for three minutes. The mixture solidified on cooling and was recrystallized three times from 95% ethanol. The pale yellow crystalline solid melted at 104–105°.

Anal. Calc'd for $C_{12}H_{16}N_4S$: C, 58.03; H, 6.49; N, 22.56. Found: C, 58.56; H, 6.39; N, 22.48.

1,1-Dimethyl-2-(β-cyanoethyl)hydrazine hydrochloride. A dioxane solution of 1,1-dimethyl-2-(β-cyanoethyl)hydrazine reacted with dry hydrogen chloride gas to form an insoluble oil which, after separation from the dioxane by decantation, solidified to a pale yellow wax. Three recrystallizations from a mixture of absolute ethanol and petroleum ether (b.p. 60–70°) (2:1) yielded a white crystalline deliquescent solid melting at 90–92°.

Anal. Calc'd for $C_5H_{12}ClN_3$: C, 40.12; H, 8.08. Found: C, 39.91; H. 8.40.

1-Carbamylmethyl-1,1-dimethylhydrazinium chloride. Dry monochloroacetamide (9.3 g., 0.10 mole) was mixed with 7.5 g. (0.13 mole) of *unsym*-dimethylhydrazine. After the initial exothermic reaction the mixture cooled and solidified. Three crystallizations of the solid from absolute ethanol yielded 7.5 g. (48%) of white crystals, m.p. 145–148°.

Anal. Calc'd for $C_4H_{12}ClN_3O$: C, 31.27; H, 7.87. Found: C, 31.09; H, 7.31.

N,N-Dimethylaminoacetamide hydrochloride. (*A*). A one-gram sample of 1-carbamylmethyl-1,1-dimethylhydrazinium chloride was subjected to Ainsworth's method[4] for hydrogenolysis of the nitrogen-nitrogen bond with Raney nickel. A few milligrams of crystalline material was obtained, which melted at 195–196° and did not depress the m.p. of the authentic specimen prepared as described below. (*B*). Dry dimethylamine gas was passed through a dioxane solution of monochloroacetamide. The white crystals which separated were removed by filtration and recrystallized from absolute ethanol. The product melted at 195–196°.

Anal. Calc'd for $C_4H_{11}ClN_2O$: C, 34.65; H, 8.01; N, 20.24. Found: C, 35.02; H, 8.01; N, 19.64.

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(1) H. A. Bruson in R. Adams, *Org. Reactions*, **5**, 79 (1949).
(2) C. D. Harries and T. Haga, *Ber.*, **31**, 58 (1898).
(3) O. Westphal, *Ber.*, **74**, 759 (1941).
(4) C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 1635 (1956).
(5) J. H. Ford, *J. Am. Chem. Soc.*, **67**, 876 (1945).
(6) H. R. Snyder and C. T. Elston, *J. Am. Chem. Soc.*, **76**, 3039 (1954).
(7) Melting points and boiling points are uncorrected.

Some N-Substituted-5-oxo-2-pyrrolidinecarboxamides

R. B. Angier and V. K. Smith

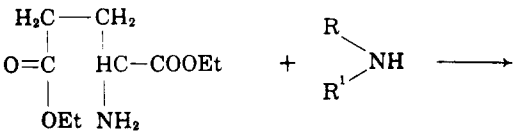
Recieved August 13, 1956

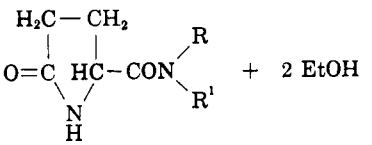
The detection of a very slight anti-neoplastic activity[1] in N-benzyl-5-oxo-2-pyrrolidinecarboxamide (Ib)[2] led to the preparation of a number of its derivatives and analogs. This report describes a series of N-substituted derivatives of 5-oxo-2-pyrrolidinecarboxamide (Ia).

Several N-aryl derivatives of Ia have been de-

(1) Private communication from S. Halliday and D. McKenzie of this laboratory.
(2) Angier, U. S. Patent 2,651,639 (Sept. 8, 1953).

scribed.[3] These were prepared by heating a mixture of L-glutamic acid and the aryl amine at 150–210°. However, the only previously described N-alkyl derivative of Ia is N-amyl-5-oxo-2-pyrrolidinecarboxamide, prepared by heating ethyl 5-oxo-2-pyrrolidinecarboxylate with amylamine at 150°.[4] Ia has previously been prepared by the action of alcoholic or aqueous ammonia on diethyl L-glutamate[5] and this method was utilized for preparation of the compounds listed in Table I. An excess of the amine was mixed with diethyl glutamate and allowed to react under the prescribed





Ia: R = R¹ = H
Ib: R = Benzyl, R¹ = H

conditions after which the product was isolated. Although no rate studies were conducted it was evident after several reactions that the aminolysis of diethyl glutamate (or the possible intermediate ethyl 5-oxo-2-pyrrolidinecarboxylate) was a facile reaction, and that the reactivity of diethyl glutamate in this respect compared favorably with that of methyl lactate.[6] This might be expected since diethyl glutamate, like methyl lactate, has an electron-attracting group in the α-position which, as Gordon, *et al.*[6] explain, should increase the rate of aminolysis. Since it is known that certain secondary amines react readily with methyl lactate to form amides[7] two secondary amines, dimethylamine and pyrrolidine, were allowed to react with diethyl glutamate and the expected amides were obtained in good yield.

No significant anti-neoplastic activity was noted in any of these compounds.

EXPERIMENTAL[8]

Diethyl L-glutamate. L-Glutamic acid (1 kg.) was slurried in 3 l. of absolute ethanol and dry hydrogen chloride gas was bubbled through the mixture rapidly until solution was complete. One liter of absolute ethanol was added and the solution was refluxed on a steam-bath for one hour. The ethanol then was distilled *in vacuo* and 500 cc. of water was added to the residue before it could solidify. This was cooled to 15° and mixed with 500 cc. of ether. With good stirring concentrated ammonium hydroxide was added slowly to *p*H 9.4 while controlling the temperature at 15°. The two layers were separated and the water layer was washed with 500 cc. of ether. The ether extracts were combined, dried over $MgSO_4$, and then evaporated under reduced pressure to remove the ether; yield 900 g. This material (a liquid) was quite satisfactory for the preparation of the various pyrrolidine derivatives.

Amides listed in Table I. Three general procedures were used. Examples are given below.

Method A. Diethyl L-glutamate (550 g.) (2.46 moles) and an excess of benzylamine (900 g.) (8.4 moles) were mixed and heated on the steam-bath for three hours. The reaction mixture was cooled to room temperature, diluted with 4 l. of ether, and cooled overnight. The product was collected, washed well with ether, and dried; yield 435 g. (74%); m.p. 131–132.5°. For analysis a sample was recrystallized once from ethanol; m.p. 134–136°.

Method B. Diethyl L-glutamate (88 g.) (0.43 mole) and an excess of allylamine (122 g., 160 cc.) (2.14 moles) were mixed and allowed to stand at room temperature for three days. The allylamine then was evaporated at atmospheric pressure (reduced pressure is necessary in other reactions) on a steam-bath during a period of 1.5 hours and then evacuated for a short time to remove residual amine. To this sirup was added 75 cc. of ethanol and 100 cc. of ether and the solution was cooled to give a crystalline mass. More ether (about 500 cc.) was added to give a slurry which could be filtered. The product was collected and recrystallized from 450 cc. of ethyl acetate; yield 32 g. (46%); m.p. 93–95°. A sample was recrystallized again from ethyl acetate; m.p. 94–95°.

Method C. The amines used in this procedure were prepared as exemplified below using a modification of the method of Galat and Elion.[9]

Hexamethylene tetramine (220 g.) (1.57 moles) and sodium iodide (240 g.) (1.60 moles) were dissolved in 3 l. of hot 95% ethanol. To this hot solution was added 250 g. (1.55 moles) of 4-chlorobenzyl chloride.[10]

The crystalline quaternary salt formed quite quickly. After standing overnight hydrogen chloride was bubbled through the mixture until it was saturated. During this time the crystalline precipitate dissolved and ammonium chloride separated. The ammonium chloride was filtered off and the filtrate was evaporated to dryness. The dry residue was slurried with water and made alkaline with sodium hydroxide. The amine separated as an oil. It was extracted with ether, and the ether was dried over magnesium sulfate and filtered. Evaporation of the ether gave 110 g. of crude 4-chlorobenzylamine. This material was satisfactory for the subsequent reaction.

This amine (110 g.) was mixed with 88 g. of diethyl L-glutamate and allowed to react at room temperature for 2 days at which time the product had crystallized. The mixture was diluted with several volumes of ether, cooled, and filtered; yield 57 g. This was recrystallized from 750 cc. of

(3) Gray, *J. Chem. Soc.*, 1264 (1928); Dewing, Gray, Platt, and Stephanson, *J. Chem. Soc.*, 239 (1942).

(4) Sauer and Adkins, *J. Am. Chem. Soc.*, **60**, 402 (1938).

(5) Abderhalden and Rossner, *Z. physiol. Chem.*, **152**, 281 (1926); Angier, *et al.*, *J. Am. Chem. Soc.*, **72**, 74 (1950).

(6) Gordon, Miller, and Day, *J. Am. Chem. Soc.*, **70**, 1946 (1948).

(7) Arnett, Miller, and Day, *J. Am. Chem. Soc.*, **73**, 5393 (1951).

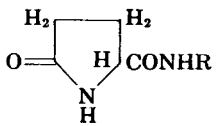
(8) All melting points, including those in Table I, are uncorrected unless otherwise noted.

(9) Galat and Elion, *J. Am. Chem. Soc.*, **61**, 3585 (1939).

(10) 4-Chloro-, 4-methyl- and 2,4-dimethyl-benzyl chloride were all obtained from Ohio Apex Inc., Nitro, W. Virginia.

TABLE I

N-SUBSTITUTED-5-OXO-2-PYRROLIDINECARBOXAMIDES



R	Conditions	Precipitating Solvent	Recrystallizing Solvent	Yield,[a] %	M.P., °C.	Optical Rotation[b]	Formula	Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
Isopropyl	A: 4 days @ 25°	Ether	Ethanol	74	140–142		$C_8H_{14}N_2O_2$	56.5	56.6	8.3	8.6	16.5	16.2
Butyl	B: 3 hrs. @ 100°	Ether	Ethyl acetate	43	96–97		$C_9H_{16}N_2O_2$	58.7	58.9	8.8	8.8	15.2	15.0
Allyl	B: 3 days @ 25°	Ethanol-ether	Ethyl acetate	46	94–95	$[\alpha]_D^{20}$ −25.0°	$C_8H_{12}N_2O_2$	57.1	57.4	7.1	7.6	16.6	16.8
2-Hydroxyethyl	A: 18 hrs @ 25°	Acetone	Ethanol	59	175–176		$C_7H_{12}N_2O_3$	48.8	50.0	7.0	7.8	16.3	16.3
2-Aminoethyl	B: 1 day @ 25°	Ethanol	Ethanol	60	177–179		$C_7H_{13}N_3O_2$	49.1	49.5	7.6	8.0	24.6	24.3
Cyclohexyl	A: 3 days @ 25°	Ether	Ethanol	60	164–165		$C_{11}H_{18}N_2O_2$	62.8	63.1	8.6	8.7	13.3	13.3
3-Hydroxypropyl	A: 1 day @ 25°	Acetone	Acetone	51	168–170	$[\alpha]_D^{26}$ −12.8°	$C_8H_{14}N_2O_3$	51.6	51.7	7.6	7.8	15.0	14.9
2,2-Diethoxyethyl	A: 3 days @ 25°	Ether	Ethanol-ether	57	125–126	$[\alpha]_D^{23}$ −22.6°	$C_{11}H_{20}N_2O_4$	54.1	54.1	8.3	8.9	11.5	12.0
Diethylaminoethyl	A: 2 days @ 25°	Ether	Ethyl acetate-ether	47	94–95		$C_{11}H_{21}N_3O_2$	58.2	58.4	9.3	9.3	18.5	18.5
Benzyl	A: 3 hrs @ 100°	Ether	Ethanol or water	74	134–136	$[\alpha]_D^{27}$ −29.75°	$C_{12}H_{14}N_2O_2$	66.0	66.2	6.5	6.7	12.8	13.0
Benzyl[c]	A: 3 days @ 25°	Ether	Ethanol	72	135–136	$[\alpha]_D^{30}$ +28.8°	$C_{12}H_{14}N_2O_2$	66.0	66.1	6.5	6.6	12.8	13.1
4-Chlorobenzyl	C: 2 days @ 25°	Ether	Ethanol	41	191–192		$C_{12}H_{13}ClN_2O_2$	57.0	57.3	5.2	5.5	11.1	11.2[d]
4-Methylbenzyl	C: 2 days @ 25°	Ether	Ethyl acetate	35	110–112		$C_{13}H_{16}N_2O_2$	67.2	67.5	6.9	7.1	12.1	12.6
2,4-Dimethylbenzyl	C: 2 days @ 25°	Ether	Ethanol-ether	48	128–129		$C_{14}H_{18}N_2O_2$	68.3	67.7	7.4	7.6	11.4	11.4
2-Phenylethyl	A: 2 days @ 25°	Ether	Ethanol	70	140–141	$[\alpha]_D^{28}$ −36.5°	$C_{13}H_{16}N_2O_2$	67.2	67.4	6.9	7.2	12.1	12.4
Furfuryl	A: 4 days @ 25°	Ether	Ethanol	54	129–130	$[\alpha]_D^{26}$ −29.4°	$C_{10}H_{12}N_2O_3$	57.6	57.5	5.8	6.0	13.4	13.6
Thenyl	A: 6 days @ 25°	Ether	Ethyl acetate	54	105–107	$[\alpha]_D^{25}$ −32.4	$C_{10}H_{12}N_2O_2S$	53.6	54.0	5.4	5.6	12.5	12.5[e]

[a] Based on diethyl glutamate—although these yields may represent either recrystallized or unrecrystallized material they represent products with m.p.'s within 4° of the analytical sample. [b] All rotations taken on 2% water solutions. [c] This compound was prepared from diethyl D-glutamate which, in turn, was prepared from D-glutamic acid in exactly the same manner as is described in the experimental section for diethyl L-glutamate. [d] Cl: Calc'd: 14.0. Found: 13.9. [e] S: Calc'd: 14.3. Found: 14.0.

absolute ethanol; yield 45 g. (41%); m.p. 187–188°. A sample was recrystallized again from ethanol; m.p. 191–192°.

N-Guanyl-5-oxo-2-pyrrolidinecarboxamide. A mixture of 50 g. (0.53 mole) of guanidine hydrochloride and 28 g. (0.52 mole) of sodium methoxide in 200 cc. of methanol was stirred for 10 minutes. The sodium chloride then was filtered off and the filtrate was mixed with 55 g. (0.27 mole) of diethyl L-glutamate. After about two minutes the product crystallized; yield 33 g. (72%); m.p. 180–182°. A portion of the compound was recrystallized from water; m.p. 187–189°.

Anal. Calc'd for $C_6H_{10}N_4O_2$: C, 42.3; H, 5.9; N, 32.9. Found: C, 42.0; H, 6.2; N, 32.9.

N,N-Dimethyl-5-oxo-2-pyrrolidinecarboxamide. Diethyl L-glutamate (66 g.) (0.32 mole) and an excess of anhydrous dimethylamine (68 g., 100 cc.) (1.5 moles) were mixed in a pressure bottle and allowed to stand at room temperature for 4 weeks. The excess dimethylamine then was evaporated and the residue was distilled; b.p. 210–214°/0.3 mm. Shortly the product began to crystallize. The mixture was quickly poured into a small amount of ethanol, cooled, and the solid was collected; yield 32 g. (63%); m.p. 114–116°. The product then was recrystallized from 350 cc. of ethyl acetate; yield 28.8 g.; m.p. 115–117° (corrected); $[\alpha]_D^{23}$ −33.5° (*c*, 2 in water).

Anal. Calc'd for $C_7H_{12}N_2O_2$: C, 53.8; H, 7.7; N, 17.9. Found: C, 53.6; H, 7.1; N, 18.3.

N,N-Tetramethylene-5-oxo-2-pyrrolidinecarboxamide. Diethyl L-glutamate (88 g.) (0.43 mole) and an excess of pyrrolidine (136 g., 160 cc.) (1.9 moles) were mixed and allowed to stand at room temperature for 4 weeks. The excess pyrrolidine then was distilled under reduced pressure on the steam-bath. The resulting sirup was diluted with two volumes of ethyl acetate and seeded with crystals obtained by distilling the product from a previous small run (b.p. 225°/0.4 mm.). After cooling, the product was collected; yield 47 g. (60%). This was recrystallized from 250 cc. of ethyl acetate; yield 38 g.; m.p. 111–112° (corrected); $[\alpha]_D^{23}$ −40.5° (*c*, 2 in water).

Anal. Calc'd for $C_9H_{14}N_2O_2$: C, 59.3; H, 7.7; N, 15.4. Found: C, 59.5; H, 8.0; N, 15.4.

N,N'-(2-Hydroxytrimethylene)bis-(5-oxo-2-pyrrolidinecarboxamide). 1,3-Diamino-2-hydroxypropane (35 g., 30 cc.) (0.33 mole), an excess of diethyl L-glutamate (198 g.) (0.97 mole), and 150 cc. of absolute ethanol were mixed and allowed to stand at room temperature for 4 days. The mixture then was cooled overnight and the product was collected; yield 78 g. This was dissolved in 350 cc. of warm water, decolorized with Norit, and the filtrate was diluted with one liter of acetone. Upon cooling overnight the product crystallized; yield 52 g. (50%); m.p. 227–229° (corrected).

A sample of this material was dissolved in 50 cc. of water, diluted with 150 cc. of acetone, filtered hot, and cooled overnight; yield 7.7 g. This process was repeated twice; yield 4.7 g., m.p. 235–237° (corrected); $[\alpha]_D^{23}$ −22.1° (*c*, 2 in water).

Anal. Calc'd for $C_{13}H_{20}N_4O_5$: C, 50.0; H, 6.4; N, 17.9. Found: C, 50.2; H, 7.0; N, 18.2.

Attempts to prepare and isolate the monosubstituted derivative of 1,3-diamino-2-hydroxypropane were unsuccessful.

Acknowledgment. The authors are indebted to Mr. Louis Brancone and staff for microanalytical data, to Messrs. William Fulmor and George Morton for the data on optical rotations, and to Mr. Louis Binovi for the preparation of large quantities of diethyl L-glutamate.

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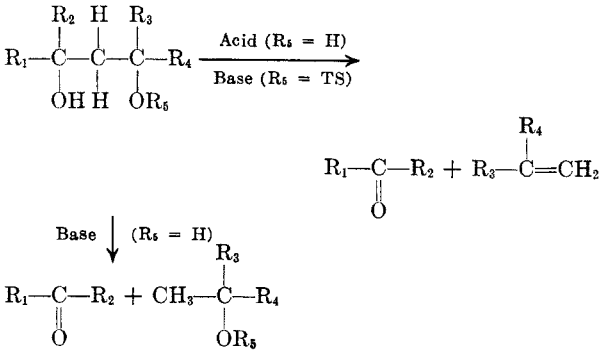
The Acid Catalyzed Cleavage of a Substituted Cyclopentane-1,3-diol. I. 1,3-Diphenyl-1,3-dihydroxy-2,2-dimethylhydrindene

FREDERICK V. BRUTCHER, JR. AND HARRY J. CENCI

Received August 13, 1956

The cleavage reactions of 1,3-diols have been studied in some detail.[1–5] The products obtained from the acid catalyzed cleavage[1,2] are the corresponding carbonyl compound and olefin while the products from the base cleavage depend on whether the free diol or monotosylate is employed. The free diol with base yields a carbonyl compound[6] and, unlike the other cleavage reactions, a derived alcohol,[4] while the monotosylate[3] gives a carbonyl compound and olefin much like the acid catalyzed cleavage.



These studies, however, have not included the cleavage of a cyclopentane-1,3-diol. We have prepared 1,3-diphenyl-1,3-dihydroxy-2,2-dimethylhydrindene (I) and studied its behavior under acidic conditions which previously led to cleavage in simpler aliphatic cases. This paper reports the acid catalyzed cleavage of I and a structural proof of its cleavage product.

A mixture of I, readily prepared by the method of Geissman and Tulagin,[7] and fused potassium bisulfate was heated for 8 hours at 150–160° to yield a non-crystalline material characterized by a strong band in the infrared at 5.98μ. This band suggested the presence of a conjugated carbonyl group. Ozonization of the oil and subsequent workup led

(1) J. English Jr. and F. V. Brutcher Jr., *J. Am. Chem. Soc.*, **74**, 4279 (1952).

(2) H. E. Zimmerman and J. English Jr., *J. Am. Chem. Soc.*, **76**, 2285, 2291, 2294 (1954).

(3) R. B. Clayton and H. B. Henbest, *Chemistry & Industry*, 1315 (1953).

(4) S. Searles and E. K. Ives, *Abstracts of 127th Meeting Amer. Chem. Soc.*, Cincinnati, Ohio, P. 24N, 1955.

(5) For a recent review see H. H. Wasserman in M. S. Newman, *Steric Effects in Organic Chemistry*, J. Wiley & Sons, Inc., N. Y., 1956, p. 375–378.

(6) This cleavage of the free diol with base to carbonyl compound was first reported in 1951 (F. V. Brutcher Jr., *Ph.D. Thesis*, Yale University, P. 67, 68) and later studied in some detail by S. Searles and E. K. Ives.[4]

(7) T. A. Geissman and V. Tulagin, *J. Am. Chem. Soc.*, **63**, 3354 (1941).