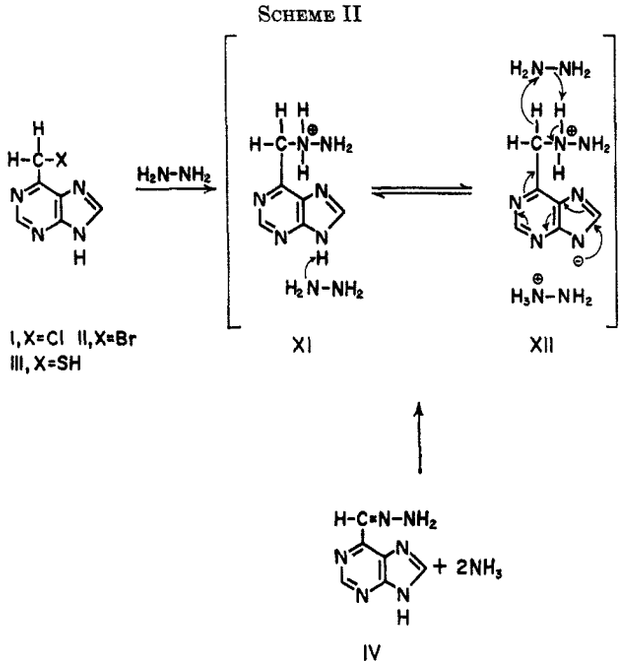
TABLE I

REACTION OF HYDRAZINE, HYDROXYLAMINE, AND PHENYLHYDRAZINE WITH 6-METHYLPURINE AND 5-METHYLURACIL DERIVATIVES

Base	Reagent	Mol ratio of reagent/ 1 mole of base	Reflux time, hr	Product	Yield, %
6-Chloromethylpurine (I)	Hydrazine[a]	5–10	1–4	Hydrazone (IV)	94
6-Chloromethylpurine (I)	Hydrazine (10%)	1	4	Hydrazone (IV)	28
6-Bromomethylpurine (II)	Hydrazine[a]	5–10	4	Hydrazone (IV)	85
6-Mercaptomethylpurine (III)	Hydrazine[a]	5–10	4	Hydrazone (IV)	24
6-Chloromethylpurine (I)	Hydroxylamine[b]	4–10	1	Oxime (V)	37
6-Chloromethylpurine (I)	Phenylhydrazine	3	6	Phenylhydrazone (VI)	62
5-Chloromethyluracil (VII)	Phenylhydrazine	5	6	Phenylhydrazone (IX)	39
5-Mercaptomethyluracil (VIII)	Phenylhydrazine	3	5	Phenylhydrazone (IX)	47
5-Chloromethyluracil (VII)	Hydroxylamine[b]	20	6	Oxime (X)	98

[a] No variation in the yields was observed by using different concentrations of the hydrazine solution; its range was 10–95%. [b] A 1 *M* solution in ethanol (*cf.* ref 12).

SCHEME II



chloromethylpurine with hydrazine, undergoes ionization in the basic reaction medium giving XII. One molecule of hydrazine would be reduced to give the hydrazone (IV) with evolution of 2 moles of ammonia.[15]

Experimental Section

The purine or uracil derivative was refluxed with the corresponding solution of reagent in ethanol (see Table I for conditions and product yields). After cooling, the resulting precipitate was collected by filtration. The filtrate was evaporated to dryness *in vacuo*, and the residue was suspended in water, filtered, washed with ethanol, and combined with the first precipitate. The reaction products were in all cases found to be identical with the previously described purine-6-carboxaldehyde[3] and 5-uracilcarboxaldehyde derivatives,[9] by mixture melting point, ultraviolet spectra at different values of pH, and paper chromatography in the following solvent systems: water saturated with *n*-butyl alcohol (1:1, v/v); *n*-butyl alcohol saturated with water (same proportions) with or without 1% ammonia and in *n*-butanol (77%), formic acid (10%), and water (13%) (v/v). The ammonia which evolved from the reaction of 6-chloromethylpurine and hydrazine was drawn up in a stream of dry nitrogen which was passed through the reaction mixture and through a cooled trap (to condense any hydrazine which could accompany the nitrogen) into a 5% aqueous solution of boric acid and determined by titration with standard HCl. The recovery of ammonia was between 80 and 95% of the expected value.

Acknowledgment.—The authors wish to thank Dr. G. B. Brown for helpful discussions and continued interest and Mr. S. Adler for excellent technical assistance.

(15) We are indebted to Dr. S. Cohen, for valuable discussion concerning the proposed mechanism.

The Reaction Product from Aspartic and Maleic Acids in Aqueous Ammoniacal Solution[1]

FERDINAND B. ZIENTY, BERNARD KATLAFSKY, AND EMILE D. PIERRON

The Advanced Organic Chemicals Research Laboratory, Organic Chemicals Division, Monsanto Company, Saint Louis, Missouri 63166

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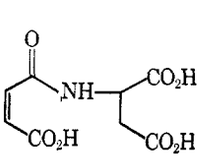
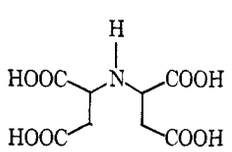
The reaction of aspartic acid with maleic anhydride has been investigated by several workers seeking the elusive N-maleoylaspartic acid (1) as an intermediate in polypeptide synthesis; thus far the product has not been made.[2] The reaction of fumaric acid with aqueous ammonia produces chiefly DL-aspartic acid and a small amount of iminodisuccinic acid,[8] $C_8H_{11}NO_8$ (2).



$C_8H_9NO_7$

1



$C_8H_{11}NO_8$

2

(1) Presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964.

(2) Although many N-maleoylamino acids have been prepared by shaking an aqueous solution of the amino acid with a benzene solution of maleic anhydride,[3-5] and by reaction of amino acids with maleic anhydride dry[6] or in acetic acid solution,[7] N-maleoylaspartic acid (1) has not yet been made.

(3) R. D. Irsay, Y. Liwschitz, and A. Zilkha, *Bull. Res. Council Israel Sect. A*, **6**, 272 (1957); *Chem. Abstr.*, **52**, 265*i* (1958).

(4) Y. Liwschitz, Y. Rabinsohn, and A. Singerman, *J. Chem. Soc.*, 3726 (1962).

(5) A. K. Bose and R. E. Strube, *J. Pharm. Soc.*, **52**, 847 (1963).

(6) H. Werbin and P. E. Spoerri, *J. Am. Chem. Soc.*, **69**, 1681 (1947); S. W. Fox and F. N. Minard, *ibid.*, **74**, 2085 (1952).

(7) F. E. King, J. W. Clark-Lewis, R. Wade, and W. A. Swindin, *J. Chem. Soc.*, 873 (1957).

(8) G. Stadnikoff [*Chem. Ber.*, **44**, 48 (1911)] obtained some iminodisuccinic acid as a by-product in the preparation of DL-aspartic acid by reaction of 1 mole of fumaric acid with 3 moles of ammonium hydroxide solution at 120–130°; the acid was isolated as the tetraethyl ester.

Although **2** has been known for many years and its properties as an alkaline earth ion sequestering agent are recognized,[9] no convenient direct method for the preparation of **2** is available nor has it been characterized. In the course of a study of methods for making **1** and **2** we explored the reaction of the ammonium salts of DL-aspartic and maleic acids in aqueous solution since this appeared to offer a potentially convenient route to **2** which was desired for further investigation of its properties as an organic sequestering agent.[10]

Results

When the reaction mixture is acidified with hydrochloric acid to pH 1.5, a crystalline polycarboxylic acid is isolated in 30% yield; dried at 55° its composition is $C_8H_{13}NO_9$; when dried at 110° its composition is $C_8H_{11}NO_8$, suggesting dehydration. Determination of water by Karl Fischer titration in pyridine solution shows the product $C_8H_{11}NO_8$ to be a monohydrate and the product $C_8H_{13}NO_9$ a dihydrate; the molecular weight of the dihydrate is confirmed from the unit cell dimensions obtained by X-ray diffraction. The substance produced in this reaction clearly is an unexpected new polycarboxylic acid of the formula $C_8H_9NO_7$ which was shown to have the structure **8**.

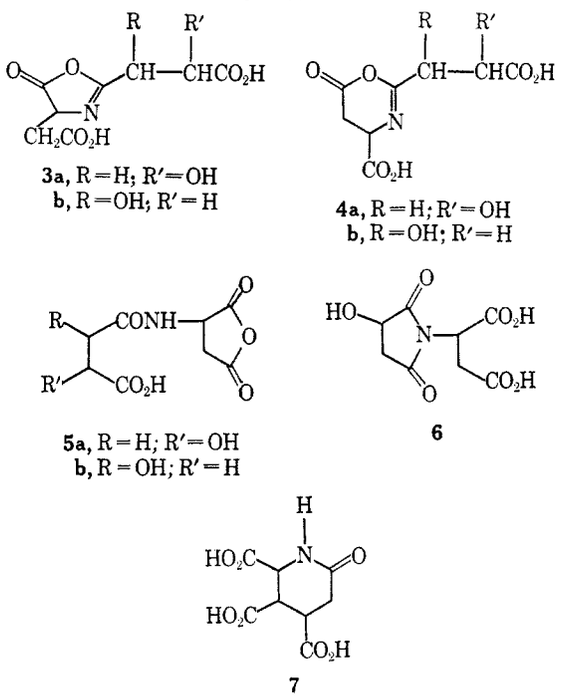
The 60-Mc nmr spectrum[11] of a saturated solution of the polycarboxylic acid (**8**) dihydrate in D_2O shows a doublet centered at 3.1 (CH_2) (J = 5.7 cps) and a triplet at 4.2 ppm (>CH); the areas of these signals are in the ratio of 2:1. A similar spectrum[12a] is obtained with a 10% solution of the new polycarboxylic acid in D_2O containing sufficient sodium hydroxide to neutralize the polycarboxylic acid; the doublet is at 2.40 (J = 6.1 cps) and the triplet at 3.35 ppm. The lack of further splitting of these signals indicates that the two $>CHCH_2$ groups are in very similar environments. Vinyl protons are absent in the nmr spectrum.[12b] The similarity of these spectra indicates that **8** is largely hydrolyzed in dilute D_2O solution to the open-chain product, N-α-maloylaspartic acid (**14**). Because of poor solubility in noninterfering solvents and formation of a solid salt in pyridine-d_5, a satisfactory nmr spectrum of **8** was not obtained.

The solid-state infrared spectrum of the new polycarboxylic acid (**8**) dihydrate shows that four carbonyl species are present. Three of these species persist in the dilute 2-propanol spectrum of the new acid and three others in the solid-state spectra of its triethylamine and pyridine salts. An NH absorbance band is observed in the spectrum of the dimethylformamide solution of the new acid dried over anhydrous sodium sulfate. The observed infrared frequencies are given in Table I.

The infrared data on the new compound (**8**) dihydrate in the solid state indicate the presence of a free carboxylic acid group (1695 cm^{-1}) and a loosely coupled carboxylate salt (1541 and 1399 cm^{-1}). In a highly polar solvent (isopropyl alcohol) the salt functionality is absent, the carboxylate ion bands disappear and a very intense carboxylic acid band is found at 1709 cm^{-1}. The 3440- and 1664-cm^{-1} bands indicate that an NHC=O group is present. Since no amide II band was observed (the symmetry and intensity of the carboxylate ion band at 1541 cm^{-1} indicate that no other absorbance band is present in this region of the spectrum), this functionality is assigned to a lactam rather than an open-chain secondary amide structure.[15] The position of the remaining carbonyl group at 1739 cm^{-1} suggests that this species is associated with a six-, seven-, or eight-membered cyclic lactone.

A number of isomeric products of empirical formula $C_8H_9NO_7$ are potentially derivable from the reaction of aspartic and maleic acids. In addition to N-maleoylaspartic acid (**1**) which is eliminated on the absence of vinyl protons in the nmr spectrum[12a] five of these isomers are shown in Chart I.

CHART I



The azlactone (oxazolone) (**3**), oxazine (**4**), anhydride (**5**), and imide (**6**) all have a 2:1 ratio of CH_2 and >CH protons. The absence of an absorption band in the region of 1750 to 1850 cm^{-1} tends to rule out all four structures. In addition, the absence of an absorption band in the 1668- to 1683-cm^{-1} region[16] rules out presence of the C=N bond required for the azlactone and oxazine; also, the infrared spectrum of the

(9) (a) F. Münz [U. S. Patent 2,240,957 (May 6, 1941); *Chem. Abstr.*, **35**, 5328 (1941)] indicated iminodisuccinic acid was effective in sequestering water-insoluble metal salts in the dyeing of textiles. (b) J. C. Cowan and C. D. Evans [U. S. Patent 2,594,294 (April 29, 1952); *Chem. Abstr.*, **46**, P7348e (1952)] showed that glyceride oils containing metallic impurities could be stabilized against oxidation by use of iminodisuccinic acid.

(10) S. Chaberek and A. E. Martell, "Organic Sequestering Agents," John Wiley and Sons, Inc., New York, N. Y., 1959.

(11) A Varian HR-60 high-resolution nmr spectrometer was used. Chemical shifts in parts per million are referred to sodium 2,2-dimethyl-2-silapentane 5-sulfonate.

(12) (a) The spectra are consistent with the spectrum of cysteine[13] and the coupling constants with those of amino acids including aspartic acid.[14] (b) Vinyl protons in N-maleoylglycine occur as doublets at 5.80 and 6.26 ppm (J = 12.2 cps). In our product there was no signal in this region.

(13) S. Fujiwara and Y. Arata, *Bull. Chem. Soc. Japan*, **36**, 578 (1963).

(14) K. G. R. Pachler, *Spectrochim. Acta*, **20**, 581 (1964).

(15) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p 185.

(16) C. N. R. Roa, "Chemical Applications of Infrared Spectroscopy," Academic Press Inc., New York, N. Y., 1963, p 459.

TABLE I

PRINCIPAL INFRARED ABSORBANCE FREQUENCIES OF NEW ACID (8) DIHYDRATE

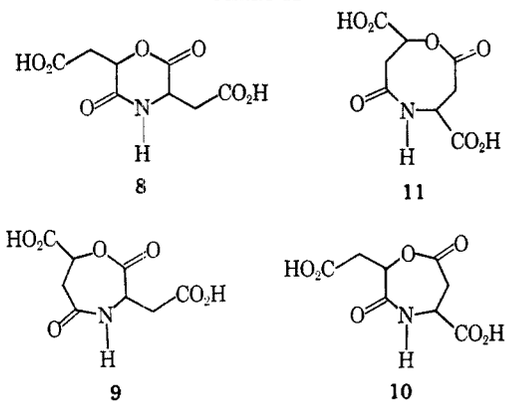
Form	State	Diluent	Infrared frequencies, cm^{-1}[a] C=O, I	C=O, II	C=O, III	C=O, IV		NH
Acid	Solid	Nujol, KBr	1739 (s)	1695 (s)	1664 (s)	1541 (m)	1399 (s)	H
Acid	Solution	*i*-PrOH	1727 (m, sh)	1709 (vs)	1647 (m)	A	I	I
Acid	Solution[b]	DMF	I	I	I	I	I	3440
TEA salt	Solid	KBr	1730 (s)	A	1634 (s)	1536 (m)	1393 (s)	H
Pyridine salt	Solid	KBr	1733 (s)	A	1661 (s)	1536 (m)	1395 (s)	H

[a] The following abbreviations are used: s = strong, m = medium, v = very, sh = shoulder, I = solvent interference, H = hydrate interference, A = absent. [b] Dried over anhydrous sodium sulfate.

new acid shows no absorption band indicative of the strained five-membered ring lactone. The anhydride is eliminated further on the absence of a pair of bands in the 1750–1800- and 1820–1870-cm^{-1} regions shown by cyclic anhydrides. The imide is eliminated on the absence of the higher frequency band of the imide doublet in the 1750–1800-cm^{-1} region. δ-Valerolactam-2,3,4-tricarboxylic acid (7) which might have been formed by a carbon–carbon cyclization is eliminated since it requires three >CH and two CH_2 protons and since it has no ester carbonyl.

The structures of four isomeric lactone lactams, (**8**, **9**, **10**, and **11**) shown in Chart II are more nearly

CHART II

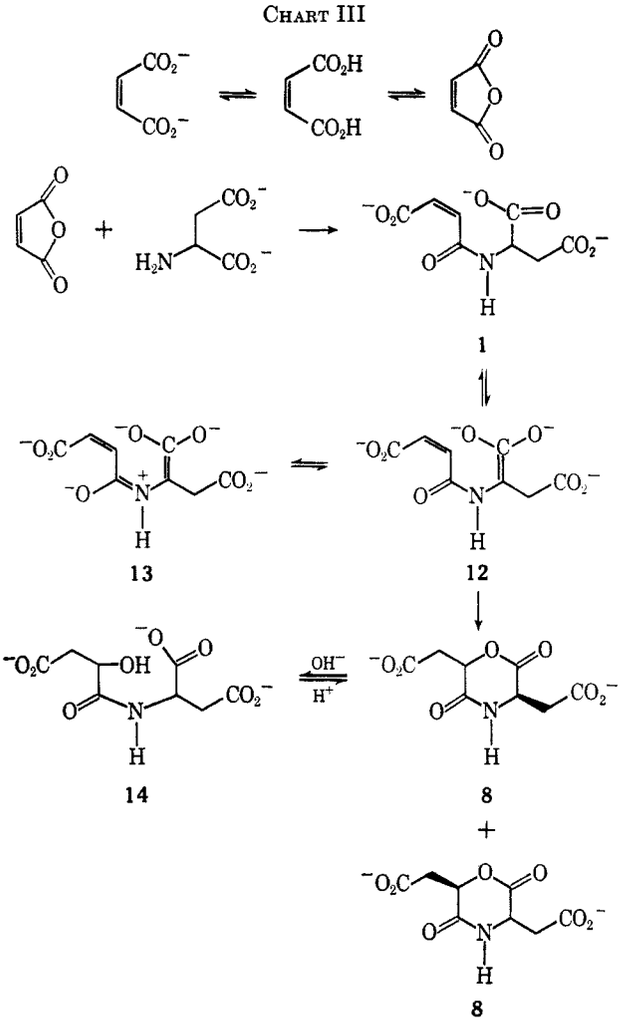


compatible with the infrared and nmr findings and the chemical and other analytical evidence. The indication that ring opening occurs on solution of the new polycarboxylic acid (**8**) in D_2O suggests easy hydrolysis of the lactone, and provides strong evidence of a six-membered ring system rather than seven- or eight-membered ring systems. Measurements of Dreiding models show that of the lactone lactams only **8** could fit into the unit volume occupied by one molecule as determined by X-ray diffraction. Assignments of the infrared absorption bands of **8** discussed earlier in this paper to the lactone and lactam groups are consistent with the frequencies of these groups in substituted 2,5-morpholinediones[17a,18,19] isolated from *Claviceps purpurea*[17] and in structural studies on the enniatin antibiotics[20] and on the antibiotics amidomycin,[18] valinomycin,[21] and lateritiin.[22] Thus, it is concluded the new polycarboxylic acid is (**8**), 3,6-dioxo-2,5-morpholinediacetic acid.

Discussion

The formation of morpholinedione (**8**) in the reaction of aspartic and maleic acids in ammoniacal solution suggests that the aspartic acid is acylated under these conditions, possibly through the intermediacy of maleic anhydride as shown in Chart III. The

CHART III



feasibility of such a reaction is supported by the recent work of Higuchi, *et al.*,[23] on the facilitated formation of amides of dicarboxylic acids, including maleic acid, with aromatic amines in aqueous solution. The

(17) (a) T. Wieland, B. Heinke, and K. H. Shin, *Chem. Ber.*, **93**, 3031 (1960); (b) M. Abe, T. Yamano, S. Yamatodani, Y. Kozu, M. Kusumoto, H. Komatsu, and S. Yamade, *Bull. Agr. Chem. Soc. Japan*, **23**, 246 (1959).

(18) L. C. Vining and W. A. Taber, *Can. J. Chem.*, **35**, 1109 (1957).

(19) J. McGee and P. D. Ritchie [*J. Chem. Soc.*, 1782 (1961)] postulated formation and cyclization of an N-acryloylamino acid in the pyrolytic formation of morpholinediones from α-anilinocarboxylic acids.

(20) P. A. Plattner and U. Nager, *Helv. Chim. Acta*, **31**, 665, 2192, 2203 (1948).

(21) H. Brockman and H. Geeren, *Ann. Chem.*, **603**, 216 (1957).

(22) A. H. Cook, S. F. Cox, and T. H. Farmer, *J. Chem. Soc.*, 1022 (1949).

(23) T. Higuchi, T. Miki, A. C. Shah, and A. K. Herd, *J. Am. Chem. Soc.*, **85**, 3655 (1963); T. Higuchi and T. Miki, *ibid.*, **83**, 3899 (1961); T. Higuchi, S. O. Eriksson, H. Uno, and J. J. Windheuser, *J. Pharm. Sci.*, **53**, 280 (1964).

product first formed in the reaction presumably is N-maleoylaspartic acid[2] (1) which apparently cyclizes by addition of a carboxyl anion to the double bond.[19] The α-carboxyl group of the aspartic acid portion of N-maleoylaspartic acid (1) must add to the α position of the double bond as the result of the tendency to form a six-membered ring rather than seven- or eight-membered rings. This tendency to form a six-membered ring apparently overcomes the expected greater nucleophilicity of the β-carboxyl group and the fact that the β position on the double bond would be expected to be the more positive as in the usual Michael reaction.

Under conditions of the reaction the cyclization of N-maleoylaspartic acid (1) is, in effect, a hydroxylation since morpholinedione (8) hydrolyzes to N-α-maloylaspartic acid (14) which cyclizes again on acidification as shown in Chart III. The fact that N-maleoylaspartic acid loses its unsaturation under conditions of the reaction rather than on strong acidification (to pH 1.5) is supported by the following finding. Examination of nmr in D_2O of the product obtained by evaporation to dryness of the reaction mixture shows no vinyl protons and only a doublet at 3.1 (J = 5.6 cps) for CH_2 and a triplet at 4.1 for >CH in the ratio of 2:1 as previously observed for product 14. Obviously, any unsaturated intermediate such as N-maleoylaspartic acid already is consumed.

3,6-Dioxo-2,5-morpholinediacetic acid (8) dihydrate prepared from DL-aspartic acid by the method described is optically inactive[24] and is the racemate of one of the two possible diastereoisomers. Examination of Dreiding models of 8 in the light of the unit cell dimensions, the number of molecules per unit cell, and the space group shows that 8 is the DL,LD diastereoisomer and not the DD,LL diastereoisomer.[25]

When L-aspartic acid is used in the reaction apparently the DL,LD product also is obtained since it is optically inactive, melts at 208–209° (effervesces), shows no depression in the mixture melting point with 8 dihydrate, and has the same X-ray powder diffraction pattern as 8 dihydrate. This finding suggests that racemization has occurred since L-aspartic acid would have been expected to yield a mixture of the DL and LL epimers, either of which would have been different from the DL,LD product derived from DL-aspartic acid.

The fact that L-aspartic acid is found to undergo only slight racemization when held in an environment similar to that of the reaction conditions suggests that it is not the L-aspartic acid, but the N-maleoyl-L-aspartic acid (1) or N-α-maloylaspartic acid (14) which has racemized. The easy racemization of N-acyl derivatives of α-amino acids under alkaline conditions has been observed and studied by several workers[14,26,27] and attributed to cyclization to the oxazolone[26] which can tautomerize easily. More recently it has been suggested[28,29] that stabilization of an anion plays an important role in the ease of racemization of N-acylamino acids. Under the alkaline conditions of our reaction stabilized anions like 12 or 13 would result in racemization of N-maleoylaspartic acid (1) and lead to a racemic morpholinedione (8). Similar stabilized anions could be written for N-α-maloylaspartic acid (14) and likewise would produce racemic morpholinedione.

Experimental Section

DL,LD-3,6-Dioxo-2,5-morpholinediacetic Acid (8) Dihydrate.—Maleic anhydride, 9.8 g (0.1 mole) was dissolved in 75 ml of water at 65°. Then 19.2 g (0.3 mole) of 28% aqueous ammonia solution and 13.3 g (0.1 mole) of DL-aspartic acid were added and the solution was stirred at 90–95° for 20 hr. After cooling to 25–30°, the clear, colorless solution was treated with 30 g (0.3 mole) of 37% hydrochloric acid and allowed to stand at 25° for 12 hr. The pH of the solution was 1.5. The crystalline precipitate was filtered off, washed with water, and dried at 55°, yielding 7.2–7.7 g (28.9–31.0%). The product was recrystallized from water three times.

This product was a colorless, crystalline solid, mp 208–209° (effervesces) (Kofler stage). It was relatively insoluble in methanol, acetone, toluene, dioxane, and molten maleic anhydride, and slightly soluble in water and in dimethylformamide. It formed an insoluble barium salt and showed calcium ion sequestering properties.

Anal. Calcd for $C_8H_9NO_7 \cdot 2H_2O$ (mol wt 267.19); C, 35.96; H, 4.90; N, 5.24; H_2O, 13.48; neut equiv, 89. Found: C, 36.02; H, 4.93; N, 5.05; H_2O, 13.0; neut equiv, 89.

Examination of a single crystal of 8 dihydrate by X-ray diffraction showed it to be monoclinic with unit cell dimensions of a = 15.40 A, b = 18.99 A, c = 5.825 A, and β = 136° 30′ and to belong to space group P21/m-C_{2h}^2. With a density of 1.565 and four molecules per unit cell, a molecular weight of 275 was calculated (theory 267).

From the titration curve of morpholinedione (8) dihydrate in water its acidity constants were roughly pK_1 = 2.8, pK_2 = 3.4, and pK_3 = 4.1.

Morpholinedione (8) dihydrate showed no titration in the Sörensen formal analysis[30] for amino groups in α-amino acids, and gave a negative result (no nitrogen evolution) in the Van Slyke nitrous acid method for primary amines,[31] indicating freedom from contamination with aspartic acid.

When the reaction was conducted at reflux, the yield was halved. At 60–65° only an insignificant yield was produced.

The ammonia may be replaced in whole or in part with an equivalent amount of sodium hydroxide, but with some loss of yield. The use of excess ammonia did not particularly affect the yield, although ammonia was lost through the condenser during the reaction. When fumaric acid was reacted with DL-aspartic acid, the mixture of products obtained was heavily contaminated with fumaric acid.

On reaction with aqueous ammonium hydroxide at 120–130° 8 was converted in part to DL-aspartic acid.

Optical Rotations.—Using a Rudolph No. 80 precision polarimeter, a 4-dm cell and concentrations of 2 g of product in 100 ml of 1 N hydrochloric acid, the specific rotations at 24.4° were 25.24 for L-aspartic acid, 0.73 for morpholinedione (8) dihydrate made from DL-aspartic acid, 0.45 for morpholinedione (8) dihydrate made from L-aspartic acid, and 21.25 (at 20.5°) for L-aspartic acid subjected to simulated reaction conditions.

Permanganate Titrations of Aspartic, Maleic, Fumaric, and Malic Acids and of Morpholinedione (8) Dihydrate.—A weighed sample of the substance was dissolved in 15 ml of 10% sulfuric acid held at 80° and the solution was titrated with 0.1 N potassium permanganate solution.

(24) Optical rotations were determined in hydrochloric acid solution by the method of O. Lutz and B. Jirgensons [*Chem. Ber.*, **63**, 451 (1930)] for L-aspartic acid.

(25) A. H. Cook and S. F. Cox [*J. Chem. Soc.*, 2350 (1949)] determined the configuration of a diastereoisomer of 4-methyl-3,6-diisopropyl-2,5-morpholinedione.

(26) M. Bergmann and L. Zervas, *Biochem. Z.*, **203**, 288 (1928).

(27) R. L. M. Synge, *Biochem. J.*, **33**, 1916 (1939).

(28) C. C. Barker [*J. Chem. Soc.*, 453 (1953)] studied racemization of N-acyl-L-aspartic acids by acetic anhydride.

(29) B. Liberek and Z. Grzonka [*Tetrahedron Letters*, 159 (1964)] postulated that formation of morpholinediones from N-pyruvoylamino acids[17a] may proceed *via* a stabilized anion.

(30) (a) S. P. L. Sörensen, *Biochem. Z.*, **7**, 45 (1907); (b) P. B. Hawk, B. L. Oser, and W. H. Summerson, "Practical Physiological Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1954, p 897.

(31) (a) D. D. Van Slyke, *J. Biol. Chem.*, **9**, 185 (1911); (b) ref 30b p 892.

Maleic acid (0.1036 g) consumed 17.2 ml and fumaric acid (0.0872 g) consumed 14.7 ml; the permanganate was decolorized instantly in each case. Malic acid (0.1050 g) consumed 19.5 ml; the permanganate was decolorized slowly. DL-Aspartic acid did not consume permanganate under these conditions. Morpholinedione (**8**) dihydrate (0.0716 g) consumed 6.6 ml and the rate of decolorization of permanganate was similar to the rate of decolorization by malic acid. The consumption of permanganate was equivalent to 1 mole of malic acid per mole of **8** dihydrate. After permanganate titration, the solution gave an analysis equivalent to 1 mole of **8** dihydrate using the van Slyke method.[31] This indicates cleavage of the amide bond[32] to liberate a free amino group.

Acknowledgment.—The nmr data were obtained by Dr. Martin W. Dietrich and the optical rotations by Dr. Victor W. Saeger.

(32) A. Jolles [*J. Prakt. Chem.*, [2] **63**, 518 (1901)] found that in the oxidation of N-benzoylaspartic acid by potassium permanganate in boiling dilute sulfuric acid nitrogen is split out as urea.

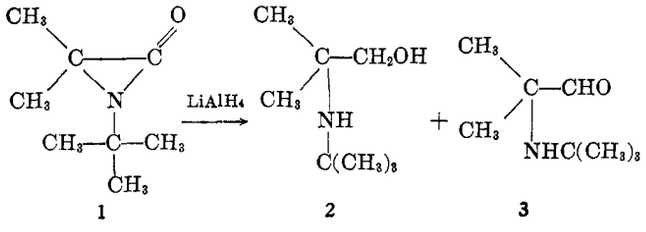
α-Lactams. III. The Reaction of 1-*t*-Butyl-3,3-dimethylaziridinone with Lithium Aluminum Hydride

JOHN C. SHEEHAN AND ISTVAN LENGYEL

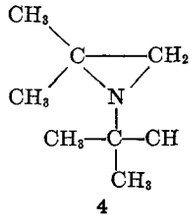
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received June 9, 1966

Recently, we reported a synthesis and some solvolytic reactions of 1-*t*-butyl-3,3-dimethylaziridinone (**1**).[1] It was pointed out that the products of solvolysis are α-substituted N-*t*-butylamides, except where the nucleophile was a strong ionic base (*e.g.*, *t*-butoxide). Now we wish to describe the lithium aluminum hydride ($LiAlH_4$) reduction of α-lactam **1**, a reaction in which cleavage of the ring occurs exclusively at the amide linkage. When a solution of **1** in ether or tetrahydrofuran is treated with $LiAlH_4$, and subsequently hydrolyzed, 2-*t*-butylamino-2-methyl-1-propanol (**2**) is formed in good yield, accompanied by a smaller amount of the corresponding aminoaldehyde, 2-*t*-butylamino-2-methylpropionaldehyde (**3**). The latter compound was isolated as the 2,4-dinitrophenylhydrazone. 1-*t*-Butyl-2,2-dimethylaziridine (**4**), an anticipated product, was not detected.

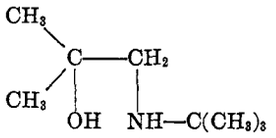


1 2 3



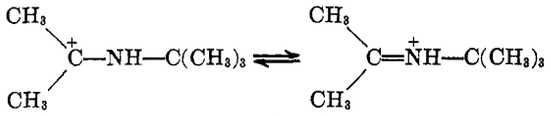
4

The structure assignment of the products is based on elemental analyses, infrared, nmr, and mass spectra. A picrate, an acetate, and a phenylurethan of the major product were also prepared. To corroborate further the structure of amino alcohol **2**, the structural isomer, 1-*t*-butylamino-2-methyl-2-propanol (**5**), was synthesized for comparison. The physical and spectral properties of this synthetic amino alcohol differed distinctly from those of compound **2**.



5

Elemental analysis and mass spectrometric molecular weight corresponded to the formula $C_8H_{19}NO$ for the major product of the reduction. The infrared spectrum showed the characteristic bands at 3600 and 3430 cm^{-1} expected for an alcohol. The nmr spectrum exhibited a singlet at 3.11 ppm (2 H), which indicates a CH_2 group next to an oxygen, thus pointing to a primary alcohol. The mass spectrum showed a very abundant ion at *m/e* 114, in agreement with structure **2**; amino alcohols of type **2** would be expected to lose CH_2OH to give the well-stabilized ion **6**.[2] A fragment with this *m/e* value cannot be derived from structure **5** and is indeed not found in the mass spectrum of **5**.



6, *m/e* 114

The product formed a monoacetate at room temperature with acetic anhydride, also indicating a *primary* alcohol. Phenyl isocyanate precipitated a phenyl urethan promptly.

For direct comparison, tertiary alcohol **5** was prepared from 1,2-epoxy-2-methylpropane[3] and *t*-butylamine by a procedure adapted from the literature.[4] The boiling point, infrared, and nmr spectra of amino alcohol **5** were different from those of compound **2**. The two picrates show a melting point difference of 50°.

Aldehyde **3**, constituting the minor product of the reduction, was isolated as the 2,4-dinitrophenylhydrazone. Elemental analysis and infrared and nmr spectra (see the Experimental Section) were in agreement with structure **3**.

Even considerable variation in the ratio of $LiAlH_4$ to starting material or in the reaction conditions did not affect drastically the relative ratio of the observed products. The aforementioned results are in good agreement with what is known about the lithium alu-

(1) Part I: J. C. Sheehan and I. Lengyel, *J. Am. Chem. Soc.*, **86**, 1356 (1964).

(2) This fragmentation pattern is common for α-amino acid esters and α-amino alcohols; see, *e.g.*, K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 87–89.

(3) H. O. House, *J. Am. Chem. Soc.*, **77**, 5086 (1955).

(4) (a) K. Krassusky and A. Stepanoff, *J. Prakt. Chem.*, **115**, 321 (1927); (b) L. J. Kitchen and C. B. Pollard, *J. Org. Chem.* **8**, 342 (1943).