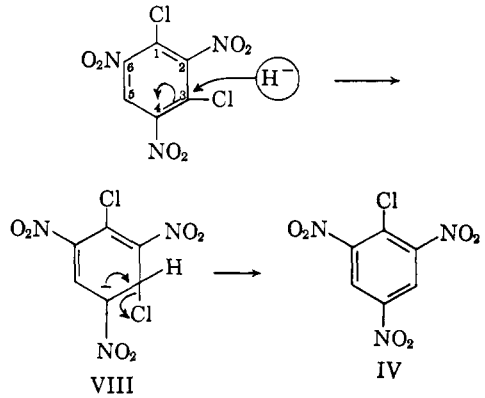
from the angle made by the O–N–O plane of the C-4 and C-6 nitro groups with the plane of the benzene ring in dichloro compound V.

Resonance interaction of the C-4 and C-6 nitro groups with the benzene ring renders C-1 and C-3 somewhat positive, and hydride attack at C-3[8] would form 1,2-cyclohexadienyl intermediate VIII. Rearomatization of the ring by the loss of chloride forms monochloride IV. Repetition of this cycle converts the monochloride to *sym*-trinitrobenzene, which is reduced to *sym*-trinitrocyclohexane under these conditions.[1] The driving force for the initial attack of



VIII IV

hydride at C-1 or C-3 would be supplied by the reduction of steric compressions on the C-2 nitro group which would occur upon the conversion of either of these trigonal carbon atoms to the tetrahedral configuration.[9]

A similar reaction path involving the loss of methoxide ion or methoxide and bromide ions would convert VI and VII to *sym*-trinitrocyclohexane.

Acknowledgment.—This work was supported by the Foundational Research Fund of the U. S. Naval Ordnance Laboratory, Task FR-44.

(8) Attack of hydride at C-1 gives the 1,4-cyclohexadienyl intermediate which rearomatizes *via* a 1,4 displacement of chloride to form monochloride IV.

(9) Alternatively, it is possible that hydride attack occurs initially at C-5. The resulting dichlorotrinitrocyclohexadienyl intermediate could then go through the above sequence to yield a trinitrocyclohexadiene which would be reduced to *sym*-trinitrocyclohexane under these conditions.

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A Mechanism for the Dehydration of Asparagine and Maleamic Acid Derivatives by N,N′-Dicyclohexylcarbodiimide

Sir:

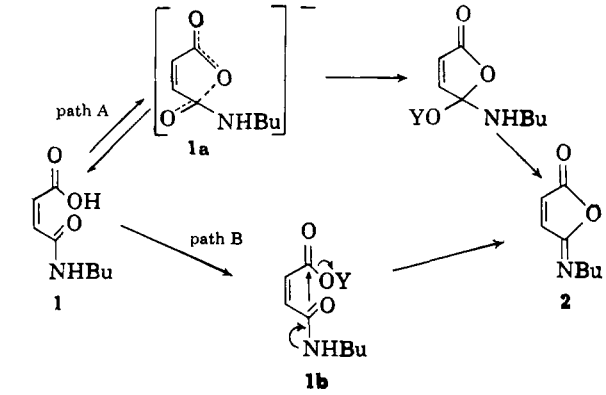
Endeavors to form the peptide linkage with the carboxyl group of N-acylasparagines lead in many cases to anomalous dehydration products.[1] There is considerable evidence that these arise by conversion of the terminal carboxamide into a nitrile, a process which occurs in this series with such extraordinary ease that some form of intramolecular participation by the carboxyl group has generally been invoked. Liberek[2] has noted the parallel between the above dehydration and that exhibited by N-substituted maleamic acids (**1**), which under similar conditions produce maleisoimides (**2**).

Cotter, *et al.*,[3] have proposed that a maleamic acid is in equilibrium with cyclic tautomer **1a**; reaction of the former amide oxygen in **1a** with a dehydrating agent such as N,N′-dicyclohexylcarbodiimide would lead, by loss of the elements of water, to isoimide **2** (Scheme I, path A). An extension[2] of this mechanism

SCHEME I

DEHYDRATION OF N-BUTYLMALEAMIC ACID TO THE ISOIMIDE

(Y = $C_6H_{11}NH$—C=NC_6H_{11})

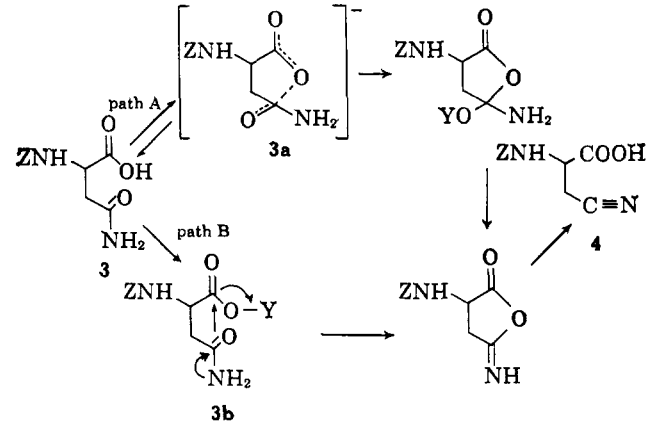


to the dehydration of asparagine derivatives would proceed through cyclic tautomer **3a** to a "succiniso-imide" and finally to nitrile **4** (Scheme II).

SCHEME II

DEHYDRATION OF CARBOBENZOXYASPARAGINE TO THE NITRILE

(Z = Carbobenzoxy)



The cyclic intermediates **1a** and **3a** resemble those proposed to explain the accelerated rates of amide hydrolyses in which internal participation by nearby hydroxyl, carboxamide, or carboxyl groups is possible.[4] On the other hand, the dehydration of maleamic and asparagine derivatives could plausibly proceed by an entirely different mechanism, in which the initial step is the customary addition of the carboxyl group to the dehydrating agent.[5] In this mechanism (path B), the resulting "anhydride" (**1b, 3b**) internally acylates the nucleophilic amide oxygen to produce an isoimide which goes on to product. Path B likewise finds analogies in the literature.[6]

In view of the relation of this problem to the general phenomenon of intramolecular acylation we have

(1) (a) D. T. Gish, P. G. Katsoyannis, G. P. Hess, and R. J. Stedman, *J. Am. Chem. Soc.*, **78**, 5954 (1956); (b) C. Ressler, *ibid.*, **78**, 5956 (1956); (c) P. G. Katsoyannis, D. T. Gish, G. P. Hess, and V. du Vigneaud, *ibid.*, **80**, 2558 (1958); (d) C. Ressler and H. Ratzkin, *J. Org. Chem.*, **26**, 3356 (1961).

(2) B. Liberek, *Bull. Acad. Polon. Sci. Ser. Sci. Chim.*, **10**, 227 (1962).

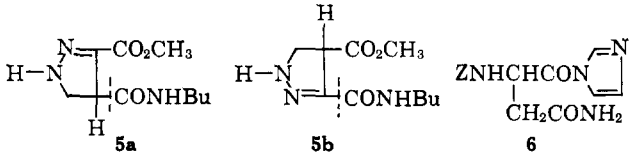
(3) R. J. Cotter, C. K. Sauers, and J. M. Whelan, *J. Org. Chem.*, **26**, 10 (1961).

(4) For a compilation of recent work in this area see, *Ann. Rept. Progr Chem.* (Chem. Soc. London), **59**, 250 (1963).

(5) C. H. Stammer, *J. Org. Chem.*, **26**, 2556 (1961).

(6) T. Wieland and H. Determann, *Angew. Chem. Intern. Ed. Engl.* **2**, 368 (1963); C. G. Overberger and E. Sarlo, *J. Am. Chem. Soc.*, **85**, 2446 (1963); A. R. Katritzky and R. A. Y. Jones, *Chem. Ind.* (London), 723 (1961); A. Patchornik, W. B. Lawson, and B. Witkop, *J. Am. Chem. Soc.*, **80**, 4748 (1958); E. J. Corey and L. F. Haefele, *ibid.*, **81**, 2225 (1959); G. L. Schmir, L. A. Cohen, and B. Witkop, *ibid.*, **81**, 2228 (1959).

used isotopic oxygen to explore the dehydrations of N-butylmaleamic acid and carbobenzoxyasparagine by the action of N,N′-dicyclohexylcarbodiimide. A sample of N-butylmaleamic acid-1,1-O^{18} was prepared by reaction of the isoimide (**2**) with 1 equiv. of potassium hydroxide-O^{18} in water containing 11% O^{18}. The position of the isotope was confirmed by reaction of the labeled acid (**1**) with excess diazomethane to give crystalline methyl 4- (or 3) N-butylcarbamoyl-2-pyrazoline-3- (or 4) carboxylate (**5a** or **5b**).[7] Mass spectrometry of **5** produced a major fragment at 127, assigned to the cleavage product shown by the dotted line. Comparison with the corresponding labeled fragment at mass 129 showed 10.7% of **5** contained one excess O^{18} per molecule in the carbomethoxy group.



5a **5b** **6**

Carbobenzoxyasparagine was labeled by treating it with N,N′-carbonyldiimidazole, to produce the acylimidazole[8,9] (**6**) followed by hydrolysis with O^{18}-water at 0°. Since direct mass spectrometric analysis was not satisfactory in the asparagine series, the extent and position of the label were established by reaction of the tagged acid with N,N′-carbonyldiimidazole at −15° and mass spectrometric assay of the carbon dioxide liberated in acylimidazole formation.[10] Since the carbon dioxide produced in this condensation derives one of its two oxygen atoms from the amino acid,[11] the assay value of 4.4 atom % COO^{18} indicated that the tagged asparagine (**3**) contained 8.8% molecules with one O^{18} in the carboxyl group.

The labeled acids (**1** and **3**) were separately subjected to the action of N,N′-dicyclohexylcarbodiimide, and the purified reaction products (**2** and **4**), as well as the corresponding N,N′-dicyclohexylurea by-products, were analyzed for O^{18} content; the results are given in Table I.

TABLE I

Compound	Per cent of the molecules containing one excess O^{18} predicted by Path A	Path B	Found ±0.3
N-Butylmaleamic acid-1,1-O^{18}[a]			10.7
N-Butylmaleisoimide-O^{18}	10.7	5.4	5.7
N,N′-Dicyclohexylurea from above	0	5.4	6.0
CO_2 from Z-asparagine-1,1-O^{18}			4.4
CO_2 from Z-β-cyanoalanine[b]	4.4	2.2	2.7
N,N′-Dicyclohexylurea from above	0	4.4	3.6

[a] Determined as **5**. [b] Obtained from Z-β-cyanoalanine plus N,N′-carbonyldiimidazole.

It is concluded from the data in Table I that the principal if not exclusive pathway for the dehydration of **1** and **3** by dicyclohexylcarbodiimide involves an *internal acylation of an amide oxygen by an "activated" carboxyl group*.[12] Appropriate caution must be taken in extending this interpretation to formally similar reactions utilizing other dehydrating agents or other bifunctional amide systems.[13]

Acknowledgment.—We wish to thank Dr. G. W. Anderson for his interest in this problem and Mr. A. H. Struck for carrying out the mass spectrometric analyses and interpretation.

(7) M.p. 164.5–166°. *Anal.* Calcd. for $C_{10}H_{17}O_3N_3$: C, 52.85; H, 7.54; N, 18.49. Found: C, 52.45; H, 7.40; N,18.45.

(8) R. Paul and G. W. Anderson, *J. Org. Chem.*, **27**, 2094 (1962).

(9) H. A. Staab, *Ann.*, **609**, 75 (1957); G. W. Anderson and R. Paul, *J. Am. Chem. Soc.*, **80**, 4423 (1958).

(10) Thin layer chromatography indicated no more than 5% of carbobenzoxy-β-cyanoalanine was formed during the reaction at −15°.

(11) R. Paul and G. W. Anderson, *J. Am. Chem. Soc.*, **80**, 4423 (1958).

(12) The possibility of **1b** forming a symmetrical anhydride and then going to **2** by an intramolecular reaction has not been eliminated by our study.

(13) NOTE ADDED IN PROOF.—Dr. C. Ressler has informed the authors that an unpublished mass spectrometric study of the dicyclohexylcarbodiimide dehydration of Z-asparagine-1,1-O^{18} in her laboratories (with D. V. Kashelkar) is consistent with the predominance of path B in this reaction.

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RECEIVED OCTOBER 25, 1963

The Reductive Aromatization of Steroidal Dienones. A New Method for the Preparation of Estrone

Sir:

Estrone (II), a key intermediate in the preparation of medicinally useful 19-norsteroids,[1a] hitherto has been prepared by the pyrolysis of androsta-1,4-diene-3,17-dione (Ia) in mineral oil–tetralin solution.[1b] We wish to report a new reaction of steroidal A-ring dienones which constitutes the basis of a superior process for the conversion of androsta-1,4-diene-3,17-dione to estrone. Treatment of the 17-ethylene ketal (Ib)[2] of androstadienedione (obtainable from the dienedione in nearly quantitative yield) with an excess of the radical anion derived from lithium metal and biphenyl in boiling tetrahydrofuran solution effects aromatization of the A-ring with expulsion of the angular methyl group as methyllithium. Acidification of the reaction mixture hydrolyzes the ketal function and affords estrone in 55–58% yield. The addition of a suitably acidic hydrocarbon such as diphenylmethane or methylnaphthalene to the reaction mixture, in order to intercept the by-product methyllithium and prevent its unwanted addition to the carbonyl group of Ib,[3] increases the over-all yield of estrone from Ib to about 75%. We suggest that this new reaction be known as reductive aromatization. A variety of aromatic hydrocarbons and ethereal solvents may be substituted for the biphenyl and tetrahydrofuran, respectively. Sodium and potassium metals may replace lithium but the yields of estrone are lower. The reaction has been applied successfully to a number of steroidal A-ring dienones and others are being studied. Although the reductive aromatization reaction involves the breaking of a C–C bond, it affords estrone from Ib in 70% yield at the remarkably low temperature of 35°.

We believe that the reductive aromatization reaction occurs by the addition of two electrons to the dienone ring to afford dianion III. In the absence of an effective proton donor, this dianion stabilizes itself by eliminating methyl carbanion with the concurrent formation of a phenoxide ion. The resonance energy thus gained must provide part of the driving force for rupture of the C–C bond; in addition, lithium ion probably coordinates with the departing methyl carbanion and assists the bond breaking process. The other possible product IV (from elimination of a C-9 carbanion)

(1) For key references see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959: (a) pp. 586–599; (b) p. 479.

(2) M. J. Gentles, J. B. Moss, M. L. Herzog, and E. B. Hershberg, *J. Am. Chem. Soc.*, **80**, 3702 (1958); R. M. Dodson and R. C. Tweit, U. S. Patent 2,875,215 (1959).

(3) In the absence of the methyllithium interceptor, 1,4-dimethylestra-1,3,5(10)-trien-17-one, the product resulting from methyllithium addition to Ib, followed by dienol–benzene rearrangement during work-up, can be isolated from the reaction liquors. We are indebted to Dr. L. J. Chinn for an authentic sample of this material. The rate of addition of diphenylmethyllithium, formed from methyllithium and diphenylmethane, to the carbonyl group of Ib appears to be very slow compared to the rate of aromatization.