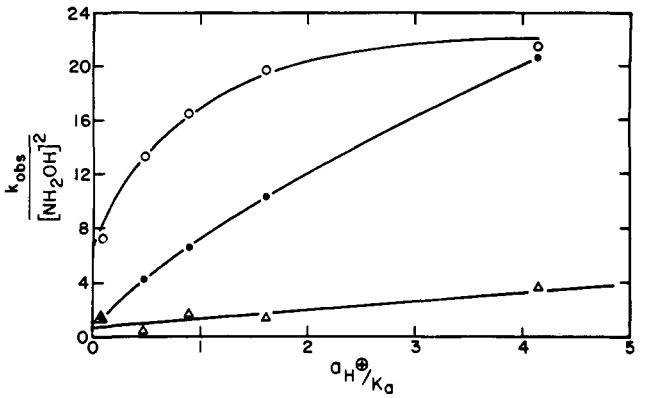

Fig. 2.—Plots of the pseudo-first-order rate constants (k_{obsd}) divided by the square of the concentration of free hydroxylamine *vs.* the hydrogen ion activity divided by the acid dissociation constant of hydroxylamine where $k_{obsd} = k_c'$ (○), $k_{obsd} = k_b'$ (●), and $k_{obsd} = k_a'$ (▲).

In Fig. 2 the values of $k_a'/(NH_2OH)^2$, $k_b'/(NH_2OH)^2$, and $k_c'/(NH_2OH)^2$ have been plotted *vs.* a_H/K_a'. Inspection of Fig. 2 reveals that the value of $k_c'/(NH_2OH)^2$, as opposed to the functions of k_a' and k_b', exhibits the same dependency on a_H/K_a' as the disappearance of ester (Fig. 1 of previous communication). Therefore, the mechanism leading directly from ester to acethydroxamic acid is that which undergoes a change in the rate-limiting step with increase in acidity justifying the assumptions leading to the postulated mechanism of the previous communication.

In separate experiments the reactions of *n*-butylmercaptan with acethydroxamic acid and O-acetylhydroxylamine were investigated. The inability to realize these back reactions under the conditions of the hydroxylaminolysis reaction assures us that the dependence of the rate constant on acidity could not be due to any conceivable equilibrium situation. Additional experiments have shown the reactions discussed to be rather insensitive to changes in ionic strength.

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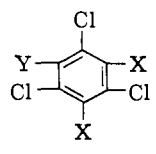
Reduction of Nitroaromatic Compounds with Sodium Borohydride

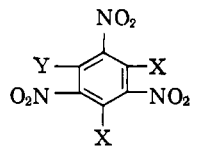
Sir:

Severin[1,2] demonstrated that the reduction of nitroaromatic compounds with sodium borohydride under alkaline conditions formed the corresponding dihydro or polyhydro product. Thus, *sym*-trinitrobenzene and 1-X-2,4-dinitrobenzene (X = Cl, CH_3, COOH, and $CH{=}CHC_6H_5$) gave *sym*-trinitrocyclohexane and 1-X-4,6-dinitrocyclohex-1-ene.

In connection with other studies, this procedure[1,2] was applied to I and II. Instead of the expected ring



I, X = Y = NO_2
II, X = NO_2; Y = H
III, X = H; Y = NO_2



IV, X = H; Y = Cl
V, X = Cl; Y = H
VI, X = OCH_3; Y = H
VII, X = Br; X = OCH_3; Y = H

(1) T. Severin and R. Schmitz, *Chem. Ber.*, **95**, 1417 (1962).
(2) T. Severin and M. Adam, *ibid.*, **96**, 448 (1963).

reduction products, *sym*-trichlorotrinitrocyclohexane and 4,6-dinitro-1,3,5-trichlorocyclohexene, benzenoid derivatives were obtained. Reduction of I afforded II (45%), m.p. 129.5–30.5° (no depression with authentic II, m.p. 129–130°, infrared spectrum identical with authentic II) as the only isolable product. The reduction of II under these conditions gave III in somewhat lower yields, m.p. 72–73° (lit.[3] 71°); infrared spectrum: 1362 and 1545 cm.$^{-1}$ (Ar–NO_2), 3060 cm.$^{-1}$ (C–H stretch), 1560 cm.$^{-1}$ (C=C stretch), 728 cm.$^{-1}$ (C-Cl); mol. wt. 226.5 (calcd.), 221 (found).[4] By carrying out the reduction of I at elevated temperatures, some of the mononitro derivative (III) was obtained together with the dinitro derivative (II), thus indicating that this denitration reaction was occurring in a stepwise fashion.

When the symmetrical chlorine substitution was replaced by nitro groups and one or two of the remaining ring positions substituted, the reaction apparently followed still a different path. The reduction of picryl chloride (IV) and styphnyl chloride (V) under conditions identical with those above yielded *sym*-trinitrocyclohexane (infrared spectrum and X-ray powder pattern identical with that of a sample, m.p. 124–125°, prepared by the reduction of *sym*-trinitrobenzene) and *not* the mono- and dichloro-*sym*-trinitrocyclohexanes.

The replacement of one or both of the chlorine atoms in V by methoxyl groups did not alter the results. The dimethoxy derivative (VI) and the bromomethoxy derivative (VII) were both converted to *sym*-trinitrocyclohexane when treated with sodium borohydride under the above conditions.

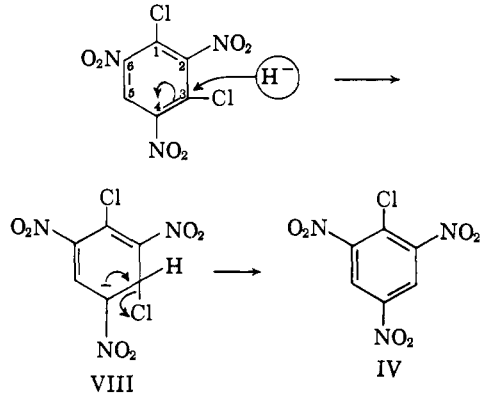
The products obtained in these reductions are either hydride displacement products or *sym*-trinitrocyclohexane. The former apparently arise from the nucleophilic displacement of one or more nitro groups as nitrite ion by hydride from borohydride ion. This reaction path prevails when the O–N–O plane of each of the nitro groups in the substrate is closer to being normal to than coplanar with the benzene ring; *i.e.*, minimal or zero resonance interaction between the nitro groups and the benzene ring. The confirmation of all the nitro groups in I, II, and III should closely approximate that of the C-2 nitro group of dichloro compound V. A crystal structure determination has shown that the O–N–O plane of this nitro group is rotated 76° out of the plane of the benzene ring.[5] Nucleophilic displacement by hydride of the *nonconjugated* nitro groups in I, II, and III would be expected since the nitro group has been shown to be a better leaving group than chlorine in nucleophilic displacements on the benzene ring.[6]

The formation of *sym*-trinitrocyclohexane from the mono- and disubstituted *sym*-trinitrobenzenes apparently depends upon having some resonance interaction between at least one of the nitro substituents and the benzene ring. In monochloro compound IV, the C-4 nitro group is only 3.6° out of the plane of the benzene ring[7] and in dichloro compound V, the C-4 and C-6 nitro groups are only 37° out of the plane of the benzene ring.[5] The dihedral 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 VI and VII has not been measured, but it probably does not differ too much

(3) J. D. Loudon, *J. Chem. Soc.*, 1525 (1940).
(4) Determined in chloroform solution with a Mechrolab vapor pressure osmometer.
(5) Private communication, Dr. J. R. Holden of these laboratories.
(6) The reaction of aniline with 1,2,3,5-tetranitrobenzene is about 2000 times faster than with 1-chloro-2,4,6-trinitrobenzene [R. E. Parker and T. O. Read, *J. Chem. Soc.*, 9 (1962)]. See also, J. F. Bunnett, *Quart. Rev.* (London), **12**, 1 (1958).
(7) Private communication, Dr. J. M. Stewart, University of Maryland.

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:

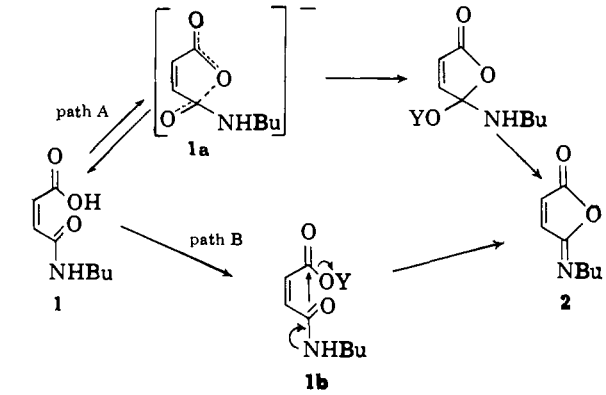
Endeavors to form the peptide linkage with the carboxyl group of N-acylasparagines lead in many cases to anomalous dehydration products.[1] There is considerable evidence that these arise by conversion of the terminal carboxamide into a nitrile, a process which occurs in this series with such extraordinary 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 = $C_6H_{11}NH—C=NC_6H_{11}$)

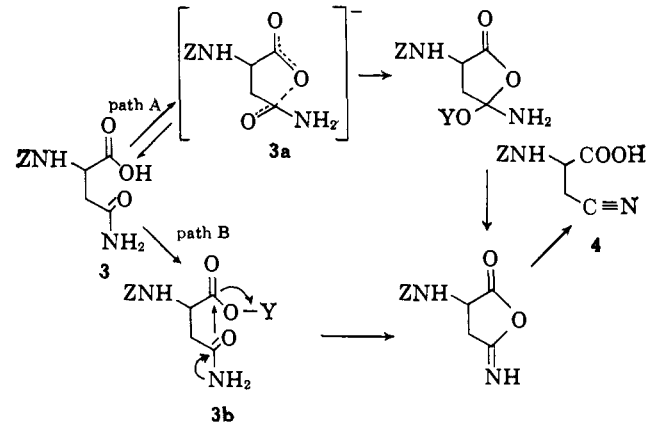


to the dehydration of asparagine derivatives would proceed through cyclic tautomer **3a** to a "succiniso-imide" and finally to nitrile **4** (Scheme II).

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).