It is worthy of note that the varying tendencies of disubstituted nitrogen radicals to dimerize[6] is probably also important in determining the behavior of various amines as inhibitors.

A complete discussion of the mechanism of inhibition by aromatic amines will appear in a subsequent publication.

The author is indebted to Dr. L. deVries who prepared the diphenyl nitric oxide and to Dr. J. C. Baird for assistance with the electron paramagnetic resonance spectroscopy.

(6) Sidgwick's "Organic Chemistry of Nitrogen," T. W. J. Taylor and W. Baker, Oxford University Press, 1942, p. 389.

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REARRANGEMENT OF ALLYLIC AZIDES

Sir:

In using azide ion as a trap for cationic intermediates in solvolysis of allylic halides[1] we have observed that allylic azides equilibrate very rapidly. In the present communication we call attention to this behavior of the pentenyl and butenyl azides.

A mixture of α,α-dimethylallyl and γ,γ-dimethylallyl azides may be obtained from treatment of γ,γ-dimethylallyl chloride with a solution of sodium azide in aqueous acetone. This mixture, b.p. 26–39° (40 mm.), has the correct C,H-analysis and displays an infrared band at 2140 cm.$^{-1}$, characteristic of azides.[2] A mixture of α- and γ-methylallyl azides, b.p. 64–72° (300 mm.), with the correct C,H-analysis is obtained analogously from *trans*-crotyl chloride. By low temperature fractionation relatively pure specimens of the four allylic azides can be obtained, and these can be stored at −80° for relatively long periods without serious rearrangement. The physical properties of the four azides are summarized in Table I, the identity of the members of each pair of allylic azides being clear from the b.p., n^{25}D and the position of olefinic absorption in the infrared spectrum.

TABLE I

PROPERTIES OF PENTENYL AND BUTENYL AZIDES

Allyl azide	B.p. °C.	B.p. Mm.	n^{25}D	Infrared abs., cm.$^{-1}$	Purity, %
α,α-Me$_2$	10.5–11.5	10	1.4260	1635	99.0
γ,γ-Me$_2$	11.0–11.5	3.0	1.4520	1665	98.5
α-Me	7.0– 8.0	25	1.4200	1635	97.8
γ-Me	12.0–12.5	10	1.4410	1667	96.7

Mixtures of the isomeric azides can be analyzed vapor phase chromatographically with a Silicone on Celite column at 25°, and this makes it possible to follow the rearrangement of the pure materials into equilibrium mixtures of the two isomers. As illustrated in Table II, the percentage of primary isomer (100 F_P) at equilibrium at 25° is *ca.* 75% for the pentenyl system and *ca.* 64% for the butenyl analog in a variety of solvents.

(1) C. Wilcox, unpublished work.

(2) E. Lieber, C. N. R. Rao, T. S. Chao and C. W. W. Hoffman, *Anal. Chem.*, **29**, 916 (1957).

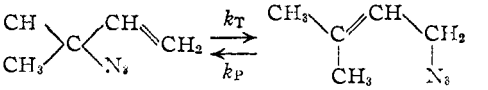
TABLE II

EQUILIBRATION OF ALLYLIC AZIDES AT 25.0°

System Solvent	Pentenyl 100 F_P[a]	Pentenyl $10^5(k_P + k_T)$[b] sec.$^{-1}$	Butenyl 100 F_P[a]	Butenyl $10^5(k_P + k_S)$[b] sec.$^{-1}$
n-C$_5$H$_{12}$	70.0	4.93	62.1	1.88
Et$_2$O	73.0	11.1	63.6	4.28
Me$_2$CO	77.0	31.0	65.2	11.0
EtOH	74.4	24.1	63.4	7.18
AcOH	76.7	36.4		
80% EtOH	74.4	62.1		
70% Me$_2$CO	77.0	90.6	65.6	24.9

[a] ±0.2. [b] Average mean deviation, ±2%.

The equilibrations of the azides in various solvents obey closely the expected kinetics for first order forward and back reactions according to the scheme



In Table II are illustrated the observed $(k_P + k_T)$ values for the pentenyl azides and the analogous $(k_P + k_S)$ values for the butenyl analogs. From these and the observed equilibrium constants, the separate k_P and k_T or k_S values are thus available. In the pentenyl series, (k_T/k_P) is *ca.* 3, while (k_S/k_P) is nearly 2 for the butenyl compounds.

The rates of the allylic azide rearrangements are remarkably insensitive to methyl substitution in the substrate azide or to solvent change. Thus, the tertiary:secondary (k_T/k_S) ratios are *ca.* 3–4, while the γ,γ-dimethylallyl:γ-methylallyl rate ratios are only *ca.* 2. The solvent change from pentane to 70% aqueous acetone increases rates of equilibration by a factor of approximately one power of ten. The small sensitivity of rate of azide isomerization to structure and solvent is in marked contrast with the high sensitivity observed with the corresponding chlorides.[1,3] With α,α-dimethylallyl chloride, for example, rates of acid production or isomerization increase by many powers of ten over the pentane → 70% acetone solvent spectrum. Thus, while rate of isomerization of α,α-dimethylallyl azide is roughly equal to that of α,α-dimethylallyl chloride in 70% acetone, it is powers of ten faster in pentane.[3]

The azide isomerization is an instructive example in the whole spectrum of merging ion pair and non-ionic cyclic rearrangement mechanisms of allylic rearrangements.[4,5] It is clear that the change from ground state to transition state in azide isomerization involves very little increase in polar character. It is also interesting that no detectable solvolysis competes with azide isomerization, even in 70% aqueous acetone.

There is considerable resemblance between the allylic azide rearrangement, here reported, and the isomerization of allylic thiocyanates to isothio-

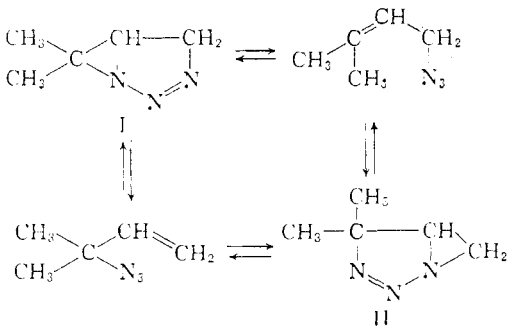
(3) A. Gagneux, unpublished work.

(4) (a) Discussion, "Symposium on Molecular Rearrangements," Queen Mary College, University of London, April 6, 1954; see *Chem. Eng. News*, **32**, 1898 (1954); *Nature*, **173**, 898 (1954); (b) S. Winstein and G. C. Robinson, THIS JOURNAL, **80**, 169 (1958).

(5) (a) W. G. Young, S. Winstein and H. L. Goering, *ibid.*, **73**, 1958 (1951); (b) F. F. Caserio, G. E. Dennis, R. H. De Wolfe and W. G. Young, *ibid.*, **77**, 4182 (1955); (c) S. H. Sharman, F. F. Caserio, R. F. Nystrom, J. C. Leak and W. G. Young, *ibid.*, **80**, 5965 (1958); (d) K. L. Olivier and W. G. Young, *ibid.*, **81**, 5811 (1959).

cyanates.[6,7] Both rearrangements show very low solvent sensitivity[6,7] and similar ΔS^* values. For isomerization of allyl thiocyanate in toluene, a ΔS^* of -9 e.u. has been reported,[7] while the ΔS^* values average -10 e.u. and -11 e.u. for isomerization of α,α-dimethylallyl and γ,γ-dimethylallyl azides, respectively, in pentane, ether and 70% acetone. With respect to sensitivity to methyl substitution, azide isomerization is even less sensitive than is the thiocyanate rearrangement.[6]

The known ability[8,9] of aryl and alkyl azides to add to olefins and acetylenes makes it conceivable that the allylic azide isomerization process partakes partly of the character of an intramolecular addition. In the extreme, one could visualize possible intermediates[10] such as I and II.



(6) A. Iliceto, A. Fava and U. Mazzucato, *Tetrahedron Letters*, **11**, 27 (1960).

(7) P. A. S. Smith and D. W. Emerson, THIS JOURNAL, **82**, 3076 (1960).

(8) K. Alder, *Ann.*, **485**, 211 (1931); **501**, 1 (1933).

(9) (a) J. H. Boyer and F. C. Canter, *Chem. Reviews*, **54**, 1 (1954); (b) F. Moulin, *Helv. Chim. Acta*, **35**, 167 (1952); (c) W. Kirmse and L. Horner, *Ann.*, **614**, 1 (1958).

(10) See E. A. Chandross and G. Smolinsky, *Tetrahedron Letters*, **13**, 19 (1960), for an analogous formulation of the isomerization of triphenylcyclopropenyl azide to a triazine.

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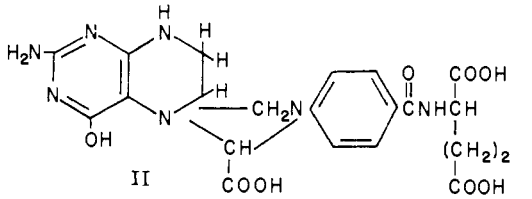
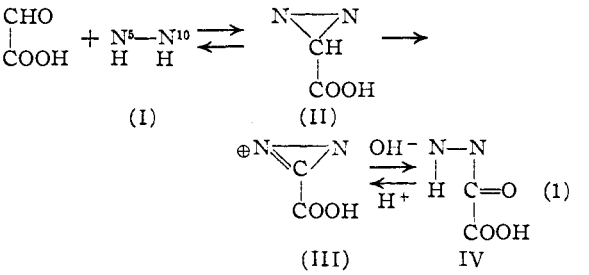
A NOVEL REACTION BETWEEN GLYOXYLATE AND TETRAHYDROFOLATE[1]

Sir:

When an excess (*ca.* 100-fold) of glyoxylate is mixed with tetrahydrofolate (I) at *p*H 4, the glyoxylate analog (II) of N^5,N^{10}-methylene tetrahydrofolate is formed within 1 min. At this *p*H



(I) displays two absorption maxima[2] at 272 and 292 mμ, while (II) has a single absorption band at 297 mμ. Similar spectral changes have been observed[3,4] when formaldehyde and (I) react to form N^5,N^{10}-methylene tetrahydrofolate. Upon further standing in the presence of excess glyoxylate, (II) is oxidized slowly (20–30 minutes) to a compound (III) having an absorption spectrum (λ_{max} at 358 mμ) comparable to that of N^5,N^{10}-methenyl tetrahydrofolate.[5,6] (III), in turn, is stable below *p*H 6, but at *p*H 8 it is hydrolyzed to the N^{10}-oxalyl analog (IV) (λ_{max} at 260, shoulder at 300 mμ) of N^{10}-formyl tetrahydrofolate[5,6]; this reaction is reversible since acidification of (IV) reconverts it quantitatively to (III). The progressive transformations of I to IV, described above, are outlined schematically in equation (1)



where the N^5- and N^{10}-positions of tetrahydrofolate are represented by the symbol $HN^5—NH^{10}$.

The conversion of (I) → (II) is identical with the synthesis of N^5,N^{10}-methylene tetrahydrofolate from (I) and formaldehyde with respect to: changes in absorption spectrum, *p*H optimum at 4, rate of reaction, inhibition by 2-mercaptoethanol, and requirement for excess aldehyde to force the equilibrium in favor of the adduct.[2-4] (II) is decomposed to (I) by the addition of hydroxylamine at *p*H 4, but not at alkaline *p*H values.[3] At *p*H 9.5, (II) is stabilized both with respect to its oxidative conversion to (III) and its spontaneous decomposition to (I) and the free aldehyde. By allowing the initial reaction (I) → (II) to occur at *p*H 4, and then adjusting the *p*H to 9.5, (II) may be purified by adsorption chromatography on columns of powdered Whatman No. 1 paper using 0.1 *M* bicarbonate buffer, *p*H 9.5: ethanol (60:40), containing 10^{-2} *M* mercaptoethanol, as the eluent.[3]

At *p*H 4 the spontaneous oxidation of (II) to (III), in the presence of excess aldehyde to repress the dissociation of (II), is of considerable interest since N^5,N^{10}-methylene tetrahydrofolate is *not* oxidized to N^5,N^{10}-methenyl tetrahydrofolate under similar conditions. The relatively facile oxidation of (II) probably is referable to the effect of the carboxyl group in enhancing the removal of the hydride ion[7] from the bridge carbon. As measured by a platinum microelectrode,[8] oxygen is consumed in the conversion of (II) → (III).

(1) Paper XII in the series "Folic Acid Coenzymes and One-carbon Metabolism." For paper XI, see C. K. Mathews and F. M. Huennekens, *J. Biol. Chem.*, in press. This work was supported by grants from the U. S. Public Health Service (CY-3310) and the Life Insurance Medical Research Fund.

(2) M. J. Osborn, Ph.D. Thesis, University of Washington, 1958.

(3) M. J. Osborn, P. T. Talbert and F. M. Huennekens, THIS JOURNAL, **82**, 4921 (1960).

(4) R. L. Blakley, *Nature*, **182**, 1719 (1958); *Biochem. J.*, **74**, 71 (1960).

(5) M. May, T. J. Bardos, F. L. Barger, M. Lansford, J. M. Ravel, G. L. Sutherland and W. Shive, THIS JOURNAL, **73**, 3067 (1951).

(6) L. D. Kay, M. J. Osborn, Y. Hatefi and F. M. Huennekens, *J. Biol. Chem.*, **235**, 195 (1960).

(7) F. M. Huennekens, H. R. Whiteley and M. J. Osborn, *J. Cell. Comp. Physiol.*, **54**, Supplement 1, 109 (1959).

(8) The authors are indebted to Dr. Bruce Mackler for making available an oxygen microelectrode, designed and built in the laboratory of Dr. B. Chance.