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VALENCE ISOMERIZATION OF IMIDOYL ISOTHIOCYANATES*

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We wish to report the preparation and novel ring closure reaction of a new class of compounds, the imidoyl isothiocyanates (I) (1). Imidoyl isothiocyanates, prepared from imidoyl chlorides and metal thiocyanates in solvents such as benzene, readily ring close to 4(3H)-quinazolinethiones (II) (2) often at temperatures as low as 80° (refluxing benzene). This ring closure, typified by the examples in Table I (3), represents a unique general synthesis of 4(3H)-quinazolinethiones, and is apparently the first such of this class of compounds to be independent of the use of anthranilic acid derivatives (5,6). It should be noted that closure occurs regardless of the presence of electron withdrawing substituents such as

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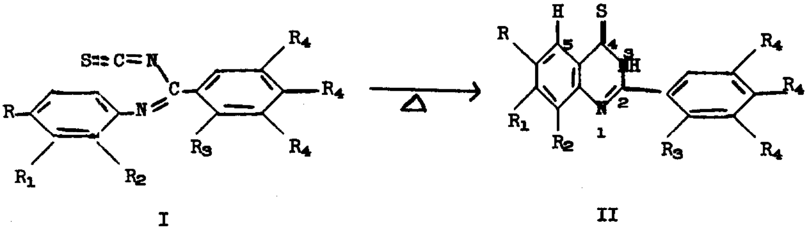
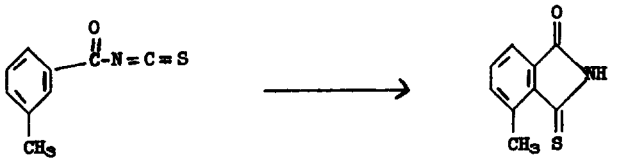
* Presented in part by H. M. Blatter at the 145th National Meeting of the American Chemical Society, New York, New York, September, 1963, p. 89Q of the abstracts.

TABLE I

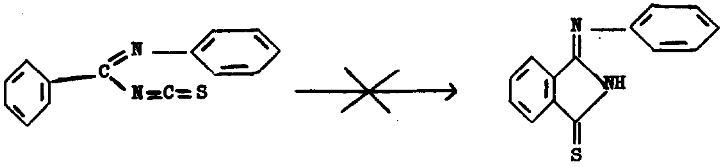


	R	R_1	R_2	R_3	R_4	% yield (4)
a	H	H	H	H	H	35-42
b	H	F	H	H	H	50
c	H	H	F	H	H	25-37
d	H	F	H	Cl	H	24
e	CH_3O	H	H	H	H	42-51
f	$C_6H_5CH_2O$	H	H	H	H	45
g	H	H	H	H	CH_3O	60
h	NO_2	H	H	H	H	55-65
i	H	NO_2	H	H	H	15

nitro or electron releasing ones such as methoxy in either benzene ring and particularly in the ring directly involved (7). Additionally, this non-catalytic, strictly thermally induced closure occurs with little variation in yield in such diverse solvents as toluene, o-xylene, dioxane, and dimethylformamide, and sometimes takes place spontaneously at the melting point. Since cyclization of aroyl isothiocyanates to monothioimides (8) e.g. III ⟶ IV, takes place only in the presence of Friedel-Crafts catalysts, the formation of analogous products, e.g. Ia ⟶ V, from the thermally induced ring closure of imidoyl isothiocyanates would not be anticipated. Indeed, thin layer and paper chromatographic analyses of the gross reaction product from the pyrolysis of N-phenylbenzimidoyl isothiocyanate (Ia) failed to reveal any trace of compound V (9). This points out the remarkable facility of the ring closure of imidoyl isothiocyanates (I) to 4(3H)-quinazolinethiones (II) in the absence of acid catalysis. The presence of catalysts such as aluminum chloride does not abet the ring closure but often simply increases the incidence of side reactions due to the presence of a receptive multifunctional molecule (I) in the vicinity of a Lewis acid.

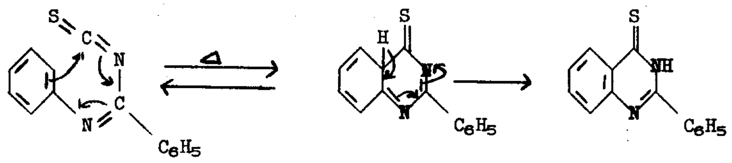


III IV



Ia V

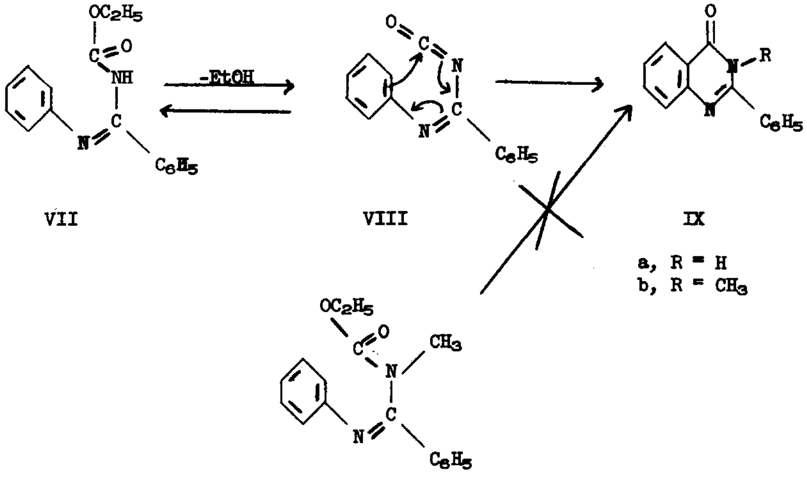
These findings favor a multicenter process dependent solely upon its own electronic resources. It seems likely therefore, that *cis* imidoyl isothiocyanates, e.g. Ia, undergo ring closure by a cyclic, concerted, thermally induced reorganization of the *sigma* and *pi* electrons within the framework of the molecule, as symbolized below.



Ia VI IIa

This would reversibly yield the less stable valence isomer (VI) which could stabilize itself through irreversible prototropic shift to form the aromatic 4(3H)-quinazolinethione (IIa in this case). This category of reaction type, which includes both the Claisen and Cope rearrangements, has been designated as "no mechanism reactions" (10); referring, of course, to the difficulty, if not the impossibility, of describing precisely the transition state or states of such reactions. Such multicenter processes (11) are neither ionic nor radical. They are thermally induced, are independent of the extramolecular environment, and are often insensitive to internal structural variation. These criteria seem to have been fulfilled here.

While there do not appear to be any direct literature references to conjugated electronic systems of the imidoyl isothiocyanate type, several reactions may be reasonably interpreted as proceeding through such an intermediate. Shah and co-workers (12,13) have reported the facile cyclization of VII to IXa at 180°-190°. Unexpectedly, however, the N-methyl derivative (X) does not undergo ring closure to IXb even under more vigorous conditions and was recovered unchanged. No explanation was offered. It seems likely though that VII reversibly loses ethanol to form a significant concentration of imidoyl isocyanate VIII which then ring closes in the manner proposed for the imidoyl isothiocyanates. This path is closed to compound X. Similarly, the Conrad-Limpach quinoline synthesis (14), which proceeds readily without catalysis and is relatively insensitive to internal structural variation,

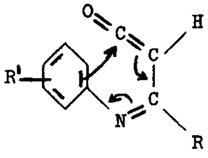


VII VIII IX

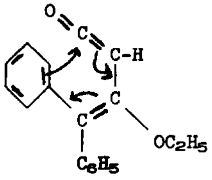
a, R = H
b, R = CH_3

X

may conceivably take place through a related ketene intermediate XI.



XI



XII

Another related intermediate, an α,β-unsaturated ketene (XII), has been proposed (15) to account for the very facile formation of 3-ethoxy-4-phenyl-1-naphthol, one of the products formed in the reaction of ethoxyacetylene with diphenyl ketene. These examples do not by any means exhaust the list; however, further comment will be reserved for our full publication.

Acknowledgement. — It is a pleasure to acknowledge the many stimulating discussions with Dr. G. deStevens throughout the course of this investigation. We wish to express our appreciation to Dr. E. Schlittler for his interest and encouragement. We are grateful to Mr. L. Dorfman and his staff for the microanalyses and for valuable help with analytical problems.

References

(1) Acceptable elemental analyses were obtained for all new compounds encountered in this investigation.

(2) Ultraviolet, infrared, and proton n.m.r. correlations, utilizing 4-methylthio-2-phenylquinazoline, 1-methyl-2-phenyl-4(1H)-quinazolinethione, and 3-methyl-2-phenyl-4(3H)-quinazolinethione (kindly supplied by Professor L. Legrand, Caen, France) as standards, indicate that at least IIa consists of a mixture of the 4(1H) and 4(3H)-quinazolinethione tautomers in solution; however, for the sake of simplicity, we are arbitrarily using the 4(3H) designation throughout.

(3) These structures are supported by infrared, ultraviolet, and n.m.r. spectroscopic data. Additionally, IIa has been synthesized by an alternate route. The downfield shift from the aromatic region in the n.m.r. of the proton on ring position 5 peri to the carbon-sulfur double bond was particularly helpful in those cases where isomeric products could result from ring closure.

(4) The yields reported for compounds II (a-f) are overall yields based on the initial imidoyl chlorides.

(5) Review by T. A. Williamson, in R. C. Elderfield (editor), "Heterocyclic Compounds", John Wiley and Sons, Inc., New York, New York, Vol. 6, p. 324 (1957).

(6) Review by W. L. F. Armarego, in A. R. Katritzky (editor), "Advances in Heterocyclic Chemistry", Academic Press, New York and London, Vol. 1, p. 253 (1963).

(7) The possible relationship of apparent rate differences to *cis* and *trans* imidoyl isothiocyanates as well as side reactions, such as dimerization, will be discussed in a forthcoming full publication.

(8) P. A. S. Smith and R. O. Kan, *J. Am. Chem. Soc.*, **82**, 4753 (1960).

(9) Prepared by the method of M. E. Baguley and J. A. Elvidge, *J. Chem. Soc.*, 709 (1957). It is stable under the conditions used for pyrolysis of compound Ia.

(10) W. v. E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

(11) Review by S. J. Rhoads, in P. de Mayo (editor), "Molecular Rearrangments", Interscience Publishers, New York and London, Part 1, p. 655 (1963).

(12) R. C. Shah and M. B. Ichaporia, *J. Chem. Soc.*, 431 (1936).

(13) H. P. Ghadiali and R. C. Shah, *J. Indian Chem. Soc.*, **26**, 117 (1949). *Chem. Abstr.* *44*, 1447^c (1950).

(14) R. H. Reitsema, *Chem. Rev.*, **43**, 47 (1948).

(15) J. Druey, E. F. Jenny, K. Schenker and R. B. Woodward, *Helv. Chim. Acta*, **45**, 600 (1962).