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Synthesis of imidazolines, diazepines, triazepines and imidazolidones from A 1, 2-diamine and 1, 1-dicarboxylic esters.

Irwin J. Pachter

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SYNTHESIS OF
IMIDAZOLINES, DIAZEPINES, TRIAZEPINES AND IMIDAZOLIDONES
FROM A 1,2-DIAMINE AND 1,1-DICARBOXYLIC ESTERS

A Thesis
Presented to
the Faculty of the Department of Chemistry
UNIVERSITY OF NEW MEXICO

In Partial Fulfillment
of the Requirements for the Degree
Master of Science

by
Irwin J. Pachter
January 1949

SYNOPSIS OF

THEORY, DESIGN, CONSTRUCTION AND INSTALLATION

OF A 1,1-DICHLOROETHYLENE SYSTEM

A Thesis

Presented to

the Faculty of the Department of Chemistry

UNIVERSITY OF ILLINOIS AT CHICAGO

IN PARTIAL FULFILLMENT

OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

BY

IRVING J. FROST

JANUARY 1963

This thesis, directed and approved by the candidate's committee, has been accepted by the Graduate Committee of the University of New Mexico in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

Barney H. Stohler
DEAN

DATE January 17, 1949

SYNTHESIS OF
IMIDAZOLINES, DIAZEPINES, TRIAZEPINES AND IMIDAZOLIDONES
FROM A 1,2-DIAMINE AND 1,1-DICARBOXYLIC ESTERS

Thesis committee

J. L. Rieckner
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This report directed and approved by the President's committee has been submitted to the President's committee on the University of the Pacific and has been approved by the members of the committee.

MASTER OF ARTS

[Faint, illegible signature]

EXHIBIT B

INVESTIGATION, RESEARCH, AND DEVELOPMENT
OF A PRACTICAL METHOD FOR THE
DETERMINATION OF THE

THESE

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ACKNOWLEDGMENTS

The writer wishes to express his gratitude to Dr. J. L. Riebsomer for suggesting the original problem and for advice and encouragement received during the course of this work.

The three complete analyses reported in this thesis were made at the laboratories of Eli Lilly Company, Indianapolis, Indiana.

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ACKNOWLEDGMENTS

The writer wishes to express his gratitude to Dr. J. L. Kinsman for suggesting the original problem and for advice and encouragement received during the course of this work. The three complete analyses reported in this thesis were made at the laboratory of Mr. Billy Conway, Indianapolis, Indiana.

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I. INTRODUCTION

In 1884 Freund (1) heated a mixture of malonic ester and ethylenediamine and obtained a product which dried to give a high melting powder. He named the compound ethylenemalonamide and attributed a seven-membered ring structure to it.

Dox (2) repeated this synthesis in 1935 and described the product obtained as a colloidal, amorphous, polymeric substance. Dox also investigated the reactions of mono- and disubstituted malonic esters with ethylenediamine and reported that, although the disubstituted esters yield thermally stable crystalline compounds with sharp melting points, the monoalkyl derivatives decompose on melting, are "amorphous and colloidal in character and probably have a polymeric structure."

For the reactions of the disubstituted esters with ethylenediamine, the following equation was proposed.

(1) Freund, Ber. 17, 137 (1884)

(2) Dox, J. Am. Chem. Soc. 55, 3871 (1933)

In 1934 Brown (1) heated a mixture of sodium azide and ethylenediamine and obtained a product which he gave a high melting point. He named the compound ethylenediamine azide and attributed a never-before-attributed structure to it:

Box (2) repeated this synthesis in 1935 and described the product as a solid, explosive, polymeric substance. Box also investigated the reaction of azide and substituted ethylenediamines with ethylenediamine and reported that, like the azide, the products were solid, explosive, and melted with sharp melting points. The monomeric derivatives, however, are "amorphous and colloidal in character and probably have a polymeric structure." For the reaction of the substituted azides with ethylenediamine, the following reaction was proposed:

- (1) Brown, *Rev. IV*, 133 (1934)
- (2) Box, *J. Am. Chem. Soc.*, **57**, 2541 (1935)

In the instances of the unsubstituted and monosubstituted esters, Dox suggested that somehow the remaining hydrogen atoms alter the course of the above reaction. On the basis of the present work this does not seem to be true.

In the presence of the undersigned and non-undersigned estate.

Box suggested that some of the remaining property should after the course

of the above reaction. On the basis of the present work this does not

seem to be true.

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FEEICB

II. THE PROBLEM

In view of the inconclusive character of much of the above mentioned work, a further investigation of the reactions between 1,2-diamines and dicarboxylic esters of the type $\text{CH}_3\text{CH}_2\text{OOCXCOOCH}_2\text{CH}_3$ ($\text{X} = \text{CH}_2, \text{CHR}, \text{NH}$) seemed warranted. In our present investigations we were guided by three main considerations.

1) The nature of the products obtained when 1,2-diamines react with 1,1-dicarboxylic esters.

2) The effect of the structure of the diamine employed on the course of the reaction.

3) The effect of the enolizable hydrogen atoms of unsubstituted and monosubstituted esters on the course of the reaction.

Since Freund and Dox used ethylenediamine in their experiments, another 1,2-diamine, namely the readily available (3) N-(2-aminoisobutyl)-isopropylamine, $\text{NH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{NHCH}(\text{CH}_3)_2$, was used in our investigations in an attempt to clarify the second point mentioned above.

(3) Commercial Solvents Corporation, Terre Haute, Indiana

11. THE PROBLEM

In view of the fact that the character of the above mentioned work, a further investigation of the reaction between 1,3-dinitrobenzene and dicarboxylic acids of the type $\text{HOOC(CH}_2\text{)}_n\text{COOH}$ ($n = 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100$) seemed warranted. In our present investigation we were guided by three main considerations.

- 1) The nature of the products obtained when 1,3-dinitrobenzene reacts with 1,1-dicarboxylic acids.
 - 2) The effect of the structure of the dicarboxylic acid on the course of the reaction.
 - 3) The effect of the catalytic action of substituted and nonsubstituted acids on the course of the reaction.
- Since benzene and hex acid oxydichloride in their experiments, and other 1,3-dinitrobenzene, namely the readily available 1,3-dinitrobenzene, isopropylamine, $\text{CH}_3\text{CH(CH}_3\text{)NH}_2$, was used in our investigations in an attempt to clarify the above point mentioned above.

A. 2-IMIDAZOLINES

The literature available for the synthesis of 2-imidazolines and their derivatives is extensive. The references accompanying each process usually refer to only a small part of these and are not listed. The most common method for the preparation of these compounds have been the direct reaction of 1,2-dichlorides with various reagents such as azides, azides, azides and azides. Recently, a number of agents was employed as an aid in carrying out reactions to completion.

(4, 8, 9, 10, 11)

CH₃COOCH₃ + H₂NCH₂CH₂NH₂ → CH₃COOCH₂CH₂CH₂NH₂
140-11950
CH₃COOCH₃ + H₂NCH₂CH₂NH₂ → CH₃COOCH₂CH₂CH₂NH₂
140-11950
CH₃COOCH₃ + H₂NCH₂CH₂NH₂ → CH₃COOCH₂CH₂CH₂NH₂
140-11950

- (4) Chittwood and Smith, J. Am. Chem. Soc., 67, 2484 (1945)
- (5) Chittwood and Smith, J. Am. Chem. Soc., 67, 2484 (1945)
- (6) Chittwood and Smith, J. Am. Chem. Soc., 67, 2484 (1945)
- (7) Chittwood and Smith, J. Am. Chem. Soc., 67, 2484 (1945)
- (8) Chittwood and Smith, J. Am. Chem. Soc., 67, 2484 (1945)
- (9) Chittwood and Smith, J. Am. Chem. Soc., 67, 2484 (1945)
- (10) Chittwood and Smith, J. Am. Chem. Soc., 67, 2484 (1945)
- (11) Chittwood and Smith, J. Am. Chem. Soc., 67, 2484 (1945)

Ethers of the readily available 2-thioimidazolidone (see p. 14) are themselves 2-imidazolines. They may combine with amines to yield 2-amino derivatives (10).

2-thioimidazolidone and chloroacetic acid condense to form 2-thioglycollic acid-2-imidazoline (11).

2-Imidazolines have been obtained from imino-alkyl ethers in two ways. One involves a condensation with a 1,2-diamine (12, 13, 14).

The other proceeds through a very different mechanism (15).

(10) I. G. Farbenind. A.- G. Ger. 539,179; C.A. 26, 1615 (1932)

(11) Johnson and Edens, J. Am. Chem. Soc. 64, 2706 (1942)

(12) Bockmühl and Knoll, U.S. 1,958,529; C.A. 28, 4540 (1934)

(13) Sonn, U.S. 2,161,938; C.A. 33, 7316 (1939)

(14) Djerassi and Scholz, J. Am. Chem. Soc. 69, 1688 (1947)

(15) Stollé, Merkle and Hanusch, J. Pract. Chem. 140, 59 (1934)

Figure 4. The reaction of 2-aminobenzimidazole (10) with 2-aminobenzimidazole (10).

are themselves 2-aminobenzimidazoles. They may combine with amines to yield

2-amino derivatives (10).

2-aminobenzimidazoles and chloroacetic acid combine to form 2-chloro-

glycolic acid-2-aminobenzimidazole (11).

2-aminobenzimidazoles have been obtained from amino-alkyl ethers in two

ways. One involves a condensation reaction with 2-aminobenzimidazole (12, 13, 14).

The other proceeds through a very different mechanism (15).

(10) I. E. Richardson, *J. Am. Chem. Soc.*, **68**, 1815 (1946).

(11) Johnson and Evans, *J. Am. Chem. Soc.*, **66**, 1738 (1944).

(12) Ruchman and Knoll, *J. Am. Chem. Soc.*, **75**, 4843 (1953).

(13) Sore, *J. Am. Chem. Soc.*, **75**, 4811 (1953).

(14) Uffers and Schell, *J. Am. Chem. Soc.*, **69**, 1833 (1947).

(15) Neill, Neill and Harrison, *J. Am. Chem. Soc.*, **70**, 35 (1948).

Aldehydes and 1,2-diamines usually condense to yield imidazolines. However, when heated with copper acetate, an intermediate complex forms which is decomposed by hydrogen sulfide to yield a 2-imidazoline (16).

When phthalide is heated with ethylenediamine an amide is obtained which cyclizes to form a 2-imidazoline. Dehydration with acetic anhydride yields the tricyclic product o-benzylene-2-imidazoline (17).

(16) I. G. Farbenind. A.-G. Ger. 676,196

(17) Betrabet and Chakravarti, J. Ind. Chem. Soc. 7, 191 (1930); C.A. 25, 701 (1931)

Aldehydes and 1,2-diketones usually react with hydrazine to form

hydrazones. However, when heated with hydrazine, an intermediate complex forms which is decomposed by hydrazine to yield a 2-aminobenzaldehyde (16).

When hydrazine is heated with ethylenediamine an amide is obtained which cyclizes to form a 2-aminobenzaldehyde. Dehydration with acetic anhydride yields the triazole product o-benzyl-2-aminobenzaldehyde (17).

(16) I. G. Torgerson, J. Am. Chem. Soc., 73, 133

(17) Betts and Charnick, J. Am. Chem. Soc., 73, 131 (1951)
C.A. 53, 701 (1951)

The compound "amarine" (A) has been known for many years. It may be obtained by condensing benzoin, benzaldehyde and ammonia together (18).

N-allylacetamide condenses with primary aromatic amines to yield imidazolines (19).

2-imidazolines have found use as foaming agents (20), as foliage fungicides (21), as blood pressure regulators (22), and as anaphylaxis inhibitors (23).

(18) Radziszewski, Ber. 15, 1493 (1882)

(19) Clayton, Ber. 28, 1665 (1895)

(20) Waldmann and Chwala, Fr. 811,423; C.A. 31, 8550 (1937)

(21) Wellman and McCallan, Contrib. Boyce Thompson Inst. 14, 151 (1946); C.A. 40, 4470 (1946)

(22) Hartmann and Isler, Arch. Exptl. Path. Pharmacol. 192, 141 (1939); C.A. 34, 4068 (1940)

(23) Meier and Bucher, Experientia 2, 140 (1946); C.A. 40, 5134 (1946)

The compound (18) has been known for many years. It may

be obtained by condensation of benzaldehyde and ethyl acetate (19).

(A)

2-allylacetamide condenses with primary aromatic amines to yield

imidazoles (20).

2-Imidazoles have been used as feeding agents (21).

Imidazoles (21) as blood pressure regulators (22) and as anesthetics

imidazoles (23).

(18) Katsunuma, *Chem. Ind. (Japan)*, 1953, 1533.

(19) Claisen, *Ber.*, 26, 1895 (1893).

(20) Waidmann and Grawert, *Ch. Z.*, 21, 5533 (1957).

(21) Waidmann and Grawert, *Ch. Z.*, 21, 5533 (1957).

(22) Waidmann and Grawert, *Ch. Z.*, 21, 5533 (1957).

(23) Waidmann and Grawert, *Ch. Z.*, 21, 5533 (1957).

(24) Waidmann and Grawert, *Ch. Z.*, 21, 5533 (1957).

(25) Waidmann and Grawert, *Ch. Z.*, 21, 5533 (1957).

(1953)

B. 1,4-DIAZEPINES AND 1,3,5-TRIAZEPINES

1. 1,4-Diazepines

The 1,4-diazepines are cyclic compounds having the following basic ring structure. They have not often been synthesized and the methods of

preparation at the present time are few.

In 1902 Scholtz (24) reported the formation of a quaternary diazepine salt. The following synthesis was also reported later by other workers (25).

(24) Scholtz, Ber. 35, 3052 (1902)

(25) v. Braun and Goll, Ber. 60B, 339 (1927)

1,2-Diamines react with carbon suboxide to yield the corresponding cyclic malonamide derivatives (26, 27).

Other diamines have been used in place of N,N'-dibenzylethylenediamine in analogous syntheses.

(3-Diketones and 1,2-diamines yield 2,3-dihydro-1,4-diazepines (28).

Diethyl-, dibutyl- and hexylethylmalonic esters yield 1,4-diazepines when they condense with ethylenediamine (2).

(26) Pauw, Rec. Trav. Chim. 55, 215 (1936); C.A. 30, 5185 (1936)

(27) Rameau, *Ibid.* 57, 192 (1938); C.A. 32, 3395 (1938)

(28) Schwarzenbach and Lutz, Helv. Chim. Acta 23, 1139 (1940); C. A. 35, 1041 (1941)

1,3-dioxane reacts with carbon dioxide to yield the corresponding

the cyclic malonate derivative (25, 26).

Other dioxanes have been used in place of 1,3-dioxane, tetrahydropyran

in analogous syntheses.

(3-Dioxanes and 1,3-dioxanes yield 2,5-dihydro-1,4-dioxepines (27).

1,3-dioxane, 1,3-dioxane, and tetrahydropyran also yield 1,4-

dioxepines when they condense with ethylenediamine (28).

(25) *Trans*, *trans*-trans-2,5,8,11-tetraoxa-2,5,8,11-tetradecane (1939)

(26) *trans*, *trans*-trans-2,5,8,11-tetraoxa-2,5,8,11-tetradecane (1939)

(27) *trans*, *trans*-trans-2,5,8,11-tetraoxa-2,5,8,11-tetradecane (1939)

U. S. Pat. 2,101,101 (1941)

Unsubstituted and monosubstituted malonic esters condense with ethylenediamine and o-phenylenediamine to yield compounds of uncertain structure. It is possible that these compounds are 1,4-diazepines (1, 2, 29).

In the few biological tests made with 1,4-diazepines, they were found to be pharmacologically inert (2, 30).

2. 1,3,5-Triazepines

The 1,3,5-triazepines are cyclic compounds having the following basic ring structure.

In 1885 it was reported that phenylthiourea and ethyl oxalyl chloride condense to form a compound $C_{16}H_{11}O_2N_3S_2$. Although it was not verified, the structure assigned to this compound was that indicated in the following equation (31).

(29) Meyer, Ann. 347, 17 (1906)

(30) McGinty and Bywater, J. Pharmacol. 84, 342 (1945)

(31) v. Stojentin, J. Pract. Chem. [2], 32, 16 (1885)

Unsubstituted and monosubstituted aromatic esters condense with ethylenediamine and *o*-phenylenediamine to yield compounds of uncertain structure. It is possible that these compounds are 1,4-diazepines (1, 2, 29).

In the few classical cases where 1,4-diazepines, they were found to be diamagnetic, diamagnetic (2, 30).

2. 1,3,5-Triazepines

The 1,3,5-triazepines are cyclic compounds having the following

basic ring structure.

In 1929 it was reported that phenylhydrazones and ethyl oxalyl

chloride condense to form a compound $C_{10}H_{10}Cl_2N_2O_2$. Although it was not verified, the structure assigned to this compound was that indicated in the following reaction (31):

(29) Meyer, Ann., 441, 11 (1905)

(30) Morley and Fowler, J. Pharmacol., 14, 345 (1945)

(31) v. Grobstein, J. Org. Chem., 11, 52, 12 (1946)

Diguanide and oxalic ester condense to yield the corresponding seven-membered ring compound (32).

Carbethoxythiourethane reacts with one equivalent of a 1,2-diamine to form a 1,3,5-triazepine derivative (33).

With *o*-phenylenediamine, the analogous bicyclic compound is obtained.

Dicyanimide and *o*-phenylenediamine condense as follows (34).

No uses have been found as yet for 1,3,5-triazepine derivatives.

(32) Rackmann, Ann. 376, 170 (1910)

(33) Guha, Rao and Saletore, J. Ind. Chem. Soc. 6, 565 (1929); C.A. 24, 1114 (1930)

(34) Acheson, King and Spensley, Nature 160, 53 (1947)

Diphenylamine and similar bases were used to give the corresponding

seven-membered ring compounds (32).

Carboxyphenylurethane reacts with one equivalent of 1,3-diamine

to form a 1,3,5-triazine derivative (33).

With *o*-phenylenediamine, the product is a 1,3,5-triazine derivative.

Diphenylamine and *o*-phenylenediamine condense as follows (34).

No uses have been found as yet for 1,3,5-triazine derivatives.

(32) Kohnen, *Ber.*, 37, 170 (1910).

(33) Kohnen, *Ber.*, 37, 170 (1910).

C.A. 34, 114 (1930).

(34) Kohnen, *Ber.*, 37, 170 (1910).

C. 2-IMIDAZOLIDONES

The 2-imidazolidones or 2-ketoimidazolidines have been synthesized in a variety of ways. The references given in this section represent a cross-section of the work done; consequently, the list is incomplete.

The most commonly employed synthetic method for the preparation of these compounds has been the condensation of 1,2-diamines with phosgene (35).

In place of phosgene, diethyl carbonate has been used (36).

In an interesting synthesis illustrating the readiness with which the 2-imidazolidone ring is formed, it was found (37) that whereas the amides of benzoyl β -aminovaleric, benzoyl ϵ -aminocaproic and of analogous higher acids yield monobenzoyl diamine derivatives in the Hofmann reaction, the amides of acylated β -amino acids formed only the

(35) Scholtz and Jaross, Ber. 34, 1513 (1901)

(36) Fischer and Koch, Ann. 232, 227 (1886)

(37) Kanevskaya, Ber. 69B, 266 (1936)

2. 3-IMIDAZOLONES

The 3-imidazolones or 3-imidazolinones have been synthe-

sized in a variety of ways. The references given in this section represent a cross-section of the work done; consequently, the list is incomplete.

The most commonly employed synthetic method for the preparation

of these compounds has been the condensation of 1,2-diamines with

phosgene (25)

or with

in place of phosgene, the following compounds have been used:

In an interesting synthesis (26) the following reaction was used:

the 3-imidazolone (27) is formed, it was found (28) that whereas the

analogous higher aliphatic 3-imidazolones, benzyl 3-imidazolone and 2-

Hofmann reagent, the ester of 3-imidazolone reacts with only one

(25) Schell and Jones, *Ann.*, **1215** (1931)

(26) Fischer and Snow, *Ann.*, **523** (1935)

(27) Knecht, *Ber.*, **30**, 100 (1905)

2-imidazolidones.

N-(3-chloroethyl)ureas yield imidazolidones on treatment with alkali (38).

Electrolytic reduction of parabanic acid yields hydantoin and 2-imidazolidone (39).

2-imidazolones have been reduced to 2-imidazolidones (40, 41).

(38) Gabriel and Stelzner, Ber. 28, 2938 (1895)

(39) Tafel and Reindl, Ber. 34, 3288 (1901)

(40) Winans and Adkins, J. Am. Chem. Soc. 55, 4167 (1933)

(41) Cheney and Bywater, U.S. 2,398,410; C.A. 40, 3778 (1946)

2-Imidazolones.

1-(6-chlorophenyl)urea and 1-imidazolones in treatment with

Alkali (32)

Electrolytic reduction of pyrimidine and pyrazine derivatives and

2-Imidazolones (33)

2-Imidazolones have been reduced to 1-imidazolones (34, 35)

- (36) G. J. Janz and J. E. H. Jones, *J. Chem. Soc.*, 1953, 1953.
- (37) J. E. H. Jones and G. J. Janz, *J. Chem. Soc.*, 1953, 1953.
- (38) J. E. H. Jones and G. J. Janz, *J. Chem. Soc.*, 1953, 1953.
- (39) J. E. H. Jones and G. J. Janz, *J. Chem. Soc.*, 1953, 1953.
- (40) J. E. H. Jones and G. J. Janz, *J. Chem. Soc.*, 1953, 1953.
- (41) J. E. H. Jones and G. J. Janz, *J. Chem. Soc.*, 1953, 1953.

The thio analogues of 2-imidazolidones, which are prepared from 1,2-diamines and carbon disulfide (42) yield 2-imidazolidones when treated with silver oxide (43).

The glyoxals react with urea to yield the 4,5-dihydroxy derivatives of 2-imidazolidones (44). With an excess of urea, an hydroxyl

group is replaced (45).

(42) Zahlova, Coll. Czech. Chem. Comm. 2, 108 (1930); C.A. 24, 2431 (1930)

(43) Klut, Archiv. fur Pharmazie 240, 677.

(44) Fisher, Ekeley and Ronzio, J. Am. Chem. Soc. 64, 1434 (1942)

(45) Seekles, Rec. Trav. Chim. 46, 77 (1927); C.A. 21, 1447 (1927)

In the past year, two new industrial methods requiring high pressures have been developed. One is a condensation between glycol and urea (46). The other is a reaction of ethylenediamine with

carbon dioxide (47).

Pharmacologically, a few 2-imidazolidones have a biotic action, and some other inhibit the action of biotin, but most are without effect (41, 48, 49). Commercially, 2-imidazolidone derivatives have found use in the textile industry (50) and in the manufacture of explosives (51).

(46) Larson, Loder and Dittmar, U.S. 2,436,311; C.A. 42, 3436 (1948)

(47) Mulvaney and Evans, Ind. Eng. Chem. 40, 393 (1948)

(48) McKennis, Jr. and du Vigneaud, J. Am. Chem. Soc. 68, 832 (1946)

(49) Duschinsky and Rubin, J. Am. Chem. Soc. 70, 2546 (1948)

(50) Hoover and Vaala, U.S. 2,373, 136; C.A. 39, 4763 (1945)

(51) Rinkenbach and Aaronson, U.S. 2,167,679; C.A. 33, 8992 (1939)

IV. THE REACTIONS OF N-(2-AMINOISOBUTYL)-ISOPROPYLAMINE WITH
UNSUBSTITUTED AND MONOSUBSTITUTED 1,1-DICARBOXYLIC ESTERS

A. The Reactions With Malonic Ester

Freund (1) believed that the high-melting condensation product obtained upon heating malonic ester with ethylenediamine had the empirical formula, based on a nitrogen analysis, of $C_5H_8O_2N_2$. He suggested the formula

for this compound and named it ethylenemalonamide. His work was later confirmed by Dox (2).

In the present investigation, the main product obtained when malonic ester was heated with N-(2-aminoisobutyl)-isopropylamine (I) was a solid crystalline material, melting point 58°C ., which was very soluble in alcohol and dilute hydrochloric acid but insoluble in water. The compound formed a picrate, melting point 97°C . Analysis yielded results which are in agreement with the structure (II).

The proof of structure of ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (II) was accomplished in several ways.

IV. THE SYNTHESIS OF 4-(2-ETHOXYCARBOXY)-1-ISOPROPYLBENZENE UNSUBSTITUTED AND MONOSUBSTITUTED 1,2-DICARBOXYLIC ESTERS

A. The Reaction with Ethyl Acrylate

Frederick (1) believes that the high-melting, crystalline product

obtained upon heating ethyl acrylate with isobutyraldehyde had the em-

pirical formula, based on a nitrogen analysis, of $C_{12}H_{18}O_4$. He

suggested the formula

for this compound and named it ethyl isobutyraldehyde. The work was later

confirmed by Fox (2).

In the present investigation, the main product obtained after

malonic ester was heated with 4-(2-ethoxycarbonyl)-1-isopropylbenzene (1)

was a solid crystalline material, melting about 80°C., which was

soluble in alcohol and dilute hydrochloric acid and insoluble in water.

The compound formed a dimer, melting point 85°C., analysis indicated

relative which are in agreement with the structure (II).

The proof of structure of ethyl 4-(2-ethoxycarbonyl)-1-isopropyl-2-

malate (II) was accomplished in several ways.

Copeland and Day (52) have shown that o-phenylenediamine condenses with ethyl cyanoacetate to yield 2-cyanomethylbenzimidazole. By a similar reaction between (I) and ethyl cyanoacetate we obtained an analogous product.

The 2-cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline (III) melted at 197-198°C. The compound was a monoacid base, formed a picrate, which melted at 177-179°C., and had a neutral equivalent and nitrogen content which conformed with the structural formula presented.

When refluxed with alcoholic hydrochloric acid, (III) was converted to a compound which melted at 58°C., formed a picrate which melted at 97°C. and was identical in all respects with (II).

Neither (II) nor (III) yielded the corresponding acid upon hydrolysis. Only the decarboxylated product 1-isopropyl-2,4,4-trimethyl-2-imidazoline was obtained. This suggested that an acetoacetic ester type condensation might be possible and useful as a method for the preparation of imidazoline derivatives.

The sodium salt of (II) reacted with benzyl chloride and upon hydrolysis, 4,4-dimethyl-1-isopropyl-2-(β-phenylethyl)-2-imidazoline (IV), boiling point 168-170° at 15 mm., was obtained.

(52) Copeland and Day. J. Am. Chem. Soc. 65, 1072 (1943)

Copeland and Day (32) have shown that *o*-propylphenolamine reacts with ethyl oxycarbonate to yield 2-oxymethylphenylamine. By a similar reaction between (I) and ethyl oxycarbonate we obtained an analogous product.

The 2-oxymethylphenyl-4,4'-dimethyl-1-isopropyl-2-imidazoline (III)

melted at 197-198°C. The compound was a monacid base, formed a hydrate,

which melted at 177-178°C, and had a neutral equivalent of nitrogen

content which conformed with the structural formula presented.

When refluxed with alcoholic hydrochloric acid, (III) was con-

verted to a compound which melted at 90°C, formed a picrate which melted

at 97°C, and was identical in all respects with (II).

Neither (II) nor (III) yielded the corresponding acid upon hy-

drolysis. Only the decarboxylated product 2-isopropyl-3,4'-dimethyl-1-2-

imidazoline was obtained. This suggested that an esterolysis ester type

condensation might be possible and useful as a method for the preparation

of imidazoline derivatives.

The sodium salt of (II) reacted with benzyl chloride and upon

hydrolysis, 4,4'-dimethyl-1-isopropyl-2-phenylethyl-2-imidazoline (IV),

boiling point 168-170°C at 15 mm, was obtained.

Compound (IV) formed a picrate, melting point $120^\circ\text{C}.$, and had the expected neutral equivalent for a monoacid base. It was identical with the product obtained by direct condensation of β -phenylpropionic acid with (I).

When (II) was heated with an excess of (I), the expected bisimidazoline (53)

was not formed. Instead, the following reaction occurred.

(53) J. L. Riebsomer. Unpublished work on the reactions of dicarboxylic acids with N-(2-aminoisobutyl)-isopropylamine.

Compound (IV) forms a dihydrate, melting point 130°C., and has the expected neutral equivalent for a monobasic base. It was identical with the product obtained by direct condensation of 2-phenylpyrazole with (1). When (II) was heated with an excess of (I), the expected diazabenzidine (83)

was not formed. Instead, the following reaction occurred.

(83) J. L. Kricheldorf, unpublished work on the reaction of dicarboxylic acids with N-(2-aminobenzyl)-isopropylamine.

2,4,4-Trimethyl-1-isopropyl-2-imidazoline (V) had a boiling point of 89-90°C. at 28 mm. which was in agreement with the boiling point of 94-96°C. at 38 mm. previously found for this compound (9). It had the expected neutral equivalent for a monoacid base.

4,4-dimethyl-isopropyl-2-imidazolidone (VI), melting point 162°C., was formed in this reaction by a mechanism which seems similar to that of the above mentioned decarboxylation of the acid.

When (II) was refluxed with an excess of aniline, a reaction of the same type occurred and a compound was obtained which melted at 239°C., caused no melting point depression when mixed with pure sym-diphenylurea and on analysis was found to have the expected nitrogen content.

In view of the readiness with which decarboxylation of (II) and (III) occurred on hydrolysis, the two reactions mentioned last are not too surprising. Urethanes, which also decarboxylate readily on hydrolysis, have long been known to undergo comparable reactions (54, 55). For example, phenylurethane and (I), as expected, yielded aniline, ethanol and compound (VI).

Since the reaction of (I) with malonic ester yielded an imidazoline ester (II), while (II) with an excess of (I) yielded products similar to those from phenylurethane and (I), the electron attracting effect of the imidazolinyll group seems stronger than that of the carbethoxy group. The imidazolinyll group exerts an effect great enough to cause the α -carbon atom to behave like the nitrogen atom of phenylurethane.

(54) Wilm and Wischin, Ann. 147, 157 (1868)

(55) Goldenring, Ber. 23, 1173 (1890)

B. The Reactions With Monosubstituted Malonic Esters

Dox (2) investigated the reactions of monosubstituted alkylmalonic esters with ethylenediamine. He found that the products were amorphous and colloidal and probably polymeric, that their melting points were high but not sharp and that decomposition occurred upon melting with darkening in color and evolution of gas.

Monosubstituted malonic esters reacted with N-(2-aminoisobutyl)-isopropylamine (I) to yield compounds which were strikingly different in nature from those mentioned above. They were relatively low melting solids, formed large crystals, were stable at their melting points and indeed were even distilled under reduced pressure at temperatures above 200°C. without decomposition. Our preparations and those of Dox, in fact, were similar only in analysis. The compounds analyzed had empirical formulas which corresponded to seven-membered rings.

Butylmalonic ester and benzylmalonic ester reacted with one equivalent of (I), as the following equation indicates, to form 6-butyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (VII), melting point 108°C., boiling point 220-224°C. at 4 mm., and 6-benzyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (VIII) melting point 151-152°C., boiling point 233°C. at 3 mm.

5. The Reaction with Acetylated Malonic Esters

Box (2) investigated the reaction of acetylated malonic esters with ethylmagnesium. It found that the products were alcohols and acetals and probably esters. It was noted that the reaction was not sharp and that decomposition occurred upon standing, resulting in color and evolution of gas.

Acetylated malonic esters reacted with 2-(2-methoxyethyl)-isopropylalcohol (I) to give compounds which were strikingly different in nature from those mentioned above. They were relatively low melting solids, formed large crystals, were stable at their melting points and indeed were even distilled under reduced pressure at temperatures above 200°C. without decomposition. The products were analyzed and empirical formulas which corresponded to acetylated malonic esters were similar only in analysis. The compounds analyzed had empirical formulas which corresponded to acetylated malonic esters.

Isopropylalcohol ester and acetylated malonic ester reacted with one equivalent of (I), as the following equation indicates, to form 2-(2-methoxyethyl)-2-methyl-3,3-dimethyl-1-isopropoxyhexanoate (VII), melting point 108°C., boiling point 120-125°C. at 5 mm., and 2-methyl-3,3-dimethyl-1-isopropoxyhexanoate (VIII) melting point 121-122°C., boiling point 110°C. at 5 mm.

The compounds obtained formed well-defined crystals and were neutral to acids and bases (in contrast to the basic products obtained from malonic ester).

In the past there has been some contention as to whether seven-membered rings similar to these are actually formed (56) or whether, instead of cyclizing, the molecules polymerize. The fact that definite melting points and boiling points were obtained for compounds (VII) and (VIII) is rather good evidence against polymerization in these compounds. More conclusive proof for the seven-membered ring structures was obtained from molecular weight determinations by the boiling point elevation method (57). For compound (VIII), molecular weight 288, in benzene solution at a concentration of 0.0508 M. a molecular weight of 350 was obtained. At a concentration of 0.110 M. the value found was 405. When concentration was plotted against apparent molecular weight, an extrapolation to zero concentration gave a molecular weight close to the expected value of 288. These data show that as the concentration increases, hydrogen bonding between diazepine rings results in a rapid increase in the apparent molecular weight.

The difference in behavior of substituted and unsubstituted malonic esters with (I) is unusual. It was thought possible that the reaction with malonic ester proceeded through an enol mechanism as follows

(56) Shriner and Upson, J. Am. Chem. Soc. 63, 2277 (1941)

(57) Livingston, Physico Chemical Expts. Rev. Edit. (Macmillan Company, New York, 1948), p. 108.

The compounds obtained from well-defined crystals and were neutral to acids and bases (in contrast to the basic products obtained from malonic ester).

In the past there has been some confusion as to what is meant by numbered rings similar to those of actually fused (57) or what is meant by overlapping the molecular fragments. The fact that boiling melting points and boiling points were obtained for compounds (VII) and (VIII) is rather good evidence against polymerization in these compounds. More conclusive proof for the seven-membered ring character was obtained from molecular weight measurements: one by the boiling point elevation method (57). For compound (VII), molecular weight 288, in benzene solution at a concentration of 0.0503 g./100 ml. a molecular weight of 350 was obtained. For compound (VIII), the value found was 405. When concentration was varied against apparent molecular weight, an extrapolation to zero concentration gave a molecular weight close to the expected value of 288. These data show that as the concentration increases, hydrogen bonding between molecules gives rise to a rapid increase in the apparent molecular weight.

The difference in behavior of substituted and unsubstituted malonic esters with (I) is unusual. It was thought possible that the reaction with malonic ester proceeded through an ionic mechanism as follows:

- (56) Shriner and Upson, J. Am. Chem. Soc., 55, 287 (1933)
 (57) Livingston, Physical Chemical Expts. Rev. Ed., (Macmillan Company, New York, 1946), p. 108.

and that the substitution of electron-donating groups such as the butyl and benzyl decreased the enolization to a value low enough that the mechanism leading to the seven-membered ring formation predominated.

If an analogy can be drawn from the fact that phenylacetoacetic ester enolizes more readily than acetoacetic ester itself, whereas the substitution of butyl or benzyl groups on the ester decreases the extent of enolization, it might be inferred that, if the imidazoline formation occurs through an enol intermediate, phenylmalonic ester would react with (I) to form an imidazoline. This was not the case however, and a seven-membered ring, 5,7-diketo-3,3-dimethyl-1-isopropyl-6-phenyl-hexahydro-1,4-diazepine (IX), melting point 222°C ., was formed.

When heated with an excess of (I) the seven-membered rings opened and reclosed, forming smaller five-membered rings.

and that the substitution of electron-donating groups such as the methyl
and benzyl decreased the epoxidation to a value low enough that the
mechanism leading to the seven-membered ring formation predominated.
If an analogy can be drawn from the fact that phenylacetone
ester epoxidizes more readily than acetone, it is evident that the
substitution of bulky or bulky groups on the ester decreases the extent
of epoxidation. It might be inferred that, in the epoxidation of
cyclohexanone, an epoxide intermediate, 2,2-dimethyl-1,3-dioxane-4-one,
which (1) is formed as an intermediate, and (2) has not been observed, and
seven-membered ring, 2,2-dimethyl-1,3-dioxane-4-one, is formed.
hexahydro-1,4-dioxane (12), melting point 122°C., was formed.
When heated with an excess of (1) the seven-membered ring opened
and reformed, forming smaller five-membered rings.

Compound (X), boiling point 157-158°C. at 18 mm., was also produced as a by-product in the formation of (IX). It was identical with an imidazoline prepared directly from (I) and phenylacetic acid. It formed a picrate, melting point 147°C., and when stirred with water or left exposed to air, it crystallized to form a solid, melting point 45-47°C. This solid reliquified when placed in a desiccator over calcium chloride overnight.

The compound (VI) obtained in this reaction was the same as that previously obtained in part IV A and it was identical with a by-product formed in the synthesis of (VII), (VIII) and (IX).

C. The Reactions With Imidodicarboxylic Ester

The reaction between ethylenediamine and carbethoxythiourethane has already been mentioned (page 11). The condensation of N-(2-aminoisobutyl)-isopropylamine (I) and diethyl imidodicarboxylate (XI) (prepared by the method of Wurtz and Henninger (58), although the method of Diels and Nawiasky (59) results in higher yield) followed a somewhat different course and the crystalline cyclic diamide 6,6-dimethyl-1-isopropyl-2,4-diketohexahydro-1,3,5-triazepine (XII), melting point 206°C., was obtained.

With a second equivalent of (I), compound (XII) opened and re-closed to form ammonia and two equivalents of 4,4-dimethyl-1-isopropyl-2-imidazolidone (VI), melting point 162°C., in almost quantitative yield.

(58) Wurtz and Henninger, Bulletin de la Soc. Chim. de Paris (2) 44, 30 (1885)

(59) Diels and Nawiasky, Ber. 37, 3679 (1904)

3. The Reaction with Isocyanic Acid

The reaction between isocyanic acid and isocyanic acid has already been mentioned (page 11). The condensation of (2-aminotoluenyl)-isocyanic acid (I) and diethyl isocyanic acid (II) prepared by the method of Frits and Hantsch (22), although the method of Frits and Hantsch (22) results in higher yield, followed somewhat different course and the crystalline cyclic dimer 6,6'-bis(2-aminotoluenyl)-2,4-bis(isocyanamido)-1,3,5-triazine (XII), melting point 208°C., was obtained.

With a second equivalent of (I), compound (XII) opened and re-closed to form a cyclic dimer, the equivalent of 4,4'-bis(2-aminotoluenyl)-2,4-bis(isocyanamido)-1,3,5-triazine (VI), melting point 182°C., in almost quantitative yield.

(22) Frits and Hantsch, *Bull. Soc. Chim. Paris* (2) 44, 30 (1885)
 (23) Frits and Hantsch, *Bull. Soc. Chim. Paris* (2) 44, 30 (1885)

We attempted to find additional proof for the structure assigned to compound (VI) by studying the reaction products from the reactions of (XI) with ethylene-diamine. The first product obtained was an amorphous powder (XIII), melting point 242-245°C., which was very sparingly soluble in water, ethanol and acetone. Compound (XIII) reacted with an excess of ethylenediamine to yield the well-known compound 2-imidazolidone (XIV), melting point 131-132°C.

The identification of (XIV) confirmed the structure assigned to compound (VI) in the reaction of (XII) with (I), and consequently, in all reactions mentioned in this paper in which (VI) was a product.

We attempted to find additional proof for the structure assigned to compound (VI) by studying the reaction between it and the reaction of (II) with acetylene-ethanol. The first product obtained was an amorphous powder (XIII), melting point 131-132°C., which was very soluble in alcohol in water, ethanol and acetone. Compound (XIII) reacted with an excess of acetylene-ethanol to give the well-known compound 2-ethyl-2-methyl-3-hydroxy-3-methylbutane (XIV), melting point 131-132°C.

The identification of (XIV) confirmed the structure assigned to compound (VI) in the reaction of (XII) with (I), and consequently, in all reactions mentioned in this paper in which (VI) was a product.

Reactions Carried Out in IV C.

V. EXPERIMENTAL

All of the following reactions involving N-(2-aminoisobutyl)-isopropylamine (I) were carried out under a 4' x 5/8" helix-packed column which was equipped with a decanter still-head. In those reactions in which water was a product, Riebsomer's technique (9) was employed. Benzene was added to the reaction mixture and as it distilled, water formed in the reaction was carried out with it in an azeotropic mixture. At the still-head, the water separated and the benzene returned to the column. In those reactions in which alcohol was the only volatile product, benzene was not added and the still-head merely served as a receptacle for the alcohol which distilled during the reaction. The absence of benzene in these latter instances did not affect the courses of the reactions since the same results were obtained when the reactions were carried out with benzene added.

Preparation of ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (II).

To 160 g. (1 mole) of malonic ester was added 65 g. (0.5 mole) of (I). The mixture was heated between 125° and 145°C. until no more water-alcohol mixture came over at the top of the column (8 hours). Benzene was added and the temperature was raised to 165°C. for one hour.

The reaction mixture was cooled and a half gram of solid material (IIa), melting point over 310°C. was filtered out. The filtrate was extracted with 45 ml. of concentrated hydrochloric acid in 50 ml. of water. The aqueous layer was made basic and an oil separated out and solidified. This product was recrystallized from alcohol and a yield of 57 g. or 51%

EXPERIMENTAL

All of the following reactions involving 1-(2-methyl-2-propenyl)-

isopropylamine (I) were carried out under a 4' x 5' x 3' bell-shaped

column which was equipped with a mechanical stirrer. In those

reactions in which water was a product, the column (I) was

employed. Benzene was added to the reaction mixture as it dis-

solved, water formed in the reaction was removed and with it the

azeotropic mixture. At the still-head, the water separated and the

benzene returned to the column. In those reactions in which alcohol

was the only volatile product, benzene was not added and the still-

head merely served as a condenser for the alcohol which distilled

during the reaction. The absence of benzene in these latter instances

did not affect the course of the reaction since the same results

were obtained when the reactions were carried out with benzene added.

Preparation of 1-(2-methyl-2-propenyl)-1-isopropyl-2-phenyl-3-oxobutane (II)

To 100 g. (1 mole) of malonic ester was added 55 g. (0.5 mole) of

(I). The mixture was heated between 100° and 110° until no more

alcohol mixture came over at the top of the column (5 hours). Benzene

was added and the temperature was raised to 100° for one hour.

The reaction mixture was cooled and a 10% solution of sodium

(II), melting solid over 210°, was filtered out. The filtrate was ex-

tracted with 25 ml. of concentrated hydrochloric acid in 50 ml. of water.

The aqueous layer was made basic and the oil separated out and redistilled.

This product was recrystallized from alcohol and a yield of 35 g. of II

of the theoretical amount of ester, melting point $58^{\circ}\text{C}.$, was obtained.

Analysis. Calculated for (II), $\text{C}_{12}\text{H}_{22}\text{O}_2\text{N}_2$: N, 12.4%; neutral equivalent, 226. Found: N, 12.7%; neutral equivalent, 222.

Analysis of (IIa). Found: N, 16.83%; neutral equivalent, 326.

A picrate of (II) was prepared. To one gram of picric acid dissolved in five ml. of ethanol was added one gram of (II) in three ml. of ethanol. The solution was boiled for a few minutes and cooled. The crystals which formed were recrystallized from ethanol. The picrate melted at $97^{\circ}\text{C}.$

Preparation of 2-cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline (III).

To 65 g. (0.5 mole) of (I) was added 113 g. (1 mole) of cyanoacetic ester and the mixture was heated to $110^{\circ}\text{C}.$ for seven hours. Benzene was then added and the temperature was raised to $160^{\circ}\text{C}.$ for two hours. The reaction mixture was cooled and the crystals were filtered and recrystallized from ethanol. A yield of 54 g. or 61% of the theoretical amount of nitrile (III) was obtained, melting point $197^{\circ}\text{C}.$

Analysis. Calculated for (III), $\text{C}_{10}\text{H}_{17}\text{N}_3$: N, 23.45%; neutral equivalent, 179. Found: N, 23.30%; neutral equivalent, 178.

A picrate of (III) was prepared by dissolving one gram of (III) in the least amount of ethanol and adding the solution to a saturated alcoholic solution of one gram of picric acid. Yellow crystals formed immediately. These were filtered and recrystallized from ethanol. The picrate melted at $177\text{-}179^{\circ}\text{C}.$

Conversion of 2-cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline (III)
to Ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (II).

A 10% alcoholic solution of hydrogen chloride was prepared by bubbling the gas into 99% ethanol. A 10 g. sample of (III) was refluxed with 150 ml. of the 10% acid solution for 4.5 hours. Ammonium chloride was removed to lessen bumping after the first hour and again after 2.5 hours.

The excess alcohol was now distilled until 50-75 ml. remained. Again the ammonium chloride was removed and the distillation continued over a water bath until no more alcohol came over. The residue was neutralized with a saturated solution of sodium bicarbonate. Warming was necessary to decompose the hydrochloride of the ester. The material which separated and solidified was filtered, dried and recrystallized from ethanol. 9.7 g. or a 78% yield was obtained, melting point 58°C.

A picrate of this material was prepared. To one gram of picric acid dissolved in five ml. of ethanol was added one gram of the ester in three ml. of ethanol. The solution was boiled for a few minutes and cooled. The crystals which formed were recrystallized from ethanol. The picrate melted at 97°C. A mixed melting point with the picrate of (II) gave no depression.

Preparation of 4,4-dimethyl-1-isopropyl-2- α -phenylethyl-2-imidazoline (IV).

To 2.5 g. of sodium dissolved in 100 ml. of absolute alcohol was added 22.6 g. (0.1 mole) of the ester (II). After the solid dissolved,

Conversion of 2-ethyl-2-methyl-3-oxobutanoic acid to 2-ethyl-2-methyl-3-oxobutanoic acid (II)

to 2-ethyl-2-methyl-3-oxobutanoic acid (II)

A 10% alcoholic solution of hydrogen chloride was prepared by bubbling the gas into 300 ml. of water. A 10 ml. sample of (II) was placed in a 100 ml. flask and the 10% acid solution for 2 hours. The acid chloride was removed by heating overnight after the first hour and again after 2.5 hours.

The excess alcohol was now distilled until 80-90 ml. remained. Again the excess alcohol was removed and the distillation continued over a water bath until no more alcohol came over. The residue was neutralized with a saturated solution of sodium bicarbonate. The water was necessary to decompose the intermediate of the ester. The water (10 ml) which separated and solidified was filtered, dried and recrystallized from ethanol. M.P. 52-53° or a 5% solution was crystallized, melting point 58-59°.

A portion of this material was prepared. To one gram of crystals acid dissolved in 10 ml. of ethanol was added one gram of the ester in 10 ml. of ethanol. The solution was boiled for a few minutes and cooled. The crystals which formed were recrystallized from ethanol. The crystals melted at 57-58°. A mixed melting point with the sample of (II) gave no depression.

Preparation of 2-ethyl-2-methyl-3-oxobutanoic acid (IV)

To 2.0 g. of sodium dissolved in 100 ml. of absolute alcohol was added 22.8 g. (0.1 mole) of the ester (II). After the solid dissolved,

12.5 g. (0.15 mole) of benzyl chloride was slowly added with stirring. The mixture was then refluxed with stirring for four hours.

The sodium chloride was filtered out and the filtrate was distilled over a water bath until no more alcohol came over. The residue was refluxed with 1.5 times the theoretical amount of 10% aqueous sodium hydroxide for two hours. The oily layer was separated and acidified with hydrochloric acid. Any insoluble material was discarded. The acid solution was treated with 10% sodium hydroxide and an oil separated out. This layer was dried over magnesium sulfate and distilled, boiling point 168-170°C. at 15 mm. The yield was 10.0 g. or 41% of theoretical. It was later found that hot alkali results in some disruption of the imidazoline ring. The yield may possibly be raised if the hydrolysis is carried out in acid solution.

Analysis. Calculated for the β -phenylethyl imidazoline (IV) $C_{16}H_{24}N_2$: neutral equivalent, 244. Found: neutral equivalent, 245.

A picrate was prepared. To one gram of picric acid dissolved in five ml. of ethanol was added one gram of (IV) in three ml. of ethanol. The solution was boiled for a few minutes and cooled. The crystals which formed were recrystallized from ethanol. The picrate melted at 120°C. Since the melting point of the picrate is similar to that of picric acid (122°C.) we verified that we actually had a picrate by taking a mixed melting point with picric acid; the melting point obtained was 85-115°C. rather than 120°C. It was also found that upon shaking the picrate with 5% sodium hydroxide, a basic oily imidazoline layer was re-generated.

12.5 g. (0.1 mole) of benzyl alcohol was added with stirring.

The mixture was then refluxed with stirring for four hours.

The sodium chloride was filtered out and the filtrate was dis-

tilled over a water bath until no more alcohol came over. The residue

was refluxed with 1.5 times the theoretical amount of 10% aqueous

sodium hydroxide for two hours. The oily layer was separated and

acidified with hydrochloric acid. Any insoluble material was discarded.

The acid solution was treated with 10% sodium hydroxide and an oil

appeared out. This layer was dried over magnesium sulfate and dis-

tilled, boiling point 100-110°C. at 15 mm. The yield was 10.0 g. or

41% of theoretical. It was later found that the alkali results in some

disruption of the indole nucleus. The yield may possibly be raised

if the hydrolysis is carried out in acid solution.

Analysis. Calculated for the α -phenylethyl indole (IV)

C₁₅H₁₃N: neutral equivalent, 244. Found: neutral equivalent, 248.

A picrate was prepared. To one gram of picric acid dissolved in

five ml. of ethanol was added one gram of (IV) in three ml. of ethanol.

The solution was boiled for a few minutes and cooled. The crystals

which formed were recrystallized from ethanol. The picrate melted at

120°C. Since the melting point of the picrate is similar to that of

picric acid (123°C.) we verified that we actually had a picrate by taking

a mixed melting point with picric acid; the melting point obtained was

88-118°C. rather than 120°C. It was also found that upon adding the

picrate with 5% sodium hydroxide, a basic oily indole-like layer was re-

generated.

The melting point of the picrate, boiling point and neutral equivalent of (IV) are identical with those constants obtained from the imidazoline prepared by condensation of (I) with β -phenylpropionic acid.

Reaction of ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (II) with (I) to yield 1-isopropyl-2,4,4-trimethyl-2-imidazoline (V) and 4,4-dimethyl-1-isopropyl-2-imidazolidone (VI).

To 22.6 g. (0.1 mole) of (II) was added 16.2 g. (0.125 mole) of (I). The mixture was heated to 140-150°C. for five hours and after that the temperature was raised slowly to 200°C. over a second five hour period. The reaction mixture was cooled on ice overnight. The crystals that formed were filtered and washed with petroleum ether. The filtrate and the washings were fractionally distilled. After the petroleum ether and unreacted diamine were removed, the main fraction, 8 g. of compound (V), came over between 89-90°C. at 28 mm. From the residue in the distilling flask, an additional small amount of crystals were obtained.

The two crops of crystals were combined and recrystallized from ethanol and a yield of 13.9 g. or 89% of the theoretical amount of compound (VI), melting point 162°C., was obtained.

Analysis. Calculated for 1-isopropyl-2,4,4-trimethyl-2-imidazoline (V), $C_9H_{18}N_2$: neutral equivalent, 154. Found: neutral equivalent, 152.

Calculated for 4,4-dimethyl-1-isopropyl-2-imidazolidone (VI), $C_8H_{16}ON_2$: N, 17.93%. Found: N, 17.87%.

The melting point of the product, boiling point and neutral equivalent of (IV) are identical with those constants obtained from the imidazoline prepared by condensation of (I) with 2-phenylpropionic acid.

Reaction of ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-3-acetate (II) with (I) to yield 1-isopropyl-2,4,4-trimethyl-2-imidazoline (V) and 4,4-dimethyl-1-isopropyl-2-imidazolidone (VI).

To 22.6 g. (0.1 mole) of (I) was added 10 g. (0.125 mole) of (II). The mixture was heated to 140-150°C. for five hours and after that the temperature was raised slowly to 200°C. over a second five hour period. The reaction mixture was cooled on ice overnight. The crystals that formed were filtered and washed with petroleum ether. The filtrate and the washings were fractionally distilled. After the petroleum ether and unreacted diimide were removed, the main fraction, 8 g. of compound (V), came over between 80-90°C. at 28 mm. From the residue in the stilling flask, an additional small amount of crystals were obtained. The two crops of crystals were combined and recrystallized from ethanol and a yield of 12.8 g. or 59% of the theoretical amount of compound (VI), melting point 152°C., was obtained.

Analysis. Calculated for 1-isopropyl-2,4,4-trimethyl-2-imidazoline

(V), $C_{12}H_{21}N_2$: neutral equivalent, 104. Found: neutral equivalent, 102.

Calculated for 4,4-dimethyl-1-isopropyl-2-imidazolidone (VI),

$C_{10}H_{17}NO_2$: M , 171.17. Found: M , 171.17.

Reaction of ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (II) with aniline to yield 1-isopropyl-2,4,4-trimethyl-2-imidazoline (V) and diphenylurea.

A mixture of 4.5 g (0.02 mole) of ester (II) and 4 g. (0.043 mole) of aniline was refluxed for one hour. The mixture was cooled and filtered. The solid was recrystallized from ethanol and melted at 237-238°C. A mixed melting point with sym-diphenylurea gave no depression.

Analysis. Calculated for diphenylurea (VII), $C_{13}H_{12}ON_2$: N, 13.2%.
Found: N, 12.9%.

Reaction of Phenylurethane with (I).

To 8.25 g. (0.05 mole) of phenylurethane was added 9 g. (0.07 mole) of (I) and the mixture was heated between 130 and 175°C. for five hours. The solid material (VI) was filtered and recrystallized from ethanol. A yield of 6.4 g. or 82% of theoretical was obtained, melting point 162°C.

Analysis. Calculated for imidazolidone (VI), $C_8H_{16}ON_2$: N, 17.9%.
Found: N, 17.7%.

The procedures used for the preparation of the diazepines 6-butyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (VII), 6-benzyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (VIII), and 5,7-diketo-3,3-dimethyl-1-isopropyl-6-phenylhexahydro-1,4-diazepine (IX) were essentially the same. By the method described below for the preparation of (VIII), the yields of the three diazepines were between 55 and 70% of theoretical. At the time these experiments were carried out, it was not known that the diazepines formed undergo further reaction with an

Reaction of ethyl 2,4-dinitrophenyl-3-oxopropionate (II)

with aniline to give 2,4-dinitrophenyl-3-oxopropionate (V)

and diphenylurea.

A mixture of 4.5 g. (0.02 mole) of ester (II) and 1.0 g. (0.02 mole)

of aniline was refluxed for one hour. The mixture was cooled and filtered.

The solid was recrystallized from ethanol and melted at

237-238°C. A mixed melting point with 2,4-dinitrophenyl-3-oxopropionate

was 237-238°C. Analysis. Calcd. for $C_{15}H_{11}N_4O_7$ (339.3): C, 44.23%; H, 2.68%; N, 13.09%.

Found: C, 44.2%; H, 2.7%; N, 13.1%.

Reaction of phenylurethane with (II)

To 0.25 g. (0.002 mole) of phenylurethane was added 0.5 g. (0.01 mole)

of (I) and the mixture was heated between 150 and 175°C. for five hours.

The solid material (VI) was filtered and recrystallized from ethanol.

Yield of 0.4 g. or 82% of theoretical was obtained, melting point 153°C.

Analysis. Calcd. for $C_{15}H_{11}N_4O_7$ (339.3): C, 44.23%; H, 2.68%; N, 13.09%.

Found: C, 44.2%; H, 2.7%; N, 13.1%.

The procedures used for the preparation of the dinitrophenyl-3-oxopropionates

2,4-dinitro-3,5-dimethyl-1-isopropylphenyl-3-oxopropionate (VII), 2,4-dinitro-3,5-dimethyl-1-isopropylphenyl-3-oxopropionate (VIII), and

2,4-dinitro-3,5-dimethyl-1-isopropylphenyl-3-oxopropionate (IX)

were essentially the same. By the method described above for the preparation

of (VIII), the yields of the three dinitrophenyl-3-oxopropionates were between 85 and 90%

of theoretical. At the time these experiments were carried out, it was

not known that the dinitrophenyl-3-oxopropionates formed under a further reaction with an

additional quantity of (I) (see below), and it is believed that the yields of diazepines may be raised somewhat by using only small excesses of (I) in the mixtures rather than the 25% excesses used in the present work.

Preparation of 6-benzyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (VIII).

To 50 g. (0.20 mole) of benzylmalonic ester was added 34 g. (0.25 mole) of (I). The mixture was heated at 140-150°C. for five hours. The temperature was then slowly raised to 200°C. over a second five hour period.

After cooling to room temperature, 25 ml. of petroleum ether was added and the mixture was cooled on ice for an hour, filtered, and the solid material (VIII) obtained was recrystallized from ethanol. The melting point after recrystallization was 152°C.

The alcoholic filtrate was added to the original mother liquor and the combined liquids were distilled under reduced pressure. The fraction which came over at 150-185°C. at 30 mm. was collected. From the residue in the distilling flask, an additional yield of (VIII) was obtained.

The 150-185°C. at 30 mm. fraction was cooled on ice overnight and filtered. 10 g. of (VI), melting point 162°C., was obtained. On distillation of the filtrate, 9 g. came over at 166-170°C. at 16 mm. This liquid was identical with compound (IV) in boiling point and melting point of the picrate derivative. The neutral equivalent found was 252 rather than the expected 245, probably due to the presence of a small quantity of (VI) in the liquid.

additional quantity of (I) (see below), and it is believed that the excess of diisopropylamine may be raised somewhat by using only small excesses of (I) in the mixtures rather than the 25% excesses used in the present work.

Preparation of 6-benzyl-5,7-dinitro-3,4-dimethyl-1-phenylhexylamine

1,4-diazepine (VIII)

To 50 g. (0.35 mole) of benzylamine ester was added 25 g. (0.35 mole) of (I). The mixture was heated at 140-150°C. for 18 hours. The temperature was then slowly raised to 200°C. over a 2-hour period. The temperature was then slowly raised to 200°C. over a 2-hour period.

After cooling to room temperature, 25 ml. of petroleum ether was added and the mixture was cooled on ice for an hour, filtered, and the solid material (VIII) contained was recrystallized from ethanol. The melting point after recrystallization was 128°C.

The alcoholic filtrate was added to the original mother liquor and the combined liquids were distilled under reduced pressure. The fraction which came over at 150-160°C. at 30 mm. was collected. From the residue in the distilling flask, an additional yield of (VIII) was obtained.

The 150-160°C. at 30 mm. fraction was cooled on ice overnight and filtered. 10 g. of (VI), melting point 152°C., was obtained. On distillation of the filtrate, 2 g. came over at 155-170°C. as 16 mm. This liquid was identical with compound (IV) in boiling point and melting point of the picrate derivative. The neutral equivalent found was 262 rather than the expected 265, probably due to the presence of a small quantity of (VI) in the liquid.

The combined yield of (VIII) in this experiment was 34.5 g. or 60% of theoretical.

The first time (VII) and (VIII) were prepared, the addition of 25 ml. of petroleum ether followed by cooling on ice did not yield a solid material. In these cases, fractional distillation was employed in the purification processes. (VII) distilled over at 220-224°C. at 4 mm. and (VIII) came over at 233°C. at 3 mm. as viscous liquids which solidified as super-cooled liquids on standing. These solids were dissolved in a few ml. of ethanol, cooled and stirred. Crystallization then occurred in each case.

In subsequent preparations of the same compounds, seed crystals were available and the first procedure described was used.

Analysis. Calculated for (VII), $C_{14}H_{26}O_2N_2$: N, 11.01%. Found: N, 10.82%.

Calculated for (VIII), $C_{17}H_{24}O_2N_2$: N, 9.72%; C, 71.15%; H, 8.39%. Found: N, 9.83%; C, 70.92%; H, 8.22%.

Calculated for (IX), $C_{16}H_{22}O_2N_2$: N, 10.01%. Found: N, 10.02%.

Calculated for (VI), $C_8H_{16}ON_2$: by-product in the formation of (VII), N, 17.93%. Found: N, 17.65%. ((VI) was also a by-product in the preparation of (VIII) and (IX)).

Reaction of 5,7 diketo-4,4-dimethyl-1-isopropyl-6-phenylhexahydro-1,4-diazepine (IX) with (I).

To 13.7 g. (0.05 mole) of (IX) was added 9.0 g. (0.075 mole) of (I). The mixture was heated at 150°C. for six hours. The temperature was raised

The compound (VII) in this experiment was 80% or

80% of (VII).

The first time (VII) and (VIII) were prepared, the addition of

25 ml. of petroleum ether followed by cooling on ice did not yield a

solid material. In these cases, fractional distillation was employed

in the purification processes. (VII) distilled over at 230-234°C. at

4 mm. and (VIII) came over at 230°C. at 5 mm. as viscous liquids which

solidified on cooling on standing. These solids were dis-

solved in a few ml. of ethanol, cooled and stirred. Crystallization

then occurred in each case.

In subsequent preparations of the same compounds, seed crystals

were available and the first procedure described was used.

Analysis. Calculated for (VII), $C_{12}H_{18}O_2$: C, 77.01%; H, 10.01%. Found:

C, 76.82%; H, 10.02%.

Calculated for (VIII), $C_{12}H_{18}O_2$: C, 77.01%; H, 10.01%. Found:

C, 76.82%; H, 10.02%.

Calculated for (IX), $C_{12}H_{18}O_2$: C, 77.01%; H, 10.01%. Found:

C, 76.82%; H, 10.02%.

(VII), C, 77.01%; H, 10.01%. Found: C, 76.82%; H, 10.02%.

preparation of (VII) and (IX).

Reaction of 5,7-dibromo-4,4-dimethyl-1-isopropyl-6-phenylhexahydro-1,4-

diisopropylidene (I) with (I):

To 12.7 g. (0.05 mole) of (I) was added 2.0 g. (0.075 mole) of (I).

The mixture was heated at 100°C. for six hours. The temperature was raised

gradually to 210°C. over a second six hour period. The mixture was cooled and filtered and the solid (VI) obtained was recrystallized from ethanol. Yield 7.5 g. or 96% of theoretical, melting point 162°C.

The original mother liquor was distilled and 4 g. came over at 156-159°C. at 17 mm. This compound (X) is identical with that formed from phenylacetic acid and (I) in boiling point, in melting point of the picrate and in that both form solids, melting point 45-47°C., when stirred with water or exposed to air for several hours.

The picrates each were prepared by dissolving one gram of imidazoline in two ml. of ethanol and adding the solution to a saturated alcoholic solution of one gram of picric acid. The crystals which formed were filtered and recrystallized from ethanol. The picrates melted at 147°C.

Preparation of 2,4-diketo-6,6-dimethyl-1-isopropylhexahydro-1,3,5-triazepine (XII).

To 24.2 g. (0.15 mole) of imidodicarboxylic ester was added 26 g. (0.20 mole) of N-(2-aminoisobutyl)-isopropylamine (I) and the mixture was heated for four hours at 120-140°C. Upon cooling, the mass solidified. Recrystallization from alcohol yielded 25 g. or an 84% of theoretical yield of (XII), melting point 206°C.

Analysis. Calculated for triazepine $C_9H_{17}O_2N_3$: N, 21.09%; C, 54.25%; H, 8.60%. Found: N, 21.00%; C, 54.01%; H, 8.36%.

gradually to 25°C. over a period of six hours. The mixture was cooled and filtered and the solid (VI) obtained was recrystallized from ethanol. Yield 7.5 g. or 38% of theoretical, melting point 162°C. The original mother liquor was distilled and a 2 g. sample over an 155-160°C. at 14 mm. This compound (X) is identical with that formed from phenylacetic acid and (I) in boiling point, its melting point of 160°C. and in that both form solids, melting point 162-163°C., when stirred with water or exposed to air for several hours.

The picrates were prepared by dissolving one gram of 155-160°C. in two ml. of ethanol and adding the solution to a saturated alcoholic solution of one gram of picric acid. The crystals which formed were filtered and recrystallized from ethanol. The picrates melted at 147°C.

Preparation of 2,4-dichloro-5,6-dimethyl-1-phenylhexan-3-one

Reaction (XII)

To 24.2 g. (0.1 mole) of 1-phenylhexan-3-one ester was added 0.20 mole of 4-(2-methyl-1-phenylhexan-3-onyl)phenol (I) and the mixture was heated for four hours at 120-130°C. Upon cooling, the mass solidified. Recrystallization from alcohol yielded 23 g. or an 84% of theoretical yield of (XII), melting point 208°C.

Analysis. Calculated for $C_{22}H_{26}Cl_2O$: C, 71.00%; H, 5.50%; Cl, 13.50%.

Found: C, 70.90%; H, 5.50%; Cl, 13.60%.

Reaction of 2,4-diketo-6,6-dimethyl-1-isopropylhexahydro-1,3,5-triazepine (XII) with (I) to yield 4,4-dimethyl-1-isopropyl-2-imidazolidone (VI).

To 17 g. (0.075 mole) of (XII) was added 20 g. (0.15 mole) of (I) and the mixture was heated for five hours with the temperature gradually being raised from 140 to 200°C. The mixture was cooled and the product solidified. Recrystallization from ethanol yielded 21.2 g. or 91.5% of the theoretical yield of (VI), melting point 162°C.

Analysis. Calculated for (VI), $C_8H_{16}ON_2$: N, 17.93%; C, 61.49%; H, 10.32%. Found: N, 17.94%; C, 61.47%; H, 10.19%.

Reaction of Ethylenediamine Hydrate with (I).

16.1 g. (0.1 mole) of imidodicarboxylic ester was heated with 0.12 mole of ethylenediamine hydrate between 110 and 120°C. for eight hours. A solid amorphous substance (XIII) which was not identified was the product. A small sample was recrystallized from a large volume of ethanol. It melted at 242-245°C. with discoloration.

When (XIII) was heated with 0.15 mole of ethylenediamine hydrate between 120 and 180°C. for eight hours, the product was a crystalline material (XIV) which, after recrystallization from chloroform, melted at 131°C.

Analysis. Calculated for 2-imidazolidone (XIV), $C_3H_6ON_2$: N, 32.56%. Found: N, 31.90%.

Reaction of 2,3-dichloro-1,4-bis(2-phenyl-1-propenyl)-5-thiazolidine

(XII) with (I) to yield 2,3-dichloro-1,4-bis(2-phenyl-1-propenyl)-5-thiazolidine (XIII)

To 17 g. (0.075 mole) of (XII) was added 20 g. (0.15 mole) of (I)

and the mixture was heated for five hours with the temperature gradually

being raised from 140 to 200°C. The mixture was cooled and the product

solidified. Recrystallization from ethanol yielded 21.2 g. or 31.3% of

the theoretical yield of (XIII), melting point 123°C.

Analysis. Calculated for (XIII), $C_{24}H_{24}Cl_2N_2S$: C, 61.43%; H, 4.12%; N, 10.72%; S, 13.73%.

Found: C, 61.43%; H, 4.12%; N, 10.72%; S, 13.73%.

Reaction of 2,3-dichloro-1,4-bis(2-phenyl-1-propenyl)-5-thiazolidine (XIII)

10.1 g. (0.03 mole) of 2,3-dichloro-1,4-bis(2-phenyl-1-propenyl)-5-thiazolidine (XIII) was heated with

0.12 mole of ethylenediamine hydrate between 110 and 130°C. for eight

hours. A solid amorphous substance (XIV) which was not identified was

the product. A small sample was recrystallized from a large volume of

ethanol. It melted at 123-124°C. with a color change.

When (XIII) was heated with 0.12 mole of ethylenediamine hydrate

between 120 and 130°C. for eight hours, the product was a crystalline

substance (XIV) which, after recrystallization from chloroform, melted at

121°C.

Analysis. Calculated for (XIV), $C_{24}H_{24}N_2S$: C, 65.63%; H, 5.25%; N, 11.92%; S, 13.20%.

Found: C, 65.63%; H, 5.25%; N, 11.92%; S, 13.20%.

V. SUMMARY AND CONCLUSIONS

A. SUMMARY

One equivalent of N-(2-aminoisobutyl)-isopropylamine (I) reacted with malonic ester to yield an imidazoline ester, ethyl 4,4-dimethyl-1-isopropyl-2-imidazoliny-2-acetate (II). The compound (II) was prepared in another way through the condensation of (I) with cyanoacetic ester followed by alcoholysis of the product. The sodium salt of compound (II) underwent a condensation reaction of the acetoacetic ester type with benzyl chloride.

With two equivalents of the diamine (I) to one of malonic ester, the products were 1-isopropyl-2,4,4-trimethyl-2-imidazoline and 4,4-dimethyl-1-isopropyl-2-imidazolidone. With aniline and compound (II) the products were 1-isopropyl-2,4,4-trimethyl-2-imidazoline and sym-diphenylurea. Phenylurethane and (I) reacted in a manner analogous to the reaction of (II) with (I). The products were 4,4-dimethyl-1-isopropyl-2-imidazolidone and aniline.

Monosubstituted malonic esters and one equivalent of (I) reacted to yield 1,4-diazepines. The benzyl-, butyl-, and phenylmalonic esters were used in condensations of this type. With two equivalents of (I), each of the monosubstituted esters yielded a 2-alkylmethyl-2-imidazoline and 4,4-dimethyl-1-isopropyl-2-imidazolidone. The 2-alkylmethyl-2-imidazolines obtained were identical with those prepared from the corresponding alkylacetic acids and (I).

Imidodicarboxylic ester reacted with one equivalent of (I) to yield 2,4-diketo-6,6-dimethyl-1-isopropylhexahydro-1,3,5-triazepine.

One equivalent of 2-(1-ethyl-3-imidazolyl)-1-propanol (I) reacted with malonic ester to yield 2-ethyl-3-imidazolyl-1-propanol (II). The compound (II) was prepared in 80% yield with the elimination of (I) which was recovered after filtration of the product. The sodium salt of compound (II) underwent a condensation reaction of the malonic ester type with benzyl chloride. With two equivalents of the diamine (I) to one of malonic ester, the products were 1-isopropyl-2,4-bis(2-ethyl-3-imidazolyl)-2-imidazoline and 2,4-bis(2-ethyl-3-imidazolyl)-2-imidazoline. With malonic ester and compound (II) the products were 1-isopropyl-2,4-bis(2-ethyl-3-imidazolyl)-2-imidazoline and 2,4-bis(2-ethyl-3-imidazolyl)-2-imidazoline. (I) reacted in a similar manner to the reaction of (II) with (I). The products were 2-ethyl-3-imidazolyl-1-propanol-2-imidazoline and malonic ester. Monomeric malonic ester and one equivalent of (I) reacted to yield 1,4-bis(2-ethyl-3-imidazolyl)-2-imidazoline. The malonic ester and phenylmalonic ester were used in condensation of this type. With two equivalents of (I), each of the monomeric malonic ester yielded 2-ethyl-3-imidazolyl-1-propanol-2-imidazoline and 2-ethyl-3-imidazolyl-1-propanol-2-imidazoline. The 2-ethyl-3-imidazolyl-1-propanol-2-imidazoline obtained were identical with those prepared from the corresponding aliphatic malonic ester (I).

Imidazolecarboxylic ester reaction with one equivalent of (I) to yield 2,4-bis(2-ethyl-3-imidazolyl)-2-imidazoline and 2-ethyl-3-imidazolyl-1-propanol-2-imidazoline.

With two equivalents of (I) the products were ammonia and two equivalents of 4,4-dimethyl-1-isopropyl-2-imidazolidone. Imidodicarboxylic ester reacted with one equivalent of ethylenediamine hydrate to yield an amorphous material of undetermined structure. With two equivalents of ethylenediamine hydrate, the product obtained was 2-imidazolidone.

Picrate derivatives were made of all imidazolines synthesized in this work.

B. CONCLUSIONS

When heated with malonic ester, ethylenediamine yields a substance which has the empirical formula of a seven-membered ring compound. N-(2-aminoisobutyl)-isopropylamine reacts with malonic ester to form an imidazoline and with substituted malonic esters to yield diazepines.

It is to be concluded, therefore, that the course of a reaction between a 1,2-diamine and a 1,1-dicarboxylic ester is affected by both the diamine and the ester employed.

With two equivalents of (1) the products were amorphous and two equivalents of 4,4-dimethyl-1-isobutyroxy-2-imidazolidone. In both cases the ester reacted with one equivalent of ethylenediamine hydrate to give an amorphous material of undetermined structure. With two equivalents of ethylenediamine hydrate, the product obtained was a crystalline solid.

These derivatives were made of all imidazolidones and

in this work.

2. CONCLUSIONS

When heated with malonic ester, ethylenediamine yields a substance which has the empirical formula of a seven-membered ring compound, N-(2-imidazolidonyl)-isobutyramine reacts with malonic ester to form an imidazolidine and with substituted malonic esters to yield diimides. It is to be concluded, therefore, that the course of a reaction between a 1,3-diamine and a 1,1-dicarboxylic ester is affected by both the diamine and the ester employed.

B. T.

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