

(or both) of the expected isomeric biphenyl derivatives without interference with the nuclear substituent.

3. The structures of the various substituted biphenylcarboxylic acids have been established.

CAMBRIDGE, MASS.

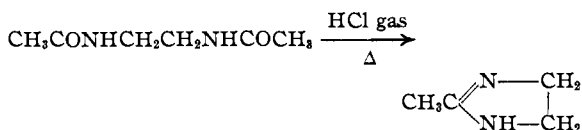
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

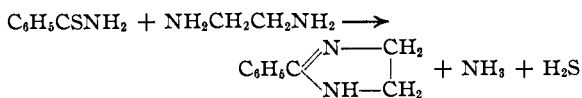
The Preparation and Cyclization of Monoacylethylenediamines¹

BY ARTHUR J. HILL AND SAMUEL R. ASPINALL²

Although 4,5-dihydroimidazoles³ as a class have been known many years, a satisfactory general synthesis for these compounds has not previously been developed. Hofmann⁴ prepared 2-alkyl-4,5-dihydroimidazoles by heating diacyl-ethylenediamines in a stream of hydrogen chloride, and Klingenstein⁵ and Landenberg⁶ carried out a similar type of reaction by heating ethylenediamine hydrochloride with the sodium salt of a low aliphatic acid.



In a recent repetition of this work, Chitwood and Reid⁷ were able to obtain only 10% yields of the 2-methyl derivative. These later workers effectively increased the yields in the low members of the series by a modification of Hofmann's procedure, but the higher alkyl derivatives were produced in rather poor yields, even when the improved method was employed. 2-Phenyl-4,5-dihydroimidazole, first reported by Hofmann,⁴ was made by Forssel⁸ by the interaction of thio-benzamide and ethylenediamine.

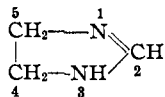


Since it appeared to the writers that appropriately substituted 4,5-dihydroimidazoles might

(1) Constructed from a dissertation presented by Samuel R. Aspinall to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy, 1938.

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(3) The 4,5-dihydroimidazole nucleus is numbered as follows:



(4) Hofmann, *Ber.*, **21**, 2332 (1888).

(5) Klingenstein, *ibid.*, **28**, 1176 (1895).

(6) Landenberg, *ibid.*, **27**, 2952 (1894).

(7) Chitwood and Reid, *THIS JOURNAL*, **57**, 2424 (1935).

(8) Forssel, *Ber.*, **25**, 2132 (1892).

possess interesting physiological properties, and because no satisfactory general synthesis for these compounds was known, a study of these cyclic amidines was undertaken. This paper reports work on a simple synthesis which produces uniformly high yields of pure 2-alkyl- and 2-aryl-4,5-dihydroimidazoles starting from readily available materials.

The first step in the synthesis of 2-alkyl-4,5-dihydroimidazoles is the preparation of monoacylethylenediamines by interaction of ethylenediamine and various aliphatic esters⁹ (see Table I).



Acetylethylenediamine.¹⁰—One mole (88 g.) of ethyl acetate and three moles (180 g.) of sodium-dried ethylenediamine were sealed in a glass tube and heated at 100° for thirty-six hours. The reaction mixture was then transferred to a Claisen flask and 170 g. of low boiling material, consisting of ethyl alcohol and excess ethylenediamine, removed under diminished pressure. When the bath temperature was increased to 165°, acetylethylenediamine distilled at 128° (3 mm.). The 11 g. of diacetylethylenediamine which remained as an undistilled residue melted at 175°¹¹ (corr.) after recrystallization from 95% alcohol.

Acetylethylenediamine sets to a very hygroscopic white solid which melts at 51° (corr.) after recrystallization from a dioxane-ether mixture.

The aliphatic monoacylethylenediamines, which are strongly basic, hygroscopic compounds, were converted to a number of derivatives for positive characterization. They react violently with phenyl isocyanate and phenyl isothiocyanate to produce crystalline ureas and thioureas (see Tables VI, VII).



(9) The method used embodies several important extensions and improvements over a similar process outlined in U. S. Patent 1,926,015.

(10) The subsequent paragraphs in this article which are set in small type are descriptive of actual experiments carried out, but are typical of all members of a given class of compounds.

(11) The previously reported m. p. of this compound is 175°, Franchimont and Dubsky, *Rec. trav. chim.*, **30**, 184 (1911).

TABLE I
 REACTION OF ESTERS WITH ETHYLENEDIAMINE^a

Reacting ester	React. temp., °C.	Method of isolation	Product	M. p.,	B. p. °C.	Yield, %	Calcd.	% N	
				corr.				Mm.	Kjeldahl I
Ethyl acetate	100	Distill.	Acetylenediamine ^b	51	128	3 ^d	85	27.45	27.32 27.07
Ethyl propionate	100	Distill.	Propionylethylenediamine ^b	liq.	130	3 ^e	85	24.14	24.03 24.06
Ethyl benzoate	100	Solvent extract.	Benzoylenediamine ^c	liq.			50	anal. only as derivs.	
Ethyl benzoate	130	Distill.	2-Phenyl-4,5-dihydroimidazole ^c	101 ^f	162	5	85	19.18	18.85 18.97
Ethyl <i>p</i> -toluate	100	Solvent extract.	<i>p</i> -Toluylenediamine ^c	liq.			50	anal. only as derivs.	
Ethyl <i>p</i> -toluate	175	Distill.	2- <i>p</i> -Tolyl-4,5-dihydroimidazole ^c	183	Sublimes <i>in vacuo</i>		85	17.50	17.39 17.32

^a Three moles of anhydrous ethylenediamine and one mole of ester were heated for thirty-six hours. ^b Soluble in all organic solvents except ether and petroleum ether; soluble in water. ^c Soluble in all organic solvents except ether and petroleum ether, and cold benzene and toluene; soluble in water. ^d Literature 135–140° (2 mm.). U. S. Patent 1,926,015. ^e Literature 138–143° (2 mm.). U. S. Patent 1,926,015. ^f Literature 101°. *Ber.*, **21**, 2335 (1888).

 TABLE II
 DEHYDRATION OF MONOACYLETHYLENEDIAMINES

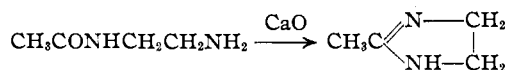
Monoamide	Dehydr. agent	Temp., °C.	Product	Yield, %	M. p., °C. corr.	B. p., °C.
Acetylenediamine	CaO	225 ^a	2-Methyl-4,5-dihydroimidazole ^{e,h}	90	103 ^d	197 ^f
Propionylethylenediamine	CaO	225 ^a	2-Ethyl-4,5-dihydroimidazole ^b	85	48 ^e	200 ^e
Benzoylenediamine	None	200 ^b	2-Phenyl-4,5-dihydroimidazole	100		
<i>p</i> -Toluylenediamine	None	200 ^b	2- <i>p</i> -Tolyl-4,5-dihydroimidazole	100		

^a Refluxed for sixteen hours in atmosphere of N₂. ^b Dehydration complete in a few seconds. ^c % N calcd. 33.3; Kjeldahl 32.7, 32.7. See Table I for other analyses. ^d Literature 105°, *THIS JOURNAL*, **57**, 2424 (1935). ^e Literature 38°, *ibid.*, **57**, 2424 (1935). ^f Sublimes *in vacuo*. Literature 195–198°, *Ber.*, **27**, 2952 (1894); 198–200°, *THIS JOURNAL*, **57**, 2424 (1935). ^g 90° (4 mm.). ^h Soluble in water and all organic solvents except ether and petroleum ether.

1 - Acetyl - 2 - phenylthiocarbonylamidoethylenediamine precipitated immediately when a benzene solution of acetylenediamine (1.02 g.) was treated with one equivalent of phenyl isothiocyanate (1.35 g.). The white thiourea melts at 172° (corr.) after recrystallization from 95% alcohol.

The picrates are well-defined solids, but the hydrochlorides are too hygroscopic to be of any use in characterization (see Table IV).

The cyclization of aliphatic monoacylethylenediamines to the 4,5-dihydroimidazole configuration was effected in excellent yields by means of a lime dehydration (see Table II).

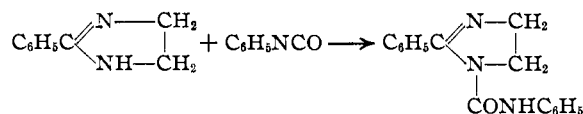


2-Methyl-4,5-dihydroimidazole.—One mole (102 g.) of acetylenediamine and 5 moles (280 g.) of finely powdered lime were intimately mixed and heated under reflux at 225° for sixteen hours in an atmosphere of nitrogen. 2-Methyl-4,5-dihydroimidazole was extracted from the lime with absolute alcohol and distilled at 197°. It solidified on cooling and was obtained as pure white non-hygroscopic needles melting at 103° (corr.) by recrystallization from benzene or by vacuum sublimation.

The strong cyclic bases were best characterized as picrates (see Table IV). The hydrochlorides, like those of the monoacylethylenediamines, were too hygroscopic to be of use. The low members of the 2-alkyl-4,5-dihydroimidazole series also react violently with phenyl isocyanate

and phenyl isothiocyanate, but crystalline derivatives could not be isolated.

The extension of the synthesis to include aromatic esters was accompanied by one important difference, namely, the extreme ease of cyclization of the aromatic monoacylethylenediamines. When ethylenediamine and an aromatic ester react in the manner described above and an attempt is made to remove the monoamide by vacuum distillation, the distillate consists of pure 2-aryl-4,5-dihydroimidazole, arising from the quantitative dehydration of the monoamide at the temperature of distillation (see Tables I, II). The 2-aryl-4,5-dihydroimidazoles were further characterized as non-hygroscopic hydrochlorides, picrates, phenyl ureas and phenyl thioureas (see Tables IV, V, VI, VII).



The presence of an aromatic monoacylethylenediamine in the reaction mixture before distillation was demonstrated by its removal by means of a solvent (see Table I).

p-Toluylenediamine.—One mole (164 g.) of *p*-toluic ester and 3 moles (180 g.) of sodium-dried ethylenediamine were sealed in a glass tube and heated at 100° for thirty-six hours. The reaction mixture was then trans-

TABLE III
 EFFECT OF TEMPERATURE AND CONCENTRATION OF REACTANTS ON YIELD OF AMIDATION PRODUCTS

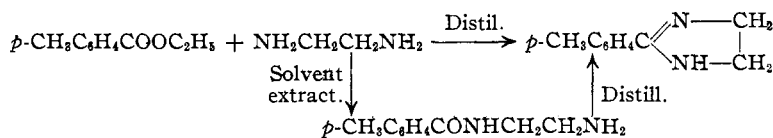
Reacting ester	Moles of ethylenediamine per mole of ester	React. temp., °C.	Product	Yield, %	Yield of diamide, %
Ethyl acetate	3	100	Acetylenediamine	85	15
	1	100		50	50
Ethyl propionate	3	100	Propionylethylenediamine	85	15
	1	100		50	50
Ethyl benzoate	3	175	2-Phenyl-4,5-dihydroimidazole	85	15
	3	150		85	15
	3	100		55	45
	1	100		30	70
Ethyl <i>p</i> -toluate	3	175	2- <i>p</i> -Tolyl-4,5-dihydroimidazole	85	15
	3	100		50	50

ferred to a Claisen flask and 181 g. of low boiling material removed under diminished pressure.

The mixture of mono- and diamide remaining in the flask was digested with toluene and filtered hot. The 73 g. of di-*p*-tolylethylenediamine which remained undissolved by this treatment melted at 244° (corr.) and gave the calculated nitrogen analysis after recrystallization from 95% alcohol.

The *p*-tolylethylenediamine which appeared as a viscous yellow oil on the bottom of the cool toluene filtrate was drawn off and freed of toluene by means of a stream of dry, carbon dioxide-free air.

The oily monoamides so obtained were characterized as non-hygroscopic hydrochlorides, phenyl ureas and phenyl thioureas in a manner analogous to that used for the cyclic bases (see Tables V, VI, VII). The course of the reaction was further established by subjecting a known sample of an aromatic monoacylethylenediamine to a distillation (see Tables I, II).



2-*p*-Tolyl-4,5-dihydroimidazole.—When *p*-tolylethylenediamine was heated in a Claisen flask at 200° and at atmospheric pressure there was a rapid evolution of one equivalent of water and, upon evacuation of the system, pure 2-*p*-tolyl-4,5-dihydroimidazole sublimed over into the receiver.

 TABLE IV
 PICRATES^a

Base	Picrate			% N Kjeldahl	
	M. p., °C. Found corr.	Lit.	Calcd.	I	II
Acetylenediamine	175		21.15	21.30	21.08
2-Methyl-4,5-dihydroimidazole	204	205 ^b	22.36	22.35	22.38
Propionylethylenediamine	148		20.29	20.18	20.18
2-Ethyl-4,5-dihydroimidazole	137	137 ^b	21.41	21.31	21.31
2-Phenyl-4,5-dihydroimidazole	244	233 ^c	18.67	18.71	18.55
2- <i>p</i> -Tolyl-4,5-dihydroimidazole	203		18.00	18.04	17.80

^a All picrates were made in water or dilute alcohol and recrystallized from 95% alcohol. ^b THIS JOURNAL, 57, 2424 (1935). ^c Ber., 25, 2135 (1882).

 TABLE V
 HYDROCHLORIDES^a

Base	M. p., °C. corr.	Salt % N Kjeldahl		
		Calcd.	I	II
Benzoylenediamine	170	13.97	14.05	14.08
2-Phenyl-4,5-dihydroimidazole	244	15.34	15.34	15.15
<i>p</i> -Tolylethylenediamine	172	13.05	13.08	12.95
2- <i>p</i> -Tolyl-4,5-dihydroimidazole	244	14.25	14.23	14.19

^a All hydrochlorides were made by passing dry hydrogen chloride into an absolute alcohol-absolute ether solution of the base, and all, except 2-*p*-tolyl-4,5-dihydroimidazole hydrochloride, were recrystallized from absolute alcohol. All hydrochlorides are extremely soluble in water and warm alcohol and acetone; insoluble in absolute ether.

Although certain of the 4,5-dihydroimidazoles synthesized in the course of this work have previously been made and are well known, the authors report their preparation in some detail in order that the superiority of this method be clearly shown. Furthermore, due to the extreme ease of cyclization of certain of the monoacylethylenediamines it seemed necessary to prepare several derivatives of each cyclic and acyclic base in order that no

doubt remain as to the course of the reaction. Table III summarizes the results of a more detailed study of the interaction of esters and ethylenediamine as regards temperature and concentration of reactants. As expected, a high concentration of the base favors production of a monoamide (or 4,5-dihydroimidazole) at the expense of diamide. High temperatures likewise favor production of a monoamide. Further investigation of this synthesis is in progress.

Summary

1. A study has been made of the formation of monoacylethylenediamines by the interaction of aliphatic esters and ethylenediamine.

2. A method for the production of the hitherto

TABLE VI
PHENYL UREAS^a

Reacting base	Phenylureido derivative	M. p., °C.		% N Kjeldahl	
		corr.	Calcd.	I	II
Acetylenediamine	1-Acetyl-2-phenylcarbonamidoethylenediamine	191	19.00	18.84	18.88
Propionylethylenediamine	1-Propionyl-2-phenylcarbonamidoethylenediamine	180	17.87	17.78	17.81
Benzoylethylenediamine	1-Benzoyl-2-phenylcarbonamidoethylenediamine	215	14.84	14.95	14.89
2-Phenyl-4,5-dihydroimidazole	2-Phenyl-3-phenylcarbonamido-4,5-dihydroimidazole	156	15.85	15.73	15.99
<i>p</i> -Tolylethylenediamine	1- <i>p</i> -Tolyl-2-phenylcarbonamidoethylenediamine	191	14.14	14.19	14.28
2- <i>p</i> -Tolyl-4,5-dihydroimidazole	2- <i>p</i> -Tolyl-3-phenylcarbonamido-4,5-dihydroimidazole	157	15.05	15.09	15.12

^a All phenyl ureas were made in acetone and recrystallized from acetone or 95% alcohol. All phenyl ureas are insoluble in water, ether, and hydrocarbon solvents.

TABLE VII
PHENYL THIOUREAS^{a,b}

Reacting base	Phenylthioureido derivative	M. p., °C.		% N Kjeldahl	
		corr.	Calcd.	I	II
Acetylenediamine	1-Acetyl-2-phenylthiocarbonamidoethylenediamine	172	17.72	17.77	17.65
Propionylethylenediamine	1-Propionyl-2-phenylthiocarbonamidoethylenediamine	143	16.73	16.76	16.50
Benzoylethylenediamine	1-Benzoyl-2-phenylthiocarbonamidoethylenediamine	150	14.05	14.10	14.12
2-Phenyl-4,5-dihydroimidazole	2-Phenyl-3-phenylthiocarbonamido-4,5-dihydroimidazole ^c	104	14.95	14.84	14.99
<i>p</i> -Tolylethylenediamine	1- <i>p</i> -Tolyl-2-phenylthiocarbonamidoethylenediamine	173	13.42	13.45	13.57

^a All thioureas except 1-acetyl-2-phenylthiocarbonamidoethylenediamine were made and recrystallized in acetone; all are insoluble in water, ether, and hydrocarbons. ^b 2-*p*-Tolyl-4,5-dihydroimidazole and phenyl isothiocyanate would not react even when refluxed together in benzene solution for three hours. ^c This compound formed readily in cold acetone, but it was yellow colored in contrast with the other thioureas, and on long standing it slowly decomposed with evolution of C₆H₅NCS.

unknown aromatic monoacylethylenediamines has been developed.

3. The conversion of monoacylethylenediamines into pure 2-alkyl- and 2-aryl-4,5-dihydroimidazoles has been effected in nearly quantita-

tive yields.

4. The cyclic and acyclic bases prepared in this study have been fully characterized as picrates, hydrochlorides, phenyl ureas and phenyl thioureas.

NEW HAVEN, CONN.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE INSTITUTE OF TECHNOLOGY, UNIVERSITY OF MINNESOTA]

Fundamental Studies with the Dropping Mercury Electrode. I. The Ilkovic Equation of Polarographic Diffusion Currents¹

BY JAMES J. LINGANE² AND I. M. KOLTHOFF

Introduction

The most important characteristic of the current-voltage curves, or "polarograms," obtained by electrolyzing solutions of electro-reducible or electro-oxidizable substances with the dropping mercury electrode, is that the current does not increase indefinitely with increasing applied e. m. f. after the decomposition potential is exceeded, but reaches a more or less constant limiting value. Under optimum conditions, such a limiting current is directly proportional to the concentration of the electro-reducible substance,

(1) This paper is based on a thesis submitted by James J. Lingane to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1938.

(2) J. T. Baker Fellow in Analytical Chemistry, 1937-1938.

and this fact is the basis of quantitative polarographic analysis.³

The limiting current is caused by an extreme state of concentration polarization at the dropping electrode, and its magnitude is determined by the rate at which the reducible substance migrates up to the surface of the mercury drops from the body of the solution. In general, re-

(3) For general reviews of the polarographic method see: (a) J. Heyrovsky, "Polarographie," in W. Böttger, "Physikalische Methoden der analytischen Chemie," Bd. 2, Akad. Verlagsgesellschaft, Leipzig, 1936; *Mikrochem.*, **12**, 25 (1932). (b) H. Hohn, "Chemische Analysen mit dem Polarographen," Verlag von Julius Springer, Berlin, 1937; *Z. Elektrochem.*, **43**, 127 (1937); (c) W. Kemula, *ibid.*, **37**, 779 (1931); (d) I. M. Kolthoff and J. J. Lingane, *Chem. Rev.*, in press (1939). A complete bibliography of the polarographic literature, with subject titles, up to 1937 inclusive, has been compiled by J. Heyrovsky and J. Klumpar, *Coll. Csech. Chem. Comm.*, **10**, 153 (1938).