THE PREPARATION OF
2,4,7-TRICHLOROIMIDAZO [4,5-d] PYRIDAZINE
AND CERTAIN OF ITS DERIVATIVES

by

PAUL HERBERT LAURSEN

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APPROVED:

Redacted for privacy
Professor of Chemistry
In Charge of Major

Redacted for privacy
Chairman of Department of Chemistry

Redacted for privacy
Chairman of School Graduate Committee

Redacted for privacy
Dean of Graduate School

Date thesis is presented  April 28, 1961
Typed by Lilah N. Potter
DEDICATION

This thesis is dedicated to the three people who have had much to do with this work being possible -- my wife Gail, my major professor Dr. B. E. Christensen, and my father Ejvind Laursen.
ACKNOWLEDGMENTS

The author wishes to gratefully acknowledge the invaluable technical and personal assistance given him by Dr. Bert E. Christensen in the preparation of this thesis.

The author also wishes to acknowledge the assistance of Dr. John A. Carbon and Abbott Laboratories for graciously sending a sample and spectra of 4,7-dibenzylaminoimidazo[4,5-d]pyridazine hydrochloride which was required to complete this problem.
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THE PREPARATION OF
2,4,7-TRICHLOROIMIDAZO[4,5-d]PYRIDAZINE
AND CERTAIN OF ITS DERIVATIVES

INTRODUCTION

In 1942 Hitchings began a study of the relationships between the chemical structure and the ability of certain pyrimidine derivatives to serve as precursors for/or to modify nucleic acid biosynthesis. Included, among the pyrimidine derivatives that were studied, were the condensed ring systems containing a pyrimidine moiety, (i.e. purine, pteridine, quinazoline, and triazolo-[d]-pyrimidine). By 1950 Hitchings had obtained data showing the effect of these various pyrimidine containing derivatives on Lactobacillus casei. From these studies he concluded that "pyrimidine derivatives could be found which do interfere with nucleic acid synthesis and metabolism in a variety of ways" (26, p. 1332 and p. 1333).

Since this discovery there has been a great deal of synthetic work in an effort to find compounds which might support this concept. In view of the presence of the purines adenine and guanine in the nucleic acid molecule (31; 32, p. 79-81; 33, p. 1929-1930), considerable interest has centered on the synthesis of these purine derivatives and analogues, and their effects on
biological systems. Compounds which will inhibit the growth of various organisms, yet the presence of the natural purines, such as adenine or guanine, will either prevent or reverse this effect, are defined as anti-purines (56, p. 81).

A study by Bendich of the behavior of several hundred purine derivatives in metabolic reactions led to three considerations for preparation of effective anti-purine agents. For example: (a) the most active analogues of naturally occurring purines are those in which the new atom or group introduced is not greatly different in size from the one replaced, (b) the more active compounds appear to result from a change in structure at a single site in the adenine, hypoxanthine, or guanine molecule i.e. positions 2 or 6, (c) active analogues do result from replacement in adenine, hypoxanthine, or guanine of carbon-2 or 8 by nitrogen (1, p. 6073).

Thus, 6-mercaptopurine (14, p. 411-414) has proved to be an active drug in the treatment of acute leukaemia in adults (22, p. 376); it is also capable of rendering malignant tumor cells in mice nonviable (11, p. 9-10). 2,6-Diaminopurine was the first compound to show anti-adenine activity in Lactobacillus casei (25, p. 765-766). Furthermore, it has proved active against transplanted
mouse leukaemia (4, p. 119-120) and against vaccinia virus in tissue culture (55, p. 530). 2-Chloro-6-aminopurine has shown anti-tumor effects (2, p. 287), as has 2-fluoro-adenine (39, p. 4559), while thioguanine is clinically active against leukaemia (5, p. 63).

6-Furfurylaminopurine (kinetin) has been reported as a cell division factor in tobacco "wound" callus tissue (36, p. 1392 and 37, p. 2662-2663) and has been shown to stimulate lettuce seed germination (38, p. 318).

The compound 8-azaguanine (48, p. 292 and 294) has been shown to exhibit antiguanine properties toward Tetrahymena (30, p. 186). 8-Azaguanine has also been shown to cause inhibition of lucerne mosaic virus in Nicotiana glutinosa, and cucumber and tobacco mosaic virus in cucumber and Nicotiana sp. (35, p. 281). 2-Azaadenine and 2-azahypoxanthine are also listed among the purine antagonists (49, p. 642). 8-Azaadenine has shown some inhibition of Escherichia coli and tobacco mosaic virus (51, p. 323 and 332).

Other purine analogues which have shown activity include a series of pyrazolopyrimidines (44, p. 787 and 50, p. 594-596) and a series of thiazolopyrimidines (15, p. 2858-2863). 8-Thiapurine has shown antiguanine activity (57, p. 805).
Benzimidazole, benzothiazole, and benzotriazole, although somewhat different structurally from the purines, have also shown antiguanine activity with *Escherichia coli* (12, p. 154). Benzimidazole and its derivatives have given good results against virus in tissue culture (53, p. 245-259 and 54, p. 227-250).

In 1956, Jones (29, p. 159-163) synthesized the first of the imidazopyridazines of 1,3,5,6-tetrazaaindenes. Because this ring system is another analogue of the purine molecule there has been some scientific interest in derivatives of this compound by investigators working for the pharmaceutical industries (6, p. 6083-6088; 8, p. 579-582; 10, p. 1534-1538). The few imidazopyridazines prepared by these workers have all been examined as potential purine antagonists, while certain of these compounds have been patented as central nervous system depressants (7, p. 6767f).

The only imidazopyridazines which have been prepared as of this date are the 1H-imidazo[4,5-d]pyridazines. This type of nitrogen heterocycle can be considered as the fusion product of the imidazole ring I

![Chemical structure](image-url)
and the pyridazine ring II. The positions of fusion must be indicated, as there is a possibility of other isomers.

Jones (29, p. 161 and 162) prepared substituted imidazo[4,5-d]pyridazines by treating an ester of 4,5-imidazoledicarboxylate III with hydrazine hydrate (see Figure 1). When $R_1$ and $R_2$ were hydrogen substituents, the dihydrazide IV was formed. This dihydrazide was cyclized to the imidazo[4,5-d]pyridazine V by refluxing with excess hydrazine hydrate, or by digestion in dilute hydrochloric acid. When $R_1$ was methyl or phenyl, and $R_2$ was a hydrogen or mercapto substituent, the cyclized imidazo[4,5-d]pyridazine V was formed directly upon the initial treatment with hydrazine. The cyclization of imidazoledicarboxylates with hydrazine is the only known method of preparing this type of ring system.

While Jones was the first to publish work on the preparation of some imidazo[4,5-d]pyridazines, work had been initiated simultaneously in at least three other laboratories. Gardner, Smith, Wenis, and Lee (19, p. 530-533) published a paper four months after the Jones publication describing the preparation of an imidazo[4,5-d]pyridazine which they called 1H-imidazo(d)pyridazine-4,7(5H,6H)-dione. Furthermore, Castle and
Seese (10, p. 1534-1538) in 1958, with no prior knowledge of Jones’ work, described a procedure for the synthesis of the compound 4,7-dihydroxyimidazo[4,5-d]pyridazine.

These investigators also described their attempts to prepare imidazopyridazines by the cyclization of diaminopyridazines with formamide -- a procedure successfully used in purine synthesis to convert 4,5-diaminopyrimidines to 2- and 6-substituted purine molecules (43, p. 263-266). Since this was the method by which we originally attempted to prepare imidazopyridazines, their failure confirms the results obtained by this laboratory. Both procedures call for the preparation of diaminopyridazines from dichloropyridazines (see Figure 2). This is often accomplished by treating the chloro substituted nitrogen heterocycle with ammonia under varying conditions of temperature and pressure (41, p. 244; 43, p. 265 and 266; 44, p. 789; 46, p. 6413). We were unsuccessful in diaminating a trichloropyridazine. Castle and Seese (10, p. 1537) have also reported that they could not diaminate a dichloropyridazine. These results reconfirm the work of Kuraishi (34, p. 13853g) who earlier concluded that it is very difficult to replace a chlorine substituent on the pyridazine ring.

An article published by Jones which described the
FIGURE 2. Proposed synthesis of imidazo[4,5-d]pyridazine from dichloropyridazine.
preparation of 4,7-dihydroxyimidazo[4,5-d]pyridazine stimulated our interest in the possibility of chlorinating this compound, inasmuch as the 4,7-dichloroimidazo[4,5-d]pyridazine could serve as a key intermediate for the preparation of a number of other disubstituted compounds. Attempts to chlorinate 2-mercapto-4,7-dihydroxyimidazo[4,5-d]pyridazine, both in this laboratory and by Carbon (6, p. 6083), by a variety of procedures, unfortunately were unsuccessful. Castle and Seese, while reporting failure in many chlorination experiments, devised one procedure which gave the desired dichloro compound in 17% yields (10, p. 1537). Furthermore these workers reported the preparation of several 4- and 7-monosubstituted and 4,7-disubstituted imidazopyridazines by means of the dimercapto intermediate. Carbon has since discovered that a methyl or phenyl substituent in the 1 position of the starting material permitted the chlorination to proceed smoothly to yield a 1-methyl (or phenyl)-4,7-dichloro[4,5-d]imidazopyridazine (6, p. 6086; 7, p. 6767f).

Concurrent with our interest in the 4,7-disubstituted imidazo[4,5-d]pyridazines, was the interest in the preparation and chlorination of the 2,4,7-trihydroxyimidazo[4,5-d]pyridazine (or 2,4,7(1H,3H,5H,6H)-imidazo[4,5-d]pyridazine-trione) VI. This compound is an analogue of uric acid VII, one of the first purines to be
chlorinated (17, p. 2208-2219; 18, p. 2220-2225). It was presumed that this compound could be prepared from diethyl 2(1H,3H)-imidazolone-4,5-dicarboxylate by reactions

![Chemical Structures](attachment:chemical.png)

with hydrazine in a manner similar to that used with other imidazole-4,5-dicarboxylates.

No mention of diethyl 2(1H,3H)-imidazolone-4,5-dicarboxylates could be found in the more recent literature. Beilstein (42, p. 663) indexes two compounds under this formula, noting that they are not identical. Diethyl \( \Delta^3 \)imidazolone-(2)-dicarboxylate(4,5) X (or \( \Delta^4 \)imidazolone-(2)-dicarboxylic (4,5)diethyl ester IX) was prepared by Geisenheimer and Anschütz in 1899 by condensing diethyl diketosuccinate with urea to form the monoureide VIII (20, p. 56). This monoureide, on treatment with \( \text{PCl}_3 \), yielded either \( \Delta^3 \) or \( \Delta^4 \)imidazolone-(2)-dicarboxylate (4,5), melting point 200°C. (see Figure 3).

Fenton and Wilks (16, p. 1580), thirteen years later, unaware of the previous work, prepared the diethyl ester of glyoxalone-4,5-dicarboxylic acid (another name
FIGURE 3. Possible structures of 4,5-imidazolodiacarboxylates prepared by Geisenheimer and Anschütz.
for diethyl $\Delta^3$ or $\Delta^4$ imidazolone-4,5-dicarboxylate) by an entirely different method. These workers cyclized the so-called dihydroxymaleic acid (which in its solid state was shown by Hartree (23, p. 6244-6249) and Gupta (21, p. 6312-6313) in 1953 to be dihydroxyfumaric acid) with urea in an ethyl alcoholic solvent in the presence of dry hydrogen chloride, to give a cyclic product, melting point 258-259°C. Although Fenton gave incomplete experimental procedures, his nitrogen analysis agreed with theory. Attempts to repeat this work by the authors, however, gave only small, varying yields of material melting at 200°C. The compound prepared in this laboratory by the method of Geisenheimer and Anschutz also melted at 200°C. Both esters reacted with hydrazine to form the dihydrazide which, on treatment with dilute hydrochloric acid, gave $2,4,7(1H,3H,5H,6H)$imidazo[4,5-$d$]-pyridazine-trione. It must be concluded that identical products are obtained by both procedures, and that Fenton made an error in reporting the melting point.

Because of the poor yields obtained with the solvent ethanol, other alcoholic solvents were tested as reaction media for the cyclization of dihydroxyfumaric acid with urea. No cyclization occurs in methanolic solution -- yielding instead the dimethyl dihydroxyfumarate previously reported by Hartree (23, p. 6248).
Cyclization experiments using n-propyl, n-butyl, and n-pentyl alcohols all gave the corresponding diester of 2-imidazolone-4,5-dicarboxylate in good yields XVIII (see Figure 8). The butyl ester proved to be the most satisfactory for cyclization purposes because of solubility factors and ease of purification.

These esters respond readily to hydrolysis to yield 2-imidazolone-4,5-dicarboxylic acid. The acidic product has a very high melting point with solubility properties very similar to the 4,5-imidazole-dicarboxylic acids described by Jones (28, p. 1085-1086).

The reaction of the esters of 2-imidazolone-4,5-dicarboxylic acids with hydrazine proceeded smoothly to give 2-imidazolone-4,5-dihydrazide XIX (see Figure 8) which was then cyclized to yield 2,4,7(1H,3H,5H,6H)-imidazo[4,5-d]pyridazine-trione XXa (see Figure 8) by digesting it with dilute hydrochloric acid. The trione was chlorinated by the procedure of Davoll and Lowry (13, p. 2936), for the chlorination of uric acid, to give 2,4,7-trichloroimidazo[4,5-d]pyridazine XXI (see Figure 8) in varying yields that exceed those reported for uric acid. This compound served as the key intermediate for further studies (see Figures 8 and 9).

Amination studies with amines such as furfurylamine, piperidine, and hydrazine revealed that two chloro
groups were easily replaced while the third was rather unreactive. Only morpholine, a very high boiling amine, yielded the tri-substituted product. It was therefore necessary to establish which two of the chloro groups were replaced. Earlier work with oxidation of 2-mercapto-4,5-dihydroxyimidazo[4,5-d]pyridazine had shown that treatment with fuming nitric acid in concentrated sulfuric acid yielded 2-mercapto-4,5-imidazoledicarboxylic acid. Attempts to oxidize the monochloro-dihydrazine-imidazo[4,5-d]pyridazine by this means to a substituted imidazoledicarboxylic acid were unsuccessful. There was vigorous evolution of gases, but no characterizable product could be isolated. Oxidation studies were then made using the 2,4,7-trichloroimidazo[4,5-d]pyridazine to ascertain if 2-chloro-4,5-imidazoledicarboxylic acid could be prepared by this method. A high melting product was isolated in good yield which gave analytical data that indicates the compound to be (??),(??)-dichloro-(??)-hydroxyimidazo[4,5-d]pyridazine. This indicates that while two of the chloro groups are more easily replaced than the third, there is a strong possibility that one of the two replaced chloro substituents is more active than the other. The ease of replacement of these chlorine atoms is currently being investigated.

Carbon (8, p. 579-582) has described the reaction
of 1-benzyl-7-chloro-4-hydrazinoimidazo [4,5-d]pyridazine with formic acid to yield 6-benzyl-5-chloroimidazo[4,5-d]-triazolo 4,3-b pyridazine (see Figure 4). Treatment of the (?)-chloro-(?),(?)-dihydrazinoimidazo [4,5-d]pyridazine with formic acid yielded a product which gave satisfactory analytical data for the isomeric compounds which could be XI, XII, or XIII depending on the position of the chloro substituent in the original intermediate.

![Chemical Structures](image-url)
Takahayashi (52, p. 865f) had formed tetraazolo-[1,5-b]pyridazines by reacting 3-hydrazinopyridazines with sodium nitrite (see Figure 5). Treatment of (?)-chloro- (?) , (?)-dihyrazinoimidazo[4,5-d]pyridazine with sodium nitrite yielded a product which gave satisfactory analytical data for the isomeric compounds XIV, XV, and XVI which would be formed depending on the position of the hydrazino groups in the starting material.
FIGURE 5. Synthesis of tetrazolo[1,5-b]pyridazine.
Carbon (6, p. 6086-6087) had reported the preparation of some 4,7-diamino compounds, as well as the removal of chloro groups from the 4 and 7 positions of the imidazo[4,5-d]pyridazine ring by catalytic and chemical reduction. Attempts to reduce (--)chloro-(--),(--)-dibenzylationimidazo[4,5-d]pyridazine to (--),(--)dibenzylationimidazo[4,5-d]pyridazine using the catalytic procedure of Carbon were unsuccessful. However, using Carbon's reduction with sodium and liquid ammonia over an extended length of time did effect removal of the chloro substituent from the (--)chloro-(--),(--)-dibenzylationimidazo[4,5-d]pyridazine. Comparison of ultraviolet spectra of this reduction product and 4,7-dibenzylationimidazo[4,5-d]pyridazine obtained from Abbott Laboratories and prepared from 4,7-dichloroimidazo[4,5-d]pyridazine, revealed some difference (see Table II). Subsequent correspondence with Dr. John A. Carbon of Abbott Laboratories revealed that the sample sent the author was not analytically pure (9, p. 1). Carbon did send an infrared spectra of analytical 4,7-dibenzylationimidazo[4,5-d]pyridazine (see Figure 6) which compared favorably with the infrared spectra (see Figure 7) of the compound we were attempting to identify.

On the basis of this identification, the remainder of the compounds formed by the disubstitution of the
FIGURE 6. Infrared spectra of 4,7-dibenzylaminoimidazo[4,5-\(d\)] pyridazine prepared from 4,7-dichloroimidazo[4,5-\(d\)] pyridazine
FIGURE 7. Infrared spectra of 4,7-dibenzylaminoimidazo [4,5-\(d\)] pyridazine from 2-chloro-4,7-dibenzylaminoimidazo [4,5-\(d\)] pyridazine.
original 2,4,7-trichloroimidazo[4,5-\textit{d}]pyridazine were assigned structures (see Figures 8 and 9). With an assignment of a structure to the dihydrazinoimidazo-
[4,5-\textit{d}]pyridazine, structures could also be assigned to the cyclic products formed by treatment of the dihydrazine compound with nitrous acid and with formic acid (see Figure 9).

The results of the infrared studies of the di-
benzylaminoimidazo[4,5-\textit{d}]pyridazine were confirmed by comparison of the ultra violet spectra (see Table II) with the known 4,7-dibenzylaminoimidazo[4,5-\textit{d}]pyridazine secured from the Abbott Laboratories.

The ultra violet spectra of isomeric derivatives of purines and pyrimidines as judged by a comparison of their absorption maxima and extinction coefficients are in general sufficiently different as to distinguish between two isomers. The chance that two isomers will have exactly the same extinction coefficient and absorption maxima is not very probable. In Table I are listed the spectral data of a number of isomeric purine and pyrimidine derivatives which served as a basis for this speculation.

There remains much work to be done in relating the spectra of the imidazo[4,5-\textit{d}]pyridazines to the spectra of similar purines. Robins (46, p. 6411) compared
**TABLE I**

Ultraviolet Data for Some Substituted Purines

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$\lambda_{\text{max}}$ at pH 1</th>
<th>Reference</th>
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<tr>
<td>$\text{NH}_2$</td>
<td>$\text{NH}_2$</td>
<td>$\text{H}$</td>
<td>242</td>
<td>$9.72 \times 10^{-3}$ (40, p. 407)</td>
</tr>
<tr>
<td>$\text{H}$</td>
<td>$\text{NH}_2$</td>
<td>$\text{NH}_2$</td>
<td>280</td>
<td>12.0 (47, p. 6675)</td>
</tr>
<tr>
<td>$\text{CH}_3\text{NH}$</td>
<td>$(\text{CH}_3)_2\text{N}$</td>
<td>$\text{H}$</td>
<td>256.5</td>
<td>16.5 (40, p. 407)</td>
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<tr>
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<td>$\text{CH}_3\text{NH}$</td>
<td>$\text{H}$</td>
<td>236</td>
<td>19.3 (40, p. 407)</td>
</tr>
<tr>
<td>$\text{H}$</td>
<td>$(\text{CH}_3)_2\text{N}$</td>
<td>$\text{CH}_3\text{NH}$</td>
<td>306</td>
<td>16.2 (47, p. 6675)</td>
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<tr>
<td>$\text{H}$</td>
<td>$\text{CH}_3\text{NH}$</td>
<td>$(\text{CH}_3)_2\text{N}$</td>
<td>287</td>
<td>16.2 (47, p. 6675)</td>
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<tr>
<td>$\text{Cl}$</td>
<td>$\text{CH}_3\text{NH}$</td>
<td>$\text{H}$</td>
<td>273</td>
<td>14.4 (40, p. 406)</td>
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<tr>
<td>$\text{H}$</td>
<td>$\text{CH}_3\text{NH}$</td>
<td>$\text{Cl}$</td>
<td>269</td>
<td>19.0 (40, p. 406)</td>
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<tr>
<td>$\text{C}_4\text{H}_3\text{OCH}_2\text{NH}$</td>
<td>$\text{C}_4\text{H}_8\text{ON}$</td>
<td>$\text{H}$</td>
<td>287</td>
<td>17.3 (3, p. 3789)</td>
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<tr>
<td>$R_1$</td>
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<td>$R_3$</td>
<td>$\lambda_{\text{max}}$ at pH 1</td>
<td>Reference</td>
</tr>
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<tr>
<td>$C_4H_8ON$</td>
<td>$C_4H_3OCH_2NH$</td>
<td>$H$</td>
<td>240 $2.6 \times 10^{-3}$</td>
<td>(3, p. 3789)</td>
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<td>290 12.9</td>
<td></td>
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<tr>
<td>$C_4H_3OCH_2NH$</td>
<td>$C_5H_{10}N$</td>
<td>$H$</td>
<td>288 19.4</td>
<td>(3, p. 3789)</td>
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<td>$C_5H_{10}N$</td>
<td>$C_4H_3OCH_2NH$</td>
<td>$H$</td>
<td>241 24.0</td>
<td>(3, p. 3789)</td>
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<td></td>
<td></td>
<td></td>
<td>292 12.0</td>
<td></td>
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<td>$C_4H_8ON$</td>
<td>$C_5H_{10}N$</td>
<td>$H$</td>
<td>245 16.3</td>
<td>(3, p. 3789)</td>
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<tr>
<td>$C_5H_{10}N$</td>
<td>$C_4H_8ON$</td>
<td>$H$</td>
<td>244 19.1</td>
<td>(3, p. 3789)</td>
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<tr>
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<td>266 22.6</td>
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many 4,6-disubstituted pyrazolo [3,4-d]pyrimidines to corresponding purines and showed a marked similarity. He also prepared pyrazolo [4,3-d]pyrimidines (45, p. 2420 and p. 2421) and compared them to the corresponding purines and noted that there was not the same similarity of spectra. No generalization can be made at present as to the spectra of imidazo [4,5-d]pyridazines. Carbon, however, has assigned structures to isomeric 4-amino-1-methylimidazo [4,5-d]pyridazine and 7-amino-1-methylimidazo [4,5-d]pyridazine on the basis of similarity to spectra of 9-methyladenine and 7-methyladenine (6, p. 6085).
<table>
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<th>( \varepsilon \times 10^{-3} )</th>
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<tr>
<td>Diethyl 2-imidazolone-4,5-dicarboxylate</td>
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<td>9.70</td>
</tr>
<tr>
<td>Dipropyl 2-imidazolone-4,5-dicarboxylate</td>
<td>311</td>
<td>9.74</td>
</tr>
<tr>
<td>Dibutyl 2-imidazolone-4,5-dicarboxylate</td>
<td>310</td>
<td>9.49</td>
</tr>
<tr>
<td>2,4,7(1H,3H,5H,6H)-Imidazo [4,5-d] -pyridazine-trione</td>
<td>280</td>
<td>4.31</td>
</tr>
<tr>
<td>2,4,7-Trichloroimidazo [4,5-d] pyridazine</td>
<td>256</td>
<td>7.13</td>
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<tr>
<td>2,4,7-Trimorpholinoimidazo [4,5-d] pyridazine</td>
<td>259</td>
<td>36.9</td>
</tr>
<tr>
<td>2-Chloro-4,7-difurfurylaminoimidazo-[4,5-d] pyridazine</td>
<td>233 247</td>
<td>26.4 25.2</td>
</tr>
<tr>
<td>2-Chloro-4,7-dipiperidinoimidazo-[4,5-d] pyridazine</td>
<td>226 243 263</td>
<td>17.2 18.5 26.3</td>
</tr>
<tr>
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<td>235 250</td>
<td>30.2 33.0</td>
</tr>
<tr>
<td>4,7-Dibenzylaminoimidazo [4,5-d] -pyridazine*</td>
<td>247</td>
<td>25.4</td>
</tr>
<tr>
<td>4,7-Dibenzylaminoimidazo [4,5-d] -pyridazine**</td>
<td>244</td>
<td>25.9</td>
</tr>
</tbody>
</table>

* Prepared by reduction of 2-chloro-4,7-dibenzylaminoimidazo [4,5-d] pyridazine
** Sample obtained from John A. Carbon, Abbott Laboratories
EXPERIMENTAL

Diethyl 2-imidazolone-4,5-dicarboxylate

Three g. (0.02 mole) of anhydrous dihydroxyfumaric acid XVII (see Figure 8) prepared by the method of Har-tree (24, p. 56-59) and 2.4 g. (0.04 mole) of dry urea were dissolved in 125 ml. of absolute ethyl alcohol and the solution then saturated at 0°C. with dry hydrogen chloride. After saturation the solution was diluted with 125 ml. of absolute alcohol and then allowed to stand 4 days at room temperature. The solution was then concentrated to a very viscous syrup by means of a rotary evaporator operating at reduced pressure with the temperature adjusted at 50°C. About 50 ml. of crushed ice were added to the syrupy residue with strong agitation to release the gummy precipitate which formed on the walls of the flask. After the ice had melted, the mixture was filtered and the product was air dried, washed with ether, and recrystallized in a 50 to 1 weight ratio from boiling water. The yields vary widely, with the majority of runs yielding very little product. Maximum yield obtained -- 1.5 g. (32.5%). Analytical samples were prepared by recrystal-lizing and decolorizing with Norite the solution of the material in 50 parts of hot water. The compound melts at 200°C.
Dipropyl 2-imidazolone-4,5-dicarboxylate

Anhydrous dihydroxyfumaric acid (7.4 g. = 0.05 mole) was dissolved in 100 ml. of reagent grade n-propyl alcohol. To this solution was added 6 g. (0.1 mole) of urea which reprecipitated the dihydroxyfumaric acid from the solution. The slurry was cooled to 0°C. and then saturated with dry hydrogen chloride. Additional n-propyl alcohol (200 ml.) was added to redissolve the dihydroxyfumaric acid. The solution, after standing at room temperature for 3 days, was then concentrated in vacuo to about 50 ml.; 300 ml. of crushed ice was added with vigorous shaking. After the ice had melted, the yellowish dipropyl 2-imidazolone-4,5-dicarboxylate was removed by filtration, washed with a small amount of cold water and air dried. The ester was recrystallized by dissolving it in a minimum amount of methyl alcohol, filtering, and pouring the filtrate into 3 volumes of crushed ice. After removing the product by filtration and drying, 6.2 g. of colorless dipropyl 2-imidazolone-4,5-dicarboxylate (48.5%), m.p. 129-130°C., were obtained.
Anal. Calc'd for C_{11}H_{16}N_{2}O_{5}:  C, 51.6; H, 6.90; N, 10.94.
Found: C, 51.9; H, 6.78; N, 11.12.

Dibutyl 2-imidazolone-4,5-dicarboxylate

Anhydrous dihydroxyfumaric acid (24 g., 0.162 mole) was dissolved in 200 ml. of reagent n-butyl alcohol. Dry urea (19.4 g., 0.324 mole) was added, which precipitated the dihydroxyfumaric acid from the solution. The suspension was cooled to 0°C. and saturated with dry hydrogen chloride; 400 ml. of reagent n-butyl alcohol was then added to redissolve the dihydroxyfumaric acid. The solution, after standing for 3 days at room temperature, was then concentrated in vacuo to about 50 ml. of thick syrup. Crushed ice (400 ml.) was added to the concentrate and the mass shaken vigorously. This converted the syrup into a yellow amorphous precipitate which was filtered, washed with ice water and dried in vacuo over phosphorus pentoxide. The ester was recrystallized by either of two methods. One procedure consisted of dissolving the ester in 400 ml. of solution containing one part each of methyl alcohol and water by bringing the temperature to 65°C., decolorizing with Norite, and cooling slowly to 4°C. with stirring. A light yellow coarse granular precipitate was obtained which was filtered and dried over phosphorus pentoxide. In the second
procedure the ester was dissolved in a minimum of methyl alcohol, filtered, and the filtrate then poured with stirring into three volumes of crushed ice. The ester was removed by filtration and dried over phosphorus pentoxide, yield 33 g. (72%) of white dibutyl 2-imidazole-4,5-dicarboxylate, m.p. 108-110°C. Analytical samples were recrystallized from aqueous methanol (1:1). Anal. Calc'd for C_{13}H_{20}N_{2}O_{5}: C, 54.9; H, 7.04; N, 9.86. Found: C, 55.0; H, 7.04; N, 9.75.

Dipentyl 2-imidazolone-4,5-dicarboxylate

The procedure used to prepare diethyl 2-imidazolone-4,5-dicarboxylate was adopted for the preparation of dipentyl 2-imidazolone-4,5-dicarboxylate. The excess pentyl alcohol was removed by distillation in vacuo using a steam bath. The esterified product was very oily, and several recrystallizations were required to give a waxy substance melting at 54-56°C. Recrystallization was effected by dissolving the ester in a minimum of warm ethyl alcohol and pouring the solution slowly, with stirring, into three volumes of crushed ice. The yield from three grams of anhydrous dihydroxyfumaric acid was 1.8 g. (28.6%) of dipentyl 2-imidazolone-4,5-dicarboxylate.
Anal. Calc'd for $C_{15}H_{24}N_{2}O_{5}$: C, 57.7; H, 7.70.

Found: C, 57.3; H, 7.34.

2-Imidazolone-4,5-dicarboxylic Acid

DIBUTYL 2-IMIDAZOLONE-4,5-DICARBOXYLATE (1.25 g.) was saponified on a steam bath for one hour using 5 ml. of 6 N NaOH; the solution was then brought to a pH of one with concentrated hydrochloric acid. The suspension was well cooled, filtered, and dried. The 2-imidazolone-4,5-dicarboxylic acid was recrystallized from 1 N hydrochloric acid yielding 0.44 g. (58%) of white product which did not melt below 300°C.

Anal. Calc'd for $C_{5}H_{4}N_{2}O_{5}$: C, 34.8; H, 2.33; N, 16.28.

Found: C, 35.1; H, 2.78; N, 16.23.

2-Imidazolone-4,5-dihydrazide

A solution containing 28.1 g. (0.1 mole) of dibutyl-2-imidazolone-4,5-dicarboxylate dissolved in 75 ml. of methanol and 15 g. (0.3 mole) of hydrazine hydrate (99-100%) was heated with occasional stirring one-half hour. A semi-solid yellow jel quickly formed, which on continued heating and stirring was converted into a thick yellow solid. The suspension was then well cooled, filtered, washed with a small amount of cold water, and air dried. The product was recrystallized by dissolving it
in cold 2 N hydrochloric acid, filtering quickly, and then precipitating with dilute ammonium hydroxide until the solution was definitely basic. The solution was well cooled, the product removed by filtration, washed with a little cold water, and air dried to yield 19.4 g. (97%) of 2-imidazolone-4,5-dihydrazide, which does not melt below 300°C.

Analytical samples were prepared by a second treatment with cold 2 N hydrochloric acid, reprecipitated with ammonium hydroxide, filtered, washed with water and ethyl alcohol, and dried over phosphorus pentoxide.

**Anal. Calc'd for C₉H₆N₆O₃: C, 30.0; H, 4.00; N, 42.00.**

**Found:**

C, 30.2; H, 4.07; N, 41.13.

2,4,7(1H,3H,5H,6H)Imidazo[4,5-d]pyridazine-trione XXa or 2,4,7-Trihydroxyimidazo[4,5-d]pyridazine XXb

2-Imidazolone-4,5-dihydrazide (17.7 g.) was placed in 200 ml. of 2 N hydrochloric acid and digested on a steam bath for 7 hours. The suspension was cooled well and the product separated by filtration was air dried. The crude product was purified by dissolving it in 250 ml. of 1 N sodium hydroxide, filtering, and reprecipitating by adding an excess of glacial acetic acid. Yield, 13.6 g. (91%) of white product which does not
melt below 300°C.

Analytical samples were prepared by dissolving the product in cold concentrated sulfuric acid, filtering through a sintered glass funnel, followed by dilution with ten volumes of ice water. The product was filtered, resuspended in ice water, filtered again, washed with a small amount of ethyl alcohol, and then dried in vacuo over phosphorus pentoxide at 110°C.

Anal. Calc'd for C₅H₄N₂O₃: C, 35.7; H, 2.38; N, 33.41. Found: C, 35.3; H, 2.61; N, 33.55.

2,4,7-Trichloroimidazo[4,5-\text{d}]pyridazine

2,4,7(1H,3H,5H,6H)Imidazo[4,5-\text{d}]pyridazine-trione (18.6 g., 0.111 mole), finely powdered and dried over phosphorus pentoxide, was suspended in 87.5 ml. of re-distilled phosphorus oxychloride to which was added 46.6 ml. (0.333 mole) of freshly distilled diethylaniline predried over potassium hydroxide. The mixture was refluxed gently for 15 hours, using a condensor so equipped as to exclude moisture, and then allowed to stand for 8 hours. The dark solution was evaporated under reduced pressure to about one-half volume, and then poured with stirring into 300 g. of crushed ice. As soon as the tarry mass had disintegrated into fine particles, the suspension was filtered. The solid was washed by
suspension in 150 ml. of ether, the ether removed by
decantation, after which the original filtrate was ex-
tracted with the decanted ether. The solid, which had
become sludgy on washing with ether, was refiltered,
then re-treated with 150 ml. of ether; the decanted
ether was again used to extract the original filtrate.
This process was repeated until no further product was
extracted -- about 8 treatments with 150 ml. of ether
per extraction. The combined ether extracts were
evaporated to dryness and the solid residue extracted
with 50 ml. of boiling 3 N ammonium hydroxide. The in-
soluble material was removed by filtration and, upon
cooling the filtrate, the ammonia salt of 2,4,7-tri-
chloroimidazo[4,5-d] pyridazine which deposited as fine
yellow needles was removed and air dried.

Neutralization of the mother liquor with glacial
acetic acid yielded a small amount of crude 2,4,7-tri-
chloroimidazo[4,5-d] pyridazine which was also removed
and air dried. The ammonia salt, together with the crude
product obtained by the neutralization of the mother
liquor, was dissolved in 75 parts boiling water and then
acidified with dilute sulfuric acid to a pH of one (pH
paper). The solution was decolorized with Norite and,
while still hot, filtered. Pale yellow needles were de-
posited on cooling (occasional stirring was required)
which were removed and dried in vacuo over phosphorus pentoxide, yield 8.5 g. (34% -- yields as high as 45% were obtained) of 2,4,7-trichloroimidazo[4,5-d]pyridazine, m.p. 230-232°C. (dec.).

Analytical samples were obtained by dissolving in cold absolute ethyl alcohol, filtering, and pouring the filtrate into three volumes of crushed ice, collecting the product and drying it over phosphorus pentoxide in vacuo.

Anal. Calc'd for C_{2}H_{4}N_{4}Cl_{3}: C, 26.8; H, 0.49; N, 25.06.
Found: C, 26.9; H, 0.95; N, 24.52.

2,4,7-Trimorpholinoimidazo[4,5-d]pyridazine XXII

2,4,7-Trichloroimidazo[4,5-d]pyridazine (200 mg.) was placed in 2 ml. of morpholine and the solution refluxed for 2½ hours. The solution was cooled and 2 ml. of water was added to the solid mass of white crystals. The suspension was stirred, the product removed by filtration, and then air dried. The product was purified by dissolving it in water containing a few drops of acetic acid, filtering, and reprecipitating by making the solution very slightly basic. After filtering, washing with a small amount of very dilute ammonium hydroxide, and drying, 280 mg. (86%) of 2,4,7-trimorpholinoimidazo[4,5-d]pyridazine were obtained,
m.p. 284-285°C. (dec.).

Anal. Calc'd for C$_{17}$H$_{25}$N$_{7}$O$_{3}$: C, 54.4; H, 6.67; N, 26.13.
Found: C, 54.2; H, 6.55; N, 26.16.

2-Chloro-4,7-dipiperidinoimidazo[4,5-d]pyridazine XXIII

2,4,7-Trichloroimidazo[4,5-d]pyridazine (0.5 g.) was placed in 10 ml. of redistilled piperidine and the solution was refluxed for 2 hours; after 30 minutes crystals began to deposit in the flask. The solution was cooled and 10 ml. of water was added which dissolved the crystals. The solution was neutralized with dilute acetic acid yielding a light pink precipitate which was filtered and dried. The product was recrystallized by dissolving it in hot glacial acetic acid, filtering, and pouring into two volumes of crushed ice. The precipitate was filtered and dried to give 540 mg. (75%) of product melting at 171.5-173°C.

Anal. Calc'd for C$_{15}$H$_{21}$N$_{6}$Cl: C, 56.2; H, 6.55; N, 26.21.
Found: C, 56.1; H, 6.74; N, 26.19.

2-Chloro-4,7-difurfurylaminoimidazo[4,5-d]pyridazine

Hydrate XXIV

2,4,7-Trichloroimidazo[4,5-d]pyridazine (0.5 g.) was refluxed in 10 ml. of freshly redistilled furfurylamine for 2 hours. The cooled solution was neutralized
with glacial acetic acid and poured into five volumes of crushed ice. The tarry brown material was separated by filtration and immediately dissolved in hot glacial acetic acid. The hot solution was decolorized with Norite and then poured into five volumes of crushed ice; colorless needles precipitated immediately which were filtered and dried. The product was recrystallized by dissolving it in hot 6 N acetic acid followed by thorough cooling of the solution; yield 0.46 g. (61%), m.p. 107-109°C. (dec.).

Analytical samples were recrystallized again from 6 N acetic acid. The 2-chloro-4,7-difurfurylaminoimidazo[4,5-d]pyridazine hydrate darkened and became a tan color after several days, even when kept in a closed container.

Anal. Calc’d for C₁₅H₁₃N₆O₂Cl·H₂O: C, 49.7; H, 4.14; N, 23.17. Found: C, 49.9; H, 4.22; N, 23.34.

2-Chloro-4,7-dihydrazinoimidazo[4,5-d]pyridazine XXV

One gram of 2,3,7-trichloroimidazo[4,5-d]pyridazine was dissolved in 10 ml. of 100% hydrazine hydrate and refluxed gently for 3 hours. After about 2 hours, white crystals began to deposit which soon filled the container. The solution was cooled, diluted with water, filtered, and air dried. The product was
resuspended in water, stirred well, and collected; yield 0.87 g. (90.5%) of material which did not melt below 300°C.

Care must be taken when running Carbon and Hydrogen analysis as the sample explodes violently upon combustion.

Anal. Calc'd for C$_7$H$_7$N$_8$Cl: C, 28.0; H, 3.26; N, 52.21.
Found: C, 28.1; H, 3.39; N, 52.09.


$2$-Chloro-$4,7$-dihydrazinoimidazo $4,5$-d pyridazine (0.5 g.) was refluxed with 10 ml. of formic acid for 3 hours. The excess formic acid was removed by evaporation in vacuo. The light colored residue was recrystallized by dissolving it in 30 ml. of boiling $N, N$-dimethylformamide, cooling well, and reprecipitating the product by addition of 30 ml. of crushed ice. The product was filtered and dried in vacuo over phosphorus pentoxide; yield 0.26 g. (47.7%) of light colored material that does not melt below 300°C.

Anal. Calc'd for C$_7$H$_3$N$_8$Cl: C, 35.8; H, 1.28; N, 47.76.
Found: C, 35.7; H, 2.13; N, 47.52.

(this compound also explodes violently upon combustion)
5-Chloro-tetrazolo[1',5':1,7]tetrazolo[1'',5'':2,3]-imidazo[4,5-d]pyridazine or 8-chloroimidazo[1,5-a]-tetrazolo[5,1-b]tetrazolo[4,3-f]pyridazine XIV

Six-tenths ml. of concentrated nitric acid was added to 4 ml. of water and the solution cooled in an ice bath to 0°C. To this was added 0.39 g. (5.6 x 10⁻³ mole) of sodium nitrite. To the resulting solution in turn was added, slowly with stirring, 0.6 g. (2.8 x 10⁻³ mole) of 2-chloro-4,7-dihydrayzinoimidazo[4,5-d]-pyridazine. After stirring for about ½ hour, the solution was warmed gently to effect a complete reaction. The solution was diluted with 5 ml. of water, and then neutralized with sodium carbonate. The light green product was removed by filtration and dried. The product was recrystallized from 20 ml. of 95% ethanol; yield 130 mg. (23%) of material which darkens slowly at 240°C. and higher.

Anal. Calc'd for C₅H₁₁N₁₀Cl: C, 25.4; H, 0.42; N, 59.20.

Found: C, 25.5; H, 1.23; N, 59.34.

(This compound also explodes violently upon combustion.)

2-Chloro-4,7-dibenzylaminoimidazo[4,5-d]pyridazine hydrochloride XXVI

2,4,7-Trichloroimidazo[4,5-d]pyridazine (0.75 g.)
and 3 ml. of benzylamine were refluxed together in 10 ml. of n-butanol for 2 hours. The solution was concentrated in vacuo to a crystalline semi-solid. Ten ml. of 3 N hydrochloric acid was added to the oily mixture and stirred well. The flocculent white precipitate was filtered, air dried, and then recrystallized from 60% ethanol-water containing 2 drops of concentrated hydrochloric acid. The precipitate was then washed with a small amount of water and dried; yield 0.80 g. (59.2%) of 2-chloro-4,7-dibenzylaminimidazo[4,5-d]pyridazine hydrochloride, m.p. 180-182°C. (dec.).

Anal. Calc'd for C_{19}H_{17}N_{6}Cl·HCl: C, 56.8; H, 4.48; N, 20.95. Found: C, 56.5; H, 4.58; N, 20.85.

4,7-Dibenzylaminimidazo[4,5-d]pyridazine Hydrochloride

XXVII

2-Chloro-4,7-dibenzylaminimidazo[4,5-d]-pyridazine hydrochloride (0.5 g., 1.25 x 10^{-3} mole) was suspended in 40 ml. of liquid ammonia. This suspension was prepared in a three neck flask equipped with a mechanical stirrer and a drying tube. With vigorous stirring, small pieces of sodium were added to the liquid ammonia suspension until a permanent blue color was visible. This operation required about 0.22 g. (8.3 x 10^{-3} mole) of ammonium chloride and then allowed to stir for
another hour. The solution was then evaporated to dryness and the residue air dried. The inorganic salts were extracted with 10 ml. of warm water which was then decanted from the very gummy free base as reported by Carbon (6, p. 6087). This residue was dissolved in 5 ml. of 3 N sodium hydroxide, a red tar removed by filtration, and the filtrate made strongly acid with concentrated hydrochloric acid. The colorless crystals were removed by filtration, washed with a small amount of water, and dried. The product was recrystallized from n-propanol; yield 0.19 g. (42.5%) of colorless needles, m.p. 200-202°C. (dec.).

Anal. Calc'd for $C_{19}H_{18}N_6\cdot HCl$: C, 62.2; H, 5.18; N, 22.92.
Found: C, 61.6; H, 5.30; N, 22.79.

(?)-(?)-Dichloro-(?)-hydroxyimidazo[4,5-d]pyridazine

2,4,7-Trichloroimidazo[4,5-d]pyridazine (0.5 g.) was dissolved in concentrated sulfuric acid and the resultant solution then cooled in an ice bath. Four ml. of fuming nitric acid (specific gravity, 1.5) was added to the cold solution; there was no visible reaction. The temperature of the solution was then raised to 90°C. and maintained there 10 minutes. During this period there was some gas evolution with the solution turning to a brown color. The solution was thereupon cooled and
poured into 50 ml. of crushed ice. The white precipitate which formed was removed by filtration and dried. The material was recrystallized from 30 ml. of 1 N hydrochloric acid, yield 0.32 g. (69.5%) of fine white crystals which did not melt below 300°C.

Anal. Calc'd for $C_5H_2N_4OCl_2$: C, 29.2; H, 0.98; N, 27.31.

Found: C, 29.1; H, 1.20; N, 27.07.
DISCUSSION

The search for alcoholic media that would give the most effective cyclization of dihydroxyfumaric acid and urea also gave some insight into the steps involved in this cyclization. The fact that cyclization does not occur in methanol is not surprising in view of the work of Hartree (23, p. 6245-6249) who studied the esterification of dihydroxyfumaric acid with methanol and ethanol. The methyl ester, which precipitates out of the reaction media, he has shown to be dimethyl dihydroxyfumarate. His ethyl ester, however, was a mixture of diethyl dihydroxymaleate and diethylketomalate in an approximate ratio of two to one. This would indicate that the first step of the cyclization is the esterification of the dihydroxyfumaric acid. The methyl ester precipitates out at this point, while the other esters studied, which are soluble, undergo isomerization to the dihydroxymaleate and ketomalate. It is feasible that either the ketomalate or the dihydroxymaleate could then cyclize with urea to give the desired product.

Early attempts to repeat the cyclization with thiourea, guanidine, and acetamidine were unsuccessful, although it would certainly be expected that they should undergo the same reaction. Concentration of the
cyclization media in all cases gave the same syrupy mass as with urea. The product failed to separate out on addition of crushed ice. Diethy-2-mercapto-4,5-imidazoledicarboxylate is very soluble in water (28, p. 1085) and it can be assumed that guanidine, which would form the hydrochloride, would also be very soluble. Further work on isolation methods should reveal this reaction scheme to be applicable for the preparation of 2-amino, 2-mercapto- and 2-methyl-4,5-imidazoledicarboxylates and the corresponding 2-substituted-4,7-dihydroxyimidazo-[4,5-d]pyridazines.

The problem of the structure of the esters of 2-imidazolone-4,5-dicarboxylic acid has not been resolved. Hofmann (27, p. 61) has compared the melting points of various imidazoles and corresponding 2(3H)-imidazolones and 2(3H)-imidazothiones. The introduction of oxygen and sulfur into the 2 position of imidazole results in a marked elevation of the melting point. Hofmann suggests that in the solid state this indicates the presence of salt-like zwitterionic structures:

\[
\begin{align*}
\text{H-C} \quad \text{N} \quad \text{c} &= \chi \quad \text{H-C} \quad \text{N} \quad \text{c} \\
=\downarrow &\quad =\downarrow &\quad =\downarrow \\
\text{H-C} \quad \text{N-H} &= \chi \quad \text{H-C} \quad \text{N-H} \\
\text{H-C} \\
\text{N-H} \\
\text{H-C} \\
\text{N-H} \\
\chi &= S \text{ or } O
\end{align*}
\]
He further supports this view by demonstrating that changes which would interfere with this "urea resonance" should lower the melting point, and that such compounds actually do have lower melting points.

A study of the melting points of the 4,5-imidazoledicarboxylic acids, however, shows that the introduction of various groups into the 2 position does not affect the melting point in the same manner as these substitutions did with other imidazoles.

### TABLE III

2-Substituted Imidazoledicarboxylic Acids

<table>
<thead>
<tr>
<th>Compound</th>
<th>Melting point</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,5-imidazoledicarboxylic acid</td>
<td>280</td>
</tr>
<tr>
<td>2-amino-4,5-imidazoledicarboxylic acid</td>
<td>261</td>
</tr>
<tr>
<td>2-mercapto-4,5-imidazoledicarboxylic acid</td>
<td>245</td>
</tr>
<tr>
<td>2-imidazolone-4,5-dicarboxylic acid</td>
<td>&gt; 300</td>
</tr>
</tbody>
</table>

Hofmann concluded that these 4,5-imidazoledicarboxylic acids are best represented by a zwitterionic structure XXVIII (27, p. 179). The resonance of the
zwitterion is such that substitution in the 2-position would not disrupt resonance and thus lower the melting point. Substitution in the 1-position does lower the melting point, which indicates that Hofmann's zwitterion is not the only resonance form present. The possibility

---

**TABLE IV**

1-Substituted Imidazoledicarboxylic Acids

<table>
<thead>
<tr>
<th>Compound</th>
<th>Melting point</th>
</tr>
</thead>
<tbody>
<tr>
<td>l-methyl-4,5-imidazoledicarboxylic acid</td>
<td>261</td>
</tr>
<tr>
<td>l-phenyl-2-mercapto-4,5-imidazole-dicarboxylic acid</td>
<td>200</td>
</tr>
</tbody>
</table>

that there may also be tautomeric forms of the 2-substituted-4,5-imidazoledicarboxylic acids and esters cannot be dismissed:

\[
\text{R} - \text{O} - \text{C} - \text{N} \leftrightarrow \text{R} - \text{O} - \text{C} - \text{N} \]

\[
\text{R} - \text{O} - \text{C} - \text{N} \rightarrow \text{R} - \text{O} - \text{C} - \text{N} \]

\[
\text{R} - \text{O} - \text{C} - \text{N} \rightarrow \text{R} - \text{O} - \text{C} - \text{N} \]

\[
\text{R} - \text{O} - \text{C} - \text{N} \rightarrow \text{R} - \text{O} - \text{C} - \text{N} \]
If the 2-hydroxy-4,5-imidazolidedicarboxylic acids and esters (or 2-imidazolone-4,5-dicarboxylic acids and esters) are actually in the keto form, there would be possible two classes of esters of this compound, XXIX and XXX. These esters would differ in the position of

\[
\begin{align*}
\text{XXIX} & : R\text{OO}C-\text{c}-N- \quad \text{XXX} & : R\text{OO}C-\text{c}-N-
\end{align*}
\]

the double bond (or the position of attachment of the hydrogen) in the imidazole ring. Structure XXX, 2(1H,5H)-imidazolidedicarboxylate, can be eliminated by subsequent reactions which occurred. If structure XXX were the form of the ester, the following reactions would have occurred:

\[
\begin{align*}
\text{R-COOE} + \text{H}_2\text{NNH}_2 & \rightarrow \text{R-COOE} \quad \text{R-COOE} \rightarrow \text{R-COOE} \\
\text{H}_2\text{NNH}_2 & \rightarrow \text{R-COOE} \\
\text{R-COOE} & \rightarrow \text{R-COOE}
\end{align*}
\]
The final product, the 2,4,7-trichloroimidazo[4,5-d]-pyridazine, was isolated as an ammonium salt. This required the presence of an acid hydrogen in the imidazo-[4,5-d]pyridazine ring — a condition satisfied when a hydrogen is attached to a nitrogen in some heterocyclic rings. This acid hydrogen would not be present if structure XXX were the original reactant.
BIBLIOGRAPHY


29. __________. Reactions of hydrazine with heterocyclic 1,2-dicarboxylic acid esters. Journal of the American Chemical Society 78:159-163. 1956.


