precipitate was finally washed with acetone, then ether, and dried at room temperature *in vacuo* to give 12 mg. (26%) of the triphosphate XIXc as a white powder, $\lambda_{max}$ 268 mμ.; $R_f$ (in solvent system *C*) 0.31.

*Anal.* Calcd. for $C_9H_{10}N_2O_{14}FP_3Li_4 \cdot 3H_2O$: P, 16.5. Found: P, 16.3.

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# Synthesis of 2,4,7-Trichloroimidazo[4,5-*d*]pyridazine and Certain of Its Derivatives[1]

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Diethyl $\Delta^3$- (or $\Delta^4$)-imidazolone-2-dicarboxylate-4,5, m.p. 279°, prepared by Fenton has been shown to be identical to diethyl $\Delta^3$- (or $\Delta^4$)-imidazolone-2-dicarboxylate-4,5, m.p. 200°, characterized by Geisenheimer and Anschutz. The structure of this ester has been established as diethyl 2-imidazolone-4,5-dicarboxylate (diethyl $\Delta^4$-imidazolone-2-dicarboxylate-4,5). Several esters of 2-imidazolone-4,5-dicarboxylate have been prepared. The dibutyl ester has been found to be the most satisfactory intermediate for cyclization purposes to 2,4,7-trihydroxyimidazo[4,5-*d*]pyridazine. Both 2,4,7-trihydroxyimidazo[4,5-*d*]pyridazine and 2,4,7-trichloroimidazo[4,5-*d*]pyridazine have been synthesized. Several new derivatives, both diaminated and triaminated, of 2,4,7-trichloroimidazo[4,5-*d*]pyridazine have been prepared. The chloro substituents in the 4,7-positions have been found to be the most reactive leading to 2-chloro-4,7-disubstituted derivatives. The position of the substituents of the monochlorodibenzylaminoimidazo[4,5-*d*]pyridazine was established by removing the chlorine atom with sodium in a liquid ammonia medium. The resulting dibenzylaminoimidazo[4,5-*d*]pyridazine was found to be identical to the 4,7-dibenzylaminoimidazo[4,5-*d*]pyridazine previously prepared by Carbon. It was assumed that the other derivatives were also diaminated in the 4- and 7-positions. Structures were assigned to the two new ring systems resulting from the treatment of 2-chloro-4,7-dihydrazinoimidazo[4,5-*d*]pyridazine with formic acid and with nitrous acid.

The change in the chemical activity of the chloro substituents in relation to their positions in several of the nitrogen heterocycles has been of interest to this laboratory for a number of years.[2] Recently Kuraishi[3] reported the chloro substituent on the pyridazine ring to be relatively inactive which confirmed our own observations while attempting to diaminate the trichloro derivative; Castle and Seese[4] had been unsuccessful in their efforts to diaminate the dichloropyridazine. For these reasons, it seemed worthwhile to expand the study to include both the chloropyridazines and the chloro-substituted imidazopyridazines.

Although 4,7-dichloroimidazo[4,5-*d*]pyridazine has been prepared in 17% yield by Castle and Seese,[4] both 2,4,7-trichloroimidazo[4,5-*d*]pyridazine and 2,4,7-trihydroxyimidazo[4,5-*d*]pyridazine are unknown. This latter compound, an analog of uric acid, should be preparable from the reactions of a 2-imidazolone-4,5-dicarboxylate ester with hydrazine.

The preparation of the starting material, diethyl 2-imidazolone-4,5-dicarboxylate for such a synthesis is not to be found in the more recent literature. However, Beilstein describes two different procedures for the preparation of the diethyl ester of $\Delta^3$- (or $\Delta^4$)-imidazolone-2-dicarboxylate-4,5, one with a melting point of 200° and the other melting at 258–259°.

The ester (m.p. 200°) had been prepared by Geisenheimer and Anschutz[5] by condensing diethyl diketosuccinate with urea to form the monoureide; this monoureide on treatment with phosphorus trichloride yielded the ester.

Fenton and Wilks[6] used an entirely different procedure to prepare the higher melting ester. These workers cyclized the so-called dihydroxymaleic acid (which in its solid state was shown by Hardtree[7] and Gupta[8] to be dihydroxyfumaric acid) with urea in an ethyl alcoholic solvent in the presence of dry hydrogen chloride.

Attempts by the authors to repeat this work, however, gave only small inconsistent yields of material melting at 200°. On the other hand, the compound prepared in this laboratory by the method of Geisenheimer and Anschutz[5] also melted at 200° as reported. Both products reacted with hydrazine to form a dihydrazide which, on treatment with dilute hydrochloric acid, gave 2,4,7(1*H*,3*H*,5*H*,6*H*)-imidazo[4,5-*d*]pyridazinetrione. It must be concluded that the two esters, m.p. 200° and 279°, are identical and that the melting point of the Fenton compound is in error.

(1) Published with the approval of Monographs Publication Committee, Oregon State University, as Research Paper No. 426, Department of Chemistry, School of Science.

(2) A. J. Tomisek and B. E. Christensen, *J. Am. Chem. Soc.*, **67**, 2112 (1945); R. K. Robins and B. E. Christensen, *ibid.*, **74**, 3624 (1952).

(3) T. Kuraishi, *Pharm. Bull.* (Tokyo), **4**, 497 (1956).

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TABLE I
ULTRAVIOLET SPECTRA

| Compound | $\lambda_{max}$ (absolute ethanol) | $\epsilon \times 10^{-3}$ |
|---|---|---|
| Diethyl 2-imidazolone-4,5-dicarboxylate | 311 | 9.70 |
| Dipropyl 2-imidazolone-4,5-dicarboxylate | 311 | 9.74 |
| Dibutyl 2-imidazolone-4,5-dicarboxylate | 310 | 9.49 |
| 2-Imidazolone-4,5-dicarboxhydrazide | 302[c] | 7.94 |
| 2,4,7(1*H*,3*H*,5*H*,6*H*)-Imidazo[4,5-*d*]pyridazinetrione | 279[c] | 5.40 |
| 2,4,7-Trichloroimidazo[4,5-*d*]pyridazine | 256 | 7.13 |
| 2,4,7-Trimorpholinoimidazo[4,5-*d*]pyridazine | 259 | 36.9 |
| 2-Chloro-4,7-difurfurylaminoimidazo[4,5-*d*]pyridazine | 233 247 | 26.4 25.2 |
| 2-Chloro-4,7-dipiperidinoimidazo[4,5-*d*]pyridazine | 226 243 263 | 17.2 18.5 26.3 |
| 2-Chloro-4,7-dibenzylaminoimidazo[4,5-*d*]pyridazine | 235 250 | 30.2 33.0 |
| 4,7-Dibenzylaminoimidazo[4,5-*d*]pyridazine[a] | 245 | 27.2 |
| 4,7-Dibenzylaminoimidazo[4,5-*d*]pyridazine[b] | 245 | 27.2 |

[a] Prepared by reduction of 2-chloro-4,7-dibenzylaminoimidazo[4,5-*d*]pyridazine. [b] Sample obtained from John A. Carbon, Abbott Laboratories. [c] Aqueous solutions at pH 1.3.

The method described by Fenton[6] although giving poor and inconsistent yields of the starting intermediate [diethyl $\Delta^3$- (or $\Delta^4$)-imidazolone-2-dicarboxylate-4,5] was an easier procedure than the alternate method. For this reason an attempt was made to improve the process by examining a number of other alcoholic solvents as reaction media for the cyclization of dihydroxyfumaric acid with urea. No cyclization occurs in methanol; instead only dimethyl dihydroxyfumarate was found. Cyclization experiments using *n*-propyl, *n*-butyl, and *n*-pentyl alcohols, however, all gave the corresponding diester of 2-imidazolone-4,5-dicarboxylate in good yield. The butyl ester proved to be the most satisfactory for cyclization purposes largely from solubility characteristics and ease of purification.

These esters hydrolyze readily to yield 2-imidazolone-4,5-dicarboxylic acid, which has a very high melting point and solubility properties similar to that of the 4,5-imidazoledicarboxylic acids described by Jones.[9]

The search for an alcoholic medium that would give the most effective cyclization of dihydroxyfumaric acid and urea also gave some insight into the steps involved in the cyclization. The fact that cyclization does not occur in methanol is not surprising in view of the work of Hardtree[7] who found that the methyl ester precipitates out of the reaction medium as dimethyl dihydroxyfumarate while the ethanolic solvent yielded a mixture of diethyl dihydroxymaleate and diethyl ketomalate. This behavior would indicate that the first step of the cyclization is the esterification of dihydroxyfumaric acid, with the soluble esters undergoing isomerization to dihydroxymaleate and ketomalate which in turn cyclize with urea giving the desired products.

The reaction of the esters with hydrazine gave 2-imidazolone-4,5-dicarboxhydrazide which was then cyclized by digesting it with dilute hydrochloric acid to yield 2,4,7-(1*H*,3*H*,5*H*,6*H*)-imidazo[4,5-*d*]-pyridazinetrione. In later experiments the product was obtained directly by refluxing a hydrazine solution of dibutyl 2-imidazolone-4,5-dicarboxylate. The trione was chlorinated by the procedure which Davoll and Lowy[10] described for the chlorination of uric acid to give 2,4,7-trichloroimidazo[4,5-*d*]-pyridazine in varying yields that exceeded those reported for the chlorination of uric acid.

Since 2,4,7-trichloroimidazo[4,5-*d*]pyridazine was isolated as an ammonium salt, it must have an acidic hydrogen bonded to a nitrogen atom of the imidazole ring.

This can only be possible if the unsaturation in the original imidazolone-2-dicarboxylate-4,5 used to synthesize the imidazo[4,5-*d*]pyridazine ring was in the $\Delta^4$-position. This resolves the problem of which isomer, $\Delta^3$- or $\Delta^4$-imidazo[4,5-*d*]pyridazine, is obtained in the initial condensation of dihydroxyfumaric acid with urea.

Amination studies with amines such as furfurylamine, piperidine, and hydrazine revealed that two chloro substituents were easily replaced while the third chloro group was much more unreactive; only morpholine yielded the trisubstituted product.

To determine which two of the chloro substituents were involved in these reactions, an unsuccessful attempt was made to oxidize the monochlorodihydrazinoimidazo[4,5-*d*]pyridazine to a substituted imidazoledicarboxylic acid using fuming nitric acid. Oxidation of 2,4,7-trichloroimidazo-[4,5-*d*]pyridazine with fuming nitric acid, on the other hand, gave a high melting product in good yield, which on the basis of analytical data, appeared to be one of the isomers of 2,4,7-dichlorohydroxyimidazo[4,5-*d*]pyridazine.

Efforts to determine the structure of the diaminated imidazo[4,5-*d*]pyridazine by catalytic reduction were unsuccessful. However, chemical reduction using Carbon's[11] procedure with sodium in liquid ammonia solvent did effect the removal of the chloro substituent of chlorodibenzylaminoimidazo[4,5-*d*]pyridazine.

(9) R. G. Jones, *J. Am. Chem. Soc.*, **74**, 1085 (1952).

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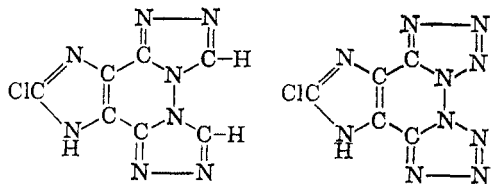

V VI

Figure 1

Comparisons of this reduction product with that of an authentic sample of 4,7-dibenzylaminoimidazo[4,5-*d*]pyridazine prepared by the procedure of Carbon showed the two compounds to be identical as judged by both infrared and ultraviolet spectral data.

On the basis of this identification the remaining compounds formed by the disubstitution of the original 2,4,7-trichloroimidazo[4,5-*d*]pyridazine were assigned structures with substituents in the 4- and 7- positions.

Because of the reactive properties of the hydrazino substituent, the 2-chloro-4,7-dihydrazinoimidazo-[4,5-*d*]pyridazine was treated with formic acid using the Carbon procedure, causing further cyclization to an even more highly condensed ring system (see Fig. 1).

Furthermore, treating the 2-chloro-4,7-dihydrazinoimidazo[4,5-*d*]pyridazine with nitrous acid likewise led to further cyclization yielding the diaza analog of the same highly condensed ring system (see Fig. 1).

## Experimental

**Di-*n*-butyl 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° 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 sirup. Crushed ice (400 ml.) was added to the concentrate and the mass shaken vigorously. This converted the sirup into a yellow amorphous precipitate which was filtered, washed with ice water, and dried *in vacuo* over phosphorus pentoxide. The ester was recrystallized by dissolving it in a minimum of methyl alcohol, filtered, and the filtrate then poured with stirring into three volumes of crushed ice in 5% sodium bicarbonate solution. The ester was removed by filtration, washed well with water and dried over phosphorus pentoxide; yield 33 g. (72%) of white dibutyl 2-imidazolone-4,5-dicarboxylate, m.p. 108–110°. Analytical samples were recrystallized from aqueous methanol (1:1).

*Anal.* Calcd. for $C_{13}H_{20}N_2O_5$: C, 54.9; H, 7.10; N, 9.86. Found: C, 55.0; H, 7.04; N, 9.75.

**Di-*n*-propyl 2-Imidazolone-4,5-dicarboxylate.**—This compound was prepared by the directions describing the preparation of the dibutyl ester. The precipitate from the aqueous solution was recrystallized by solution in a minimum amount of methyl alcohol, filtering and pouring the filtrate into three volumes of crushed ice; yield 48.5%, m.p. 129–130°.

*Anal.* Calcd. for $C_{11}H_{16}N_2O_5$: C, 51.6; H, 6.31; N, 10.9. Found: C, 51.9; H, 6.78; N, 11.1.

**Di-*n*-pentyl 2-Imidazolone-4,5-dicarboxylate.**—This compound was also prepared by the directions describing the preparation of the dibutyl ester. 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°. 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 3 g. of anhydrous dihydroxyfumaric acid was 1.8 g. (28.6%) of dipentyl 2-imidazolone-4,5-dicarboxylate.

*Anal.* Calcd. for $C_{15}H_{24}N_2O_5$: C, 57.7; H, 7.74. Found: C, 57.3; H, 7.34.

**2-Imidazolone-4,5-dicarboxylic Acid.**—Di-*n*-butyl 2-imidazolone-4,5-dicarboxylate (1.25 g.) was saponified on a steam bath for 1 hr. using 5 ml. of 6 *N* sodium hydroxide; the solution was then brought to pH 1 with concentrated hydrochloric acid. The suspension was 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°.

*Anal.* Calcd. for $C_5H_4N_2O_5$: C, 34.8; H, 2.33; N, 16.3. Found: C, 35.1; H, 2.78; N, 16.2.

**2-Imidazolone-4,5-dicarboxhydrazide.**—A solution containing 28.1 g. (0.1 mole) of di-*n*-butyl 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 for 0.5 hr. A semisolid yellow gel quickly formed, which on continued heating and stirring was converted into a thick yellow solid. The suspension was then 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, (if a precipitate of the hydrazide hydrochloride begins to form, dilute the solution with water), filtering quickly, and bringing the solution to pH 7.5 with dilute ammonium hydroxide. The solution was cooled, the product removed by filtration, washed with a little cold water, and air-dried; yield 19.4 g. (97%) of 2-imidazolone-4,5-dicarboxhydrazide, which does not melt below 300°.

Analytical samples were prepared by repeating the treatment with 2 *N* hydrochloric acid, washing the product with water and ethyl alcohol, and drying the samples over phosphorus pentoxide.

*Anal.* Calcd. for $C_5H_8N_6O_3$: C, 30.0; H, 4.00; N, 42.0. Found: C, 30.2; H, 4.07; N, 41.1.

**2-Imidazolone-4,5-dicarboxhydrazide Sulfate Monohydrate.**—One and four-tenths of a gram of 2-imidazolone-4,5-dicarboxhydrazide was dissolved in 40 ml. of concentrated sulfuric acid. The solution was filtered using a sintered glass funnel. Upon pouring the filtrate onto crushed ice, a white precipitate formed, which was filtered, washed well with water, and dried.

*Anal.* Calcd. for $C_5H_{12}N_6O_8S$: C, 19.0; H, 3.83. Found: C, 18.9; H, 3.98.

**2,4,7(1*H*,3*H*,5*H*,6*H*)-Imidazo[4,5-*d*]pyridazinetrione.**—2-Imidazolone-4,5-dicarboxhydrazide (17.7 g.) was placed in 200 ml. of 2 *N* hydrochloric acid and digested on a steam bath for 7 hr. The suspension was cooled and the product separated by filtration. 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°.

Analytical samples were prepared by dissolving the product (1 g./5 ml.) 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°.

*Anal.* Calcd. for $C_5H_4N_4O_3$: C, 35.7; H, 2.38; N, 33.3. Found: C, 35.3; H, 2.61; N, 33.6.

**2,4,7-Trichloroimidazo[4,5-*d*]pyridazine (III).**—2,4,7(1*H*,3*H*,5*H*,6*H*)-Imidazo[4,5-*d*]pyridazinetrione (18.6 g., 0.111 mole), finely powdered and dried over phosphorus pentoxide, was suspended in 87.5 ml. of redistilled phosphorus oxychloride to which was added 53 ml. (0.333 mole) of freshly distilled diethylaniline predried over potassium hydroxide. The mixture was refluxed gently for 15 hr., using a condenser so equipped as to exclude moisture, and then allowed to stand for 8 hr. 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 extracted with the decanted ether. The solid, which had become sludgy on washing with ether, was refiltered, and then retreated 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 eight treatments with 150 ml. of ether. The combined ether extracts were evaporated to dryness and the solid residue extracted with 50 ml. of boiling 3 *N* ammonium hydroxide. The insoluble material was removed by filtration, and upon cooling the filtrate with occasional stirring the ammonium salt of 2,4,7-trichloroimidazo[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-trichloroimidazo-[4,5-*d*]pyridazine which was also removed and air-dried. The ammonium salt, together with the crude product obtained by the neutralization of the mother liquor, was dissolved in 75 parts of boiling water and then acidified with dilute sulfuric acid to pH 1 (pH paper). The solution was decolorized with Norit and, while still hot, filtered. Pale yellow needles deposited 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° 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.* Calcd. for $C_5HN_4Cl_3$: C, 26.8; H, 0.45; N, 25.1. Found: C, 26.9; H, 0.95; N, 24.5.

**2,4,7-Trimorpholinoimidazo[4,5-*d*]pyridazine.**—2,4,7-Trichloroimidazo[4,5-*d*]pyridazine (200 mg.) was placed in 2 ml. of morpholine and the solution refluxed for 2.5 hr. 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° dec.

*Anal.* Calcd. for $C_{17}H_{25}N_7O_3$: C, 54.4; H, 6.71; N, 26.1. Found: C, 54.2; H, 6.55; N, 26.2.

**2-Chloro-4,7-dipiperidinoimidazo[4,5-*d*]pyridazine.**—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 hr.; after 30 min. 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°.

*Anal.* Calcd. for $C_{15}H_{21}N_6Cl$: C, 56.2; H, 6.58; N, 26.2. Found: C, 56.1; H, 6.74; N, 26.2.

**2-Chloro-4,7-difurfurylaminoimidazo[4,5-*d*]pyridazine Hydrate.**—A solution of 2,4,7-trichloroimidazo[4,5-*d*]pyridazine (0.5 g.) and 10 ml. of freshly redistilled furfurylamine was refluxed for 2 hr. 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 redissolved in hot glacial acetic acid. The hot solution was decolorized with Norit 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° 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.

*Anal.* Calcd. for $C_{15}H_{13}N_6O_2Cl \cdot H_2O$: C, 49.7; H, 4.17; N, 23.2. Found: C, 49.9; H, 4.22; N, 23.3.

**2-Chloro-4,7-dihydrazinoimidazo[4,5-*d*]pyridazine.**—One gram of 2,4,7-trichloroimidazo[4,5-*d*]pyridazine was dissolved in 10 ml. of 100% hydrazine hydrate and refluxed gently for 3 hr. After about 2 hr., 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°.

Care must be exercised when running carbon and hydrogen analysis as the sample explodes violently upon combustion.

*Anal.* Calcd. for $C_5H_7N_8Cl$: C, 28.0; H, 3.26; N, 52.2. Found: C, 28.1; H, 3.39; N, 52.1.

**8-Chloro-7 (or 8) *H*-imidazo[4,5-*d*]ditriazolo[3,4-*b*:4′,3′-*f*]pyridazine V or 5-Chlorotriazolo[3′,4′:1,7]triazolo[3″,4″:2,3]imidazo[4,5-*d*]pyridazine.**— 2-Chloro-4,7-dihydrazinoimidazo[4,5-*d*]pyridazine (0.5 g.) was refluxed with 10 ml. of formic acid for 3 hr. 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°.

*Anal.* Calcd. for $C_7H_3N_8Cl$: C, 35.8; H, 1.28; N, 47.8. Found: C, 35.7; H, 2.13; N, 47.5.

(This compound also explodes violently upon combustion.)

**8-Chloro-7(or 8)*H*-imidazo[4,5-*d*]ditetrazolo[5,1-*b*:1,5-*f*]pyridazine or 5-Chlorotetrazolo[1′,5′:1,7]tetrazolo[1″,5″:2,3]imidazo[4,5-*d*]pyridazine.**—Concentrated nitric acid (0.6 ml.) was added to 4 ml. of water and the solution cooled in an ice bath to 0°. To this was added 0.39 g. ($5.6 \times 10^{-3}$ mole) of sodium nitrite. To the resulting solution in turn was added, slowly with stirring, 0.6 g. ($2.8 \times 10^{-3}$ mole) of 2-chloro-4,7-dihydrazinoimidazo[4,5-*d*]pyridazine. After stirring for about 0.5 hr., 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 air-dried. The product was recrystallized from 20 ml. of 95% ethanol; yield 130 mg. (23%) of material which darkens slowly at 240° and higher.

*Anal.* Calcd. for $C_5HN_{10}Cl$: C, 25.4; H, 0.42; N, 59.2. Found: C, 25.5; H, 1.23; N, 59.3.

(This compound also explodes violently upon combustion.)

**2-Chloro-4,7-dibenzylaminoimidazo[4,5-*d*]pyridazine Hydrochloride.** — 2,4,7-Trichloroimidazo[4,5-*d*]pyridazine (0.75 g.) and 3 ml. of benzylamine were refluxed in 10 ml. of *n*-butyl alcohol for 2 hr. The solution was concentrated *in vacuo* to a crystalline semisolid. Ten ml. of 3 *N*

hydrochloric acid was added to the oily mixture and stirred well. The flocculent white precipitate 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-dibenzylaminoimidazo[4,5-*d*]pyridazine hydrochloride, m.p. 180–182° dec.

*Anal.* Calcd. for $C_{19}H_{17}N_6Cl\cdot HCl$: C, 56.8; H, 4.51; N, 20.9. Found: C, 56.5; H, 4.58; N, 20.9.

**4,7-Dibenzylaminoimidazo[4,5-*d*]pyridazine Hydrochloride.**—2 - Chloro - 4,7 - dibenzylaminoimidazo[4,5 - *d*]-pyridazine hydrochloride (0.5 g., $1.25 \times 10^{-3}$ 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. ($8.3 \times 10^{-3}$ mole) of ammonium chloride. The solution was allowed to stir for another hour and 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.[11] 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*-propyl alcohol; yield 0.19 g. (42.5%) of colorless needles, m.p. 200–202° dec.

*Anal.* Calcd. for $C_{19}H_{18}N_6\cdot HCl$: C, 62.2; H, 5.18; N, 22.9. Found: C, 61.6; H, 5.30; N, 22.8.

**Dichloro-(2 or 4 or 7)-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 milliliters of fuming nitric acid (sp. gr. 1.5) was added to the cold solution; there was no visible reaction. The temperature of the solution was then raised to 90° and maintained there for 10 min. 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°.

*Anal.* Calcd. for $C_5H_2N_4OCl_2$: C, 29.2; H, 0.98; N, 27.3. Found: C, 29.1; H, 1.20; N, 27.1.

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# Adjacent Nitro and Guanidino Groups. III. Preparation and Rearrangement of Some Pyrido[2,3-*e*]-*as*-triazine 1-Oxides[1]

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A series of 2-guanidino-3-nitro-5-substituted pyridines (II) has been prepared by treatment of the corresponding 2-chloro compounds (I) with guanidine in *t*-butyl alcohol. These compounds (II) undergo a rapid base-catalyzed cyclization to form 3-aminopyrido[2,3-*e*]-*as*-triazine 1-oxides (III). The cyclized compound (IIIa) rearranges in hot alkaline solution to form triazolo[4,5-*b*]pyridine 3-carboxamide (IV) and triazolo[4,5-*b*]pyridine (V). The 3-amino derivatives (III) were converted to the corresponding 3-hydroxy compounds (VI) with nitrous acid, and then to the 3-chloro compounds (VII) with phosphorus oxychloride. Displacement reactions on the 3-chloro compounds (VII) gave a series of pyrido[2,3-*e*]-*as*-triazine 1-oxides with various groups in the 3-position (VIII). The *N*-oxide function in compound IIIa was best removed by treatment with sodium dithionite at room temperature to form the 1,2-dihydro compound (X), followed by aromatization with potassium ferricyanide to form XI.

As a continuation of our work on the extension of the Arndt benzotriazine 1-oxide ring closure[2] to heterocyclic systems, we have now prepared some pyridine compounds containing adjacent nitro and guanidino groups and have studied their behavior in hot aqueous alkali. The formation of both the normal ring closed products, *e.g.*, 3-aminopyrido[2,3-*e*]-*as*-triazine 1-oxide (IIIa), and rearranged products, *e.g.*, triazolo[4,5-*b*]pyridine (IVa), was observed. The base-catalyzed rearrangement of fused ring triazine *N*-oxides, recently discovered in our laboratory, therefore occurs in the pyrido[2,3-*e*]-*as*-triazine 1-oxide series as well as in the 1,2,4-benzotriazine 1-oxide series described earlier.[1b]

Attempts to prepare 2-guanidino-3-nitropyridine (IIa) by the treatment of 2-chloro-3-nitropyridine (Ia) with a solution of guanidine in ethanol resulted predominantly in ether formation, the main product being 2-ethoxy-3-nitropyridine. A small quantity (4.6%) of the desired product (IIa) could be isolated and characterized, however. The use of guanidine in acetone solution also gave low yields with much tar formation.

Good yields of 2-guanidino-3-nitropyridine (IIa) were finally obtained by the slow addition of a solution of guanidine in *t*-butyl alcohol to a refluxing solution of 2-chloro-3-nitropyridine (Ia) in the same solvent. The reverse procedure, addition of the chloro compound to the guanidine solution, was much less satisfactory. Solutions of guanidine in *t*-butyl alcohol were conveniently prepared by adding an equivalent of guanidine hydrochloride to a suspension of sodium *t*-butoxide (prepared from sodium hydride) in *t*-butyl alcohol, heating for a

(1) For preceding papers in this series, see (a) J. A. Carbon, *J. Org. Chem.*, **26**, 455 (1961); (b) J. A. Carbon, *ibid.*, **27**, 185 (1962).

(2) F. Arndt, *Ber.*, **46**, 3522 (1913). See ref. 1 for a detailed discussion and leading references.