# The Synthesis of ω-Dialkylaminoalkylaminopyrazino[2,3-*d*]-, Pyrido[2,3-*d*]-, Imidazo[4,5-*c*]- and Imidazo[4,5-*d*]pyridazines

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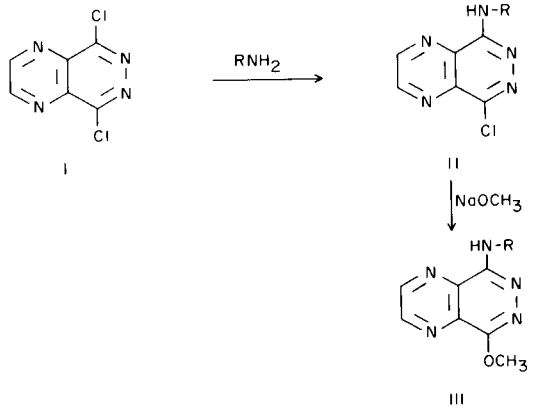
The synthesis of 5-chloro-8-(ω-dialkylaminoalkylamino)pyrazino[2,3-*d*]pyridazine (II) proceeded smoothly when 5,8-dichloropyrazino[2,3-*d*]pyridazine (I) was allowed to react with ω-dialkylaminoalkylamines. Similarly, the reaction of 5,8-dichloropyrido[2,3-*d*]pyridazine (IV) with ω-dialkylaminoalkylamines gave the two expected products 8-chloro-5-(ω-dialkylaminoalkylamino)pyrido[2,3-*d*]pyridazine (V) and 5-chloro-8-(ω-dialkylaminoalkylamino)pyrido[2,3-*d*]pyridazine (VI) in a 2:3 ratio. 4,7-Dichloroimidazo[4,5-*d*]pyridazine (XII) was found to be much less reactive towards nucleophilic substitutions and more vigorous conditions resulted in disubstituted products (XIII). 7-Chloroimidazo[4,5-*c*]pyridazine (XVIII) was also found to be much less reactive towards nucleophilic substitution. In both of these cases one of the imidazole nitrogen atoms was blocked by a tetrahydropyranyl group which increased the reactivities and led to the desired monosubstituted products XVII from XII and in the latter case the expected products (XIX).

The structural similarities of the nuclei of pyrazino[2,3-*d*]pyridazine and pyrido[2,3-*d*]pyridazine to pteridine as well as to the known quinoline antimalarials suggested the possibility of development of potential chemotherapeutic agents. The reaction of ω-dialkylaminoalkylamines with 5,8-dichloropyrazino[2,3-*d*]pyridazine (I) (2)




I II III

IIa & IIIa R = $-(CH_2)_3-N(CH_3)_2$

IIb & IIIb R = $-(CH_2)_3-N(CH_2CH_3)_2$

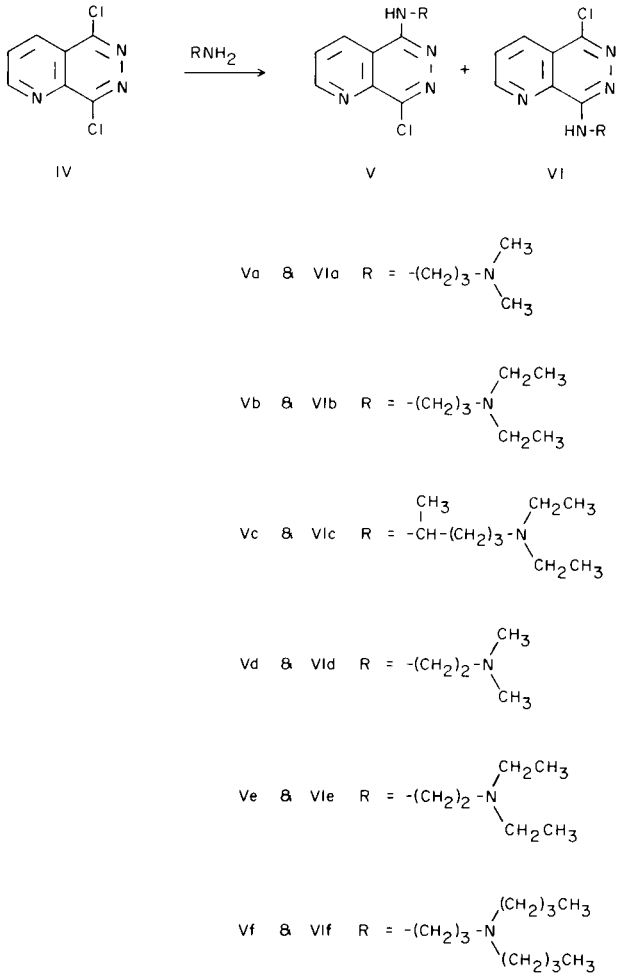
IIc R = $-CH(CH_3)-(CH_2)_3-N(CH_2CH_3)_2$

and 5,8-dichloropyrido[2,3-*d*]pyridazine (IV) (3) in ethanol led to the expected monosubstituted products (2). In the latter case the ratio of substitution at position 5 is about 1.5 times greater than that at position 8 due to resonance activation by pyridine nitrogen (4).

The two isomers 8-chloro-5-(ω-dialkylaminoalkylamino)pyrido[2,3-*d*]pyridazine (V) and 5-chloro-8-(ω-dialkylaminoalkylamino)pyrido[2,3-*d*]pyridazine (VI) were separated by column chromatography and the structures were assigned by NMR spectroscopy. The structures of V and VI were assigned on the basis that the proton at $C_4$ of the hydrochloride salt of VI is more deshielded than the corresponding proton in the hydrochloride salt of V and by independent synthesis of Vb and VIb from the known monochloromonoethoxypyrido[2,3-*d*]pyridazines.

The treatment of IIa and IIb with sodium methoxide in methanol gave the corresponding methoxides IIIa and IIIb. Similarly VIb gave the ethoxide (VIII) with sodium ethoxide in ethanol. However, the reaction of 5-ethoxy-8-chloropyrido[2,3-*d*]pyridazine and 5-chloro-8-ethoxypyrido[2,3-*d*]pyridazine (3) with 3-diethylaminopropylamine resulted in the replacement of the ethoxy groups giving Vb and VIb instead of the expected products VIII and VII respectively indicating the ethoxy group is a better leaving group than the chlorine atom particularly in these instances.

5-Hydroxy-8-chloropyrido[2,3-*d*]pyridazine (IX) (3) when heated with excess of ω-dialkylaminoalkylamines in a pressure bottle underwent substitution to give 5-hydroxy-8-(ω-dialkylaminoalkylamino)pyrido[2,3-*d*]pyridazine (X) but attempts to replace the chlorine atom in 5-chloro-8-hydroxypyrido[2,3-*d*]pyridazine (3) with ω-dialkylamino-



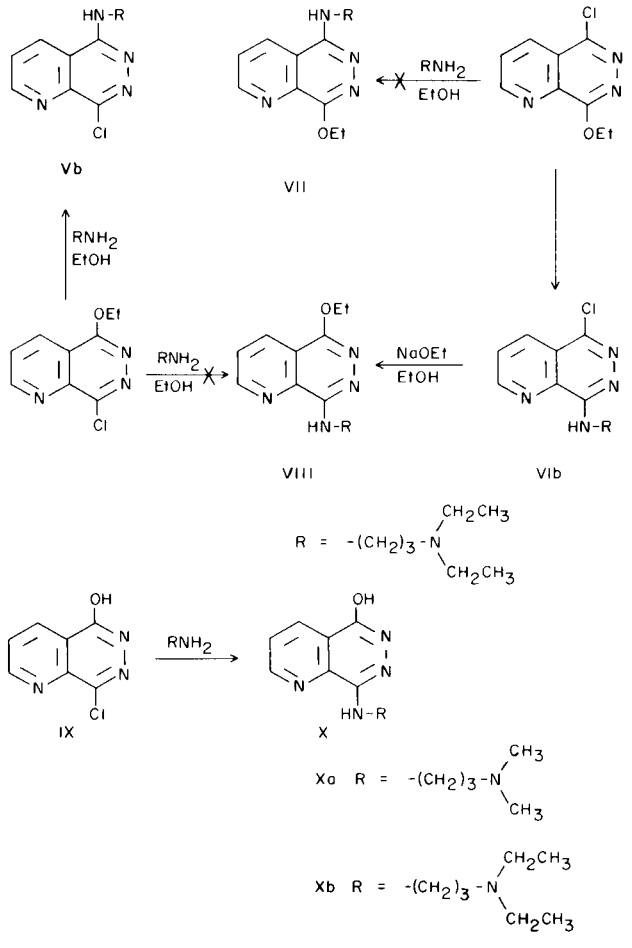
alkylamines resulted either in failures or tar formation.

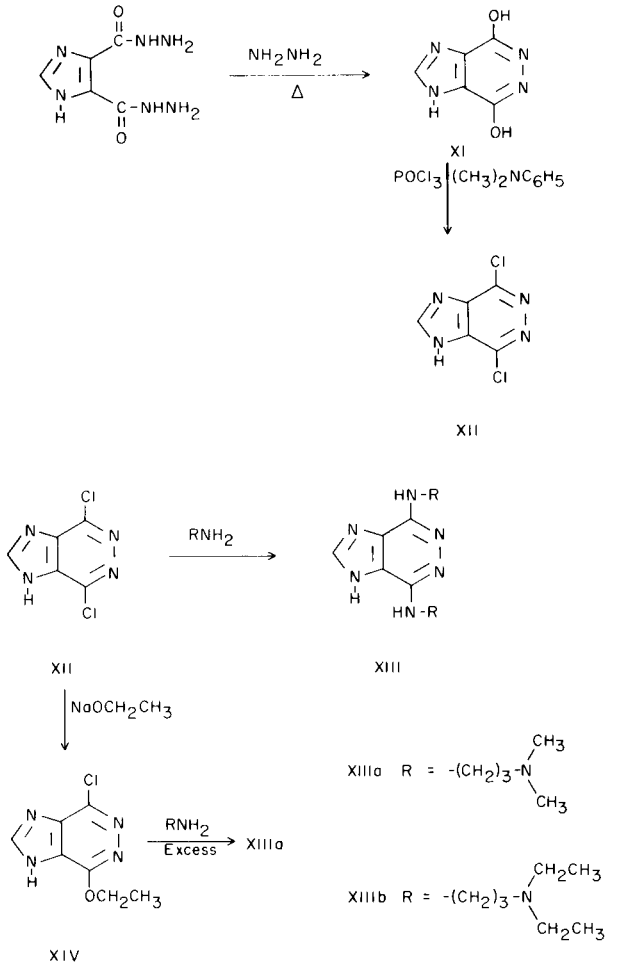
The imidazo[4,5-*c*]-, and imidazo[4,5-*d*]pyridazine ring systems can be considered as analogs of purines where only one nitrogen atom has been moved. Appropriately substituted imidazo[4,5-*c*]-, and imidazo[4,5-*d*]pyridazines may act as purine antagonists. Therefore, the synthesis of 4(7)-chloro-7(4)-(ω-dialkylaminoalkylamino)imidazo[4,5-*d*]pyridazines was undertaken. The starting material, 4,7-dichloroimidazo[4,5-*d*]pyridazine (XII), has been reported earlier from this laboratory in low yields (5). The procedure has been modified to give consistently yields of ~70%. Imidazole-4,5-dicarboxylic acid bishydrazide (5, 6, 7) has been cyclized to give 4,7-dihydroxyimidazo[4,5-*d*]pyridazine (XI) by refluxing with anhydrous hydrazine (8).

We have found that the compound XI produced by this method always gave good yields of XII upon chlorination, however, XI prepared from imidazole-4,5-dicarboxylic acid bishydrazide by heating in 10% aqueous hydrochloric acid solution either gave poor yields of XII or none at all. We have no satisfactory explanation for this observation.

4,7-Dichloroimidazo[4,5-*d*]pyridazine (XII) was found to be much less reactive towards ω-dialkylaminoalkylamines than 5,8-dichloropyrazino[2,3-*d*]pyridazine (I) or 5,8-dichloropyrido[2,3-*d*]pyridazine (IV). The reaction was carried out under a variety of conditions. The variables were temperature, pressure, solvents, absence of solvents and different molar ratios of reactants. At the reflux temperature with ethanol and 1-propanol no reaction took place and starting materials were recovered. At temperatures varying from 110 to 170° under pressure and reaction times from 12 to 22 hours in ethanol the only product isolated was 4,7-(bis-ω-dialkylaminoalkylamino)imidazo-[4,5-*d*]pyridazines (XIII) (9). No monosubstitution product could be isolated.

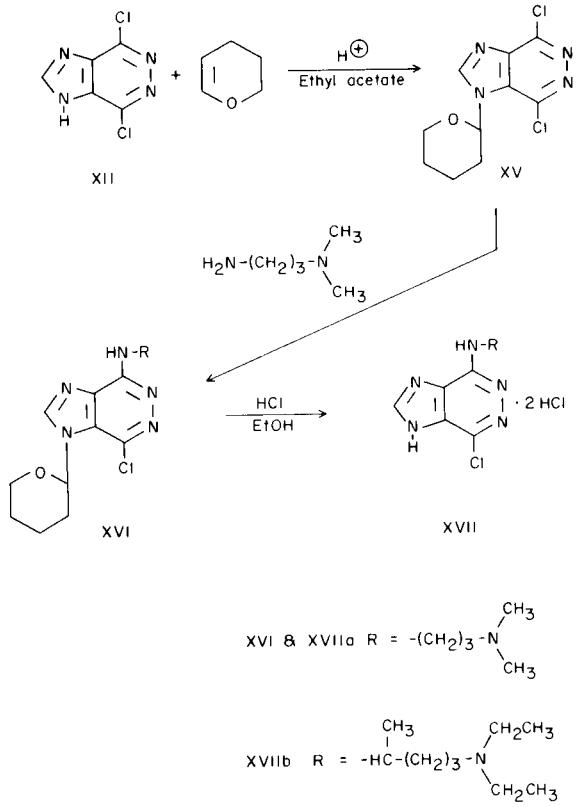
In order to obtain monodialkylamino-substituted products it was expected that these could be obtained by replacing the halogen atom of 4(7)-chloro-7(4)-ethoxyimidazo[4,5-*d*]pyridazine (XIV) by the dialkylaminoalkylamino moiety. Therefore, XII was treated with two moles of sodium ethoxide and XIV was obtained in 83% yield. When one mole of sodium ethoxide was used, the starting material XII was isolated.



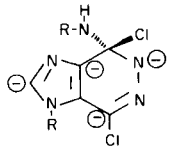


When 4(7)-chloro-7(4)-ethoxyimidazo[4,5-*d*]pyridazine (XIV) (1 mole) was allowed to react with dimethylaminopropylamine (1 or 2 moles) under a variety of temperatures and solvent conditions (1-butanol, 1-propanol, pyridine or no solvent), the principal products were 4,7-(bisdimethylaminopropylamino)imidazo[4,5-*d*]pyridazine (XIIIa) and 4(7)-dimethylaminopropylamino-7(4)-ethoxyimidazo[4,5-*d*]pyridazine. This latter product was never prepared in analytical purity but was identified by NMR spectroscopy. The movement of these two products on a neutral alumina column was so similar that they could not be separated completely by column chromatography. However, when XIV was treated with excess of dimethylaminopropylamine the only product isolated was XIIIa.

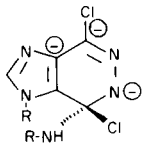
Robins (10) found that when the hydrogen atom on the $N^1$-nitrogen was blocked in purines, nucleophilic substitution took place more readily at the various positions. Likewise, Carbon (10) has shown that in the case of 1-benzyl-4,7-dichloroimidazo[4,5-*d*]pyridazine, a series of 1-benzyl-4-substituted-7-chloroimidazo[4,5-*d*]pyridazines were obtained with a variety of nucleophilic reagents. Therefore, we have blocked the $N^1$-nitrogen atom with an easily removable protective group, namely the tetrahydropyranyl group (12). 4,7-Dichloro-1-(tetrahydro-2′-pyranyl)-imidazo[4,5-*d*]pyridazine (XV) was prepared by the reaction of XII with 2,3-dihydro-4-*H*-pyran in 70% yield in the presence of catalytic amounts of acid. The pyranyl group of XV was lost by heating 2-3° above the melting point and the melt resolidified to give XII. The resolidified melt was shown to be identical with XII by TLC and melting point.



The reaction of 4,7-dichloro-1-(tetrahydro-2′-pyranyl)-imidazo[4,5-*d*]pyridazine (XV) with 3-dimethylaminopropylamine gave a mixture of 7-chloro-4-(3-dimethylaminopropylamino)-1-(tetrahydro-2′-pyranyl)imidazo[4,5-*d*]pyridazine (XVI) and 4,7-dichloroimidazo[4,5-*d*]pyridazine (XII). One can minimize but never completely eliminate the formation of XII by allowing the reaction to proceed in a dipolar aprotic solvent (DMSO) at reduced temperatures. This reaction was studied in different solvents such as water, ethanol, pyridine, benzene, toluene and DMSO. The structure of XVI was assigned on the following basis: (a) Nucleophilic attack on position 7 should be greatly reduced because of steric hindrance of the closely adjacent tetrahydropyranyl group on $N^1$ (11); (b) substitution at position 4 can be shown to be favored by the following transition state structures A and B:

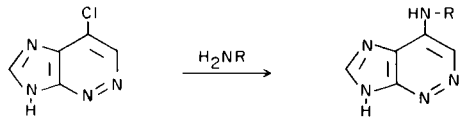


A

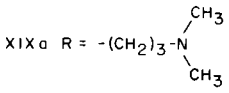


B

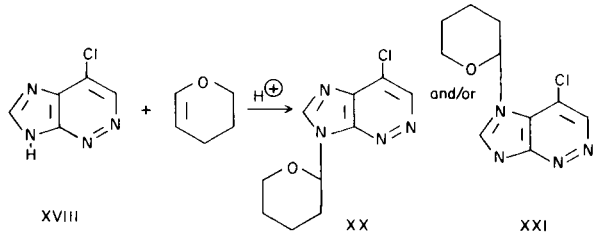
In the case of substitution at $C_4$ (A) 4 different charge-distributed structures are possible while in the case of substitution at $C_7$ (B) only 3 different charge-distributed structures are possible, therefore, (A) should be more stable and consequently 4-substitution should be favored.



XVIII XIX



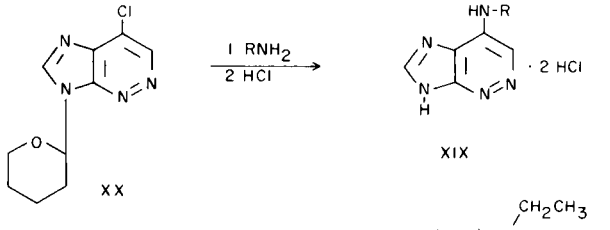
XIXa



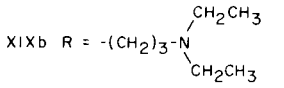
XVIII XX XXI

The removal of the protective group in XVI and the formation of the desired product, 4-(3-dimethylaminopropylamino)-7-chloroimidazo[4,5-*d*]pyridazine (XVIIa) with hydrochloric acid in ethanol proceeded smoothly. Likewise, 5-diethylamino-2-aminopentane was allowed to react with XV in DMSO followed by treatment of the product with hydrochloric acid. It gave 7(4)-chloro-4(7)-(5-diethylamino-2-pentylamino)imidazo[4,5-*d*]pyridazine (XVIIb) in 26% yield. 5-Diethylamino-2-aminopentane was less reactive than 3-dimethylaminopropylamine.

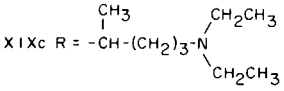
In the case of 7-chloroimidazo[4,5-c]pyridazine (XVIII) (13) replacement of the chlorine atom was found to be very difficult. The reaction of XVIII with 3-dimethylaminopropylamine at 170° in ethanol under pressure for 12 hours gave the expected product, 7-(3-dimethylaminopropylamino)imidazo[4,5-c]pyridazine (XIXa). However, the reaction of XVIII with other ω-dialkylaminoalkylamines resulted either in failure or great difficulty was experienced in the isolation of products. Because of the difficulties experienced in the nucleophilic displacement of the halogen atom in XVII, the imidazole nitrogen atom was blocked with the tetrahydropyranyl group found so successful for XII.



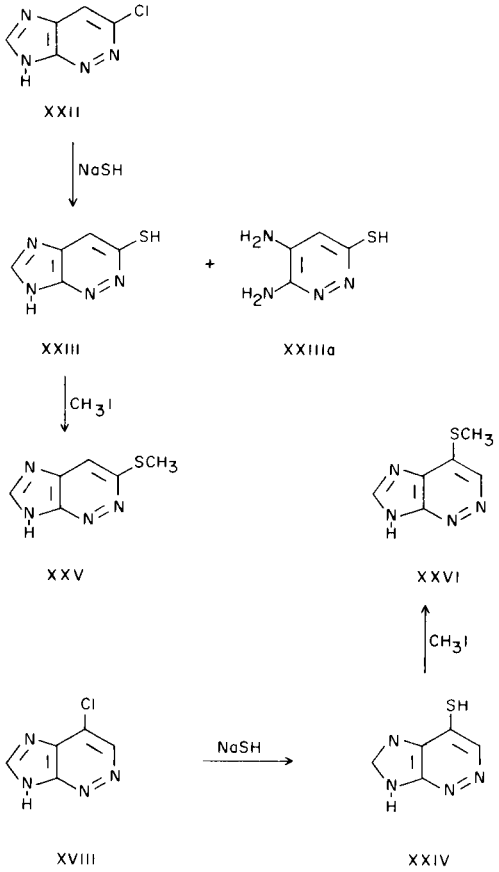
XX XIX



XIXb



XIXc



XXII XXIII XXIIIa XXV XXVI XVIII XXIV

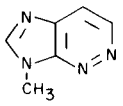
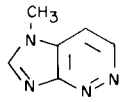
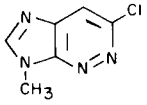
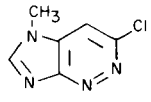
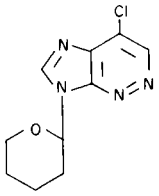
Theoretically, the reaction of XVIII with 2,3-dihydro-4*H*-pyran could give rise to either $N^3$ and $N^1$-substitution or a mixture of both isomers XX and XXI. A thorough study of the reaction mixture by TLC revealed the presence of one product along with some unreacted XVIII. Following the work-up of the reaction mixture only one spot was observed when chromatographed. The melting point of the product was sharp.

The tetrahydro-2′-pyranyl group was assigned to position $N^3$ on the following basis: (a) the steric hindrance of the chlorine atom at $C_7$ will hinder the substitution at $N^1$ of the imidazole ring (11); (b) a comparison of the ultraviolet

spectrum of 7-chloro-3-(tetrahydro-2′-pyranyl)imidazo-[4,5-c]pyridazine (XX) with the compounds in Table I prepared in this laboratory (14) eliminates the substitution at $N^1$ as a possible structure.

Compound XX, when allowed to react with 3-diethylaminopropylamine and 2-amino-5-diethylaminopentane, respectively, followed by treatment with hydrochloric acid, gave XIXb and XIXc.

TABLE I

| | λ max (ethanol) | | |
|---|---|---|---|
| | mμ | mμ | mμ |
|  | 202 | 254.5 | 286 |
|  | 209 | 270 | |
|  | 210 | 260 | 299 |
|  | 212.5 | 281.5 | |
|  | 208 | 259 | 289 |

XX

The lack of reactivity of 6-chloroimidazo[4,5-c]-pyridazine (XXII) (15) and the very low reactivity of 7-chloroimidazo[4,5-c]pyridazine (XVIII) with dialkylaminoalkylamines prompted the synthesis of imidazo-[4,5-c]pyridazine-6-thiol (XXIII) and imidazo[4,5-c]-pyridazine-7-thiol (XXIV). In the preparation of imidazo-[4,5-c]pyridazine-6-thiol (XXIII) by the reaction of XXII with sodium hydrosulfide (16), 3,4-diamino-6-pyridazinethiol (XXIIIa) was isolated as a by-product from the ring opening of the imidazole ring.

Compound XXIII and XXIV gave 6-methylthioimidazo-[4,5-c]pyridazine (XXV) and 7-methylthioimidazo[4,5-c]-pyridazine (XXVI) when treated with methyl iodide in aqueous potassium hydroxide solution (17). The nucleophilic displacement of the methylthio groups with amines and various other reagents is being studied in this laboratory.

## EXPERIMENTAL

Melting points were taken on a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared, ultraviolet and nuclear magnetic resonance spectra were recorded on Perkin-Elmer 337, Bausch and Lomb Spectronic 505 and Varian A-60 A spectrometers, respectively. The nuclear magnetic resonance spectra were compared with TMS as an internal standard except when deuterium oxide was the solvent, then DSS was used as an internal standard.

General Procedure for 5-Chloro-8-(ω-dialkylaminoalkylamino)-pyrazino[2,3-*d*]pyridazine (II).

5,8-Dichloropyrazino[2,3-*d*]pyridazine (I) (1 mole) was added to 10 ml. of absolute ethanol and to this solution ω-dialkylaminoalkylamine (2 moles) was added. The solution was heated under reflux for 4 hours. It was evaporated to dryness under reduced pressure, the residue was dissolved in 10 ml. of water and extracted with 4 x 25 ml. portions of chloroform. The chloroform extracts were combined, washed with 10 ml. of water, dried over anhydrous magnesium sulfate and evaporated to dryness to give a yellow residue.

5-Chloro-8-(3-dimethylaminopropylamino)pyrazino[2,3-*d*]pyridazine (IIa).

The yellow residue was dissolved in ethanol and treated with charcoal. The filtrate was evaporated to dryness to give IIa, 0.54 g., in quantitative yield. Recrystallization from ligroin (90-120° B.P.) gave yellow crystals, m.p. 137-138°; U.V. λ max (95% ethanol) 213 (ε, 15,900) 230 (Sh) (ε, 11,900), 268 (ε, 10,150), 387 mμ (ε, 4,350); infrared $cm^{-1}$, 3420(m), 3200(w), 3045(w), 2950(m), 2852(w), 2820(m), 2765(m), 1587(s), 1545(m), 1530(s), 1460(m), 1420(w), 1405(m), 1395(m), 1315(w), 1250(w), 1235(m), 1160(m), 1100(m), 1075(m), 1038(w), 1017(m), 992 (m),980(m), 892(m), 775(w), 685(w), 650(w), 540(w), 433(m), (potassium bromide); NMR (deuteriochloroform) 9.25 δ ($C_2$-H doublet J = 2 cps), 9.08 δ ($C_3$-H doublet J = 2 cps), 7.75-8.1 δ (-N-H broad peak), 3.86 δ ($C_2$′-H quartet), 2.53 δ ($C_3$′-H triplet), 2.31 δ (-N-$(CH_3)_2$ singlet), 1.7-2.25 δ ($C_2$′-H multiplet).

*Anal.* Calcd. for $C_{11}H_{15}ClN_6$: C, 49.53; H, 5.67; N, 31.51. Found: C, 49.63; H, 5.76; N, 31.83.

5-Chloro-8-(3-diethylaminopropylamino)pyrazino[2,3-*d*]pyridazine (IIb).

The yellow residue was dissolved in ethanol and treated with charcoal. The filtrate was evaporated to dryness and the residue was recrystallized from ligroin (90-120° B.P.) to give golden yellow needles, m.p. 144-145°, 0.73 g. (yield 82%); U.V. λ max (95% ethanol) 213 (ε, 16,300), 231 (Sh) (ε, 12,200) 269 (ε, 9,800), 390 mμ (ε, 4,300).

*Anal.* Calcd. for $C_{13}H_{19}ClN_6$: C, 52.97; H, 6.49; N, 28.52. Found: C, 53.07; H, 6.64; N, 28.29.

5-Chloro-8-(5-diethylamino-2-pentylamino)pyrazino[2,3-*d*]pyridazine (IIc).

The yellow oily residue was purified on a neutral alumina (50 g. Woelm, Grade I) column and eluted with ~300 ml. of ligroin (90-120° B.P.) followed by elution with ethyl acetate. The ethyl acetate fraction on evaporation gave an oily product which was recrystallized from petroleum ether to give 0.7 g. (yield 55%) of yellow needles, m.p. 53-54°; U.V. λ max (95% ethanol) 213 (ε, 15,700), 229 (Sh) (ε, 11,800), 269 (ε, 9,650), 390 mμ (ε, 5,300).

*Anal.* Calcd. for $C_{15}H_{23}ClN_6$: C, 55.81; H, 7.18; N, 26.03. Found: C, 55.38; H, 6.99; N, 26.37.

8-(3-Dimethylaminopropylamino)-5-methoxypyrazino[2,3-*d*]pyridazine Dihydrochloride (IIIa).

An excess of sodium metal was dissolved in 1 ml. of absolute methanol under anhydrous conditions. To this 1.0 g. (0.037 mole) of IIa was added and refluxed for 3 hours. The solvent was removed under reduced pressure and the residue was suspended in 10 ml. of water and extracted with 4 x 25 ml. portions of chloroform. The combined chloroform extract was dried over anhydrous magnesium sulfate and evaporated to dryness to give an orange residue. This was dissolved in absolute ethanol and concentrated hydrochloric acid was added. The ethanolic solution was evaporated to dryness followed by repeated addition of a benzene and ethanol mixture and evaporation until the excess hydrochloric acid was removed. A tan-colored powder, 0.795 g. (yield 61%) m.p. 157-159°, was obtained; U.V. λ max (95% ethanol) 216 (ε, 15,400), 272 (ε, 10,550), 333 mμ (ε, 1,300); infrared $cm^{-1}$, 3425(w), 3020(w), 2950(w), 2900(w), 2575(w), 2450(w), 1650(s), 1600(s), 1570(s), 1500(m), 1485(m), 1465(m), 1450(w), 1430(w), 1420(w), 1400(w), 1390(m), 1360(w), 1315(w), 1265(w), 1235(m), 1227(m), 1175(w), 1128(s), 1080(w), 1055(w), 1025(w), 994(w), 970(w), 930(w), 900(w), 860(w), 850(w), 812(w), 770(m), 725(w), 705(w), 675(w), 655(w), 605(w), 555(w), 480(w), 435(m), (potassium bromide); NMR (deuterium oxide) 9.4 δ ($C_2$-H and $C_3$-H singlet), 4.25 δ (-$OCH_3$ singlet), 3.9 δ ($C_1'$-H triplet), 3.25-3.6 δ ($C_2'$-H multiplet), 3.0 δ (-N-($CH_3$)$_2$ singlet), 2.16-2.7 δ ($C_2'$-H multiplet).

*Anal.* Calcd. for $C_{12}H_{18}N_6O \cdot 2HCl \cdot H_2O$: C, 40.79; H, 6.28; N, 23.79. Found: C, 41.04; H, 6.57; N, 23.33.

8-(3-Diethylaminopropylamino)-5-methoxypyrazino[2,3-*d*]pyridazine (IIIb).

The procedure was the same as that described for the preparation of IIIa. The free base was recrystallized from ligroin (90-120° B.P.), after treatment with charcoal, to give yellow plates 0.874 g. (yield 82%), m.p. 93-95°; U.V. λ max (95% ethanol) 215 (ε, 17,100), 272 (ε, 11,100), 335 mμ (ε, 1,400).

*Anal.* Calcd. for $C_{14}H_{22}N_6O$: C, 57.91; H, 7.64; N, 28.94. Found: C, 58.16; H, 7.85; N, 28.96.

5-Chloro-8-(3-dimethylaminopropylamino)pyrido[2,3-*d*]pyridazine Dihydrochloride (VIa).

To a suspension of 3.0 g. of 5,8-dichloropyrido[2,3-*d*]pyridazine (IV) (0.015 mole) in 50 ml. of absolute ethanol was added dropwise 3.0 g. of 3-dimethylaminopropylamine (0.03 mole). The mixture was heated under reflux on the steam bath for four hours, then the solvent was removed by evaporation under reduced pressure. The residue was dissolved in water and extracted with chloroform. The chloroform solution was dried with magnesium sulfate, filtered, and evaporated under reduced pressure to a semi-solid residue containing the two isomeric products. The two components were separated by passing the mixture through a column containing 150 g. of neutral aluminum oxide using as an eluent a solution composed of four parts of benzene and one part of ethyl acetate. 5-Chloro-8-(3-dimethylaminopropylamino)pyrido-[2,3-*d*]pyridazine was collected as the first eluate. This component was isolated as the dihydrochloride salt. This was accomplished by dissolving it in anhydrous ether and passing dry hydrogen chloride through the solution. It was purified by solution in absolute ethanol and precipitation by the addition of anhydrous ether to give 1.8 g. (31%) of the dihydrochloride salt which analyzed as the monohydrate, m.p. 243°; U.V. λ max (water) 204 (ε, 32,200), 221 (Sh) (ε, 12,200), 258 (ε, 6,900), 334 mμ (ε, 5,100); infrared $cm^{-1}$, 3410(m), 3350-2100 broad absorption(s), 1650(s), 1580(s), 1560(s), 1530(s), 1480(s), 1450(s), 1400(m), 1360(s), 1310(s), 1260(w), 1238(w), 1183(s), 1170(s), 1152(m), 1115(w), 1052(m), 1035(m), 990(s), 932(w), 877(w), 838(s), 812(s), 778(m), 750(m), 725(w), 655(m), 630(m), 612 (w), 560(w), 528(m), 480(w), 420(w), (potassium bromide); NMR (deuterium oxide), 9.37 δ ($C_2$-H doublet of doublet $J_{23}$ = 6, $J_{24}$ = 1.5 cps), 8.87 δ ($C_4$-H doublet of doublet $J_{43}$ = 8.5, $J_{42}$ = 1 cps), 8.28 δ ($C_3$-H two doublets J = 4.5 cps), 3.88 δ ($C_1'$-H triplet), 3.47 δ ($C_3'$-H multiplet), 3.02 δ (-N-($CH_3$)$_2$ singlet), 2.37 δ ($C_2'$-H multiplet).

*Anal.* Calcd. for $C_{12}H_{16}ClN_5 \cdot 2HCl \cdot H_2O$: C, 40.56; H, 5.63; N, 19.71. Found: C, 40.65; H, 5.79; N, 19.32.

8-Chloro-5-(3-dimethylaminopropylamino)pyrido[2,3-*d*]pyridazine Dihydrochloride (Va).

8-Chloro-5-(3-dimethylaminopropylamino)pyrido[2,3-*d*]pyridazine (Va) was collected as the second eluate by the procedure as described above. This component was isolated as an ether insoluble solid upon evaporation of the eluent. However, to facilitate handling, it was converted to the dihydrochloride salt by suspending it in dry benzene and passing dry hydrogen chloride through the solution. It was purified by solution in absolute ethanol and precipitation by the addition of anhydrous ether to give 2.2 g. (38%) of the dihydrochloride salt, m.p. 246°; U.V. λ max (water), 208 (ε, 24,400), 226 (Sh) (ε, 11,800), 259 (ε, 5,400), 350 mμ (ε, 4,550); infrared $cm^{-1}$, 3450(w), 3150-2450 broad absorption(s), 1640(s), 1600(m), 1570(m), 1490(m), 1460(s), 1440(m), 1400(m), 1330(s), 1320(w), 1240(m), 1185(w), 1171(m), 1112(w), 1080(w), 1028(m), 1001(s), 990(m), 929(w), 870(w), 838(w), 825(w), 810(m), 790(m), 748(w), 680(w), 655(m), 612(w), 558(w), 532(w), 470(w), (potassium bromide); NMR (deuterium oxide), 9.37 δ ($C_2$-H doublet of doublet $J_{23}$ = 4.5, $J_{24}$ = 1 cps), 9.06 δ ($C_4$-H doublet of doublet $J_{43}$ = 8.5, $J_{42}$ = 1.5 cps), 8.22 δ ($C_3$-H two doublets J = 4.5 cps), 3.83 δ ($C_1'$-H triplet), 3.45 δ ($C_3'$-H multiplet), 3.02 δ (-N-($CH_3$)$_2$ singlet), 2.35 δ ($C_2'$-H multiplet).

*Anal.* Calcd. for $C_{12}H_{16}ClN_5 \cdot 2HCl$: C, 42.73; H, 5.33; N, 20.77. Found: C, 42.60; H, 5.54; N, 20.61.

5-Chloro-8-(3-diethylaminopropylamino)pyrido[2,3-*d*]pyridazine (VIb).

Two g. of 5,8-dichloropyrido[2,3-*d*]pyridazine (IV) (0.01 mole) in 30 ml. of absolute ethanol was allowed to react with 2.6 g. of 3-diethylaminopropylamine (0.02 mole) under conditions similar to those described for VIa. The product was separated from its isomer by a procedure similar to that described for VIa except that benzene was used as the eluent. Recrystallization from ligroin (90-120° B.P.) yielded 1.0 g. (34%) of colorless needles, m.p. 89-90°; U.V. λ max (95% ethanol), 205 (ε, 26,200), 224 (Sh) (ε, 13,300), 260 (ε, 6,450), 347 mμ (ε, 5,400).

*Anal.* Calcd. for $C_{14}H_{20}ClN_5$: C, 57.23; H, 6.85; N, 23.89. Found: C, 57.73; H, 6.84; N, 24.17.

8-Chloro-5-(3-diethylaminopropylamino)pyrido[2,3-*d*]pyridazine (Vb).

8-Chloro-5-(3-diethylaminopropylamino)pyrido[2,3-*d*]pyridazine (Vb) was obtained as the second eluate by the procedure described for VIb. Recrystallization from ligroin (90-120° B.P.) yielded 1.0 g. (34%) of slightly yellowish needles, m.p. 120.5-121.5°; U.V. λ max (95% ethanol), 208 (ε, 27,200), 228 (Sh) (ε, 11,800), 260 (ε, 5,900), 354 mμ (ε, 5,500).

*Anal.* Calcd. for $C_{14}H_{20}ClN_5$: C, 57.23; H, 6.85; N, 23.89. Found: C, 57.54; H, 6.80; N, 24.05.

8-Chloro-5-(3-diethylaminopropylamino)pyrido[2,3-*d*]pyridazine (Vb) from 8-Chloro-5-ethoxypyrido[2,3-*d*]pyridazine.

To a solution of 0.42 g. of 8-chloro-5-ethoxypyrido[2,3-*d*]-pyridazine (0.002 mole) in 10 ml. of absolute ethanol was added 0.26 g. of 3-diethylaminopropylamine (0.002 mole). The mixture was heated under reflux on the steam bath for 48 hours, then the solvent was removed by evaporation under reduced pressure. The residue was dissolved in dilute hydrochloric acid and extracted with chloroform. The starting material (0.17 g.) was recovered from the chloroform solution. The aqueous layer was made basic with dilute sodium hydroxide and extracted with chloroform. The chloroform solution was dried with magnesium sulfate and evaporated under reduced pressure to an oil. The oil was dissolved in hot ligroin (90-120° B.P.) and allowed to cool. The product was collected from the ligroin solution by filtration. The yield was 0.05 g. (8%) m.p. 120-121°.

5-Chloro-8-(diethylamino-2-pentylamino)pyrido[2,3-*d*]pyridazine Dihydrochloride (VIc).

Three g. of 5,8-dichloropyrido[2,3-*d*]pyridazine (IV) (0.015 mole) was treated with 4.74 g. of 5-diethylamino-2-aminopentane (0.03 mole) under conditions similar to those described for VIa. The product was separated from its isomer by a similar procedure except that a 4% solution of ethyl acetate in benzene was used as the eluent and the column was prepared from basic aluminum oxide, activity 1. The product was isolated as the dihydrochloride salt. The yield was 1.1 g. (19%), m.p. 174-175°; U.V. λ max (water), 205 (ε, 39,500), 219 (Sh) (ε, 13,900), 259 (ε 6,700), 339 mμ (ε, 5,150).

*Anal.* Calcd. for $C_{16}H_{24}ClN_5 \cdot 2HCl$: C, 48.68; H, 6.69; N, 17.74. Found: C, 48.95; H, 6.65; N, 17.87.

8-Chloro-5-(5-diethylamino-2-pentylamino)pyrido[2,3-*d*]pyridazine Dihydrochloride (Vc).

8-Chloro-5-(5-diethylamino-2-pentylamino)pyrido[2,3-*d*]pyridazine (Vc) was obtained as the second eluate from VIc above. It was isolated as the dihydrochloride salt. The yield was 1.1 g. (19%), m.p. 178-181°; U.V. λ max (water), 206 (ε, 29,150), 227 (Sh) (ε, 8,900), 259 (ε, 4,500), 347 mμ (ε, 4,000).

*Anal.* Calcd. for $C_{16}H_{24}ClN_5 \cdot 2HCl$: C, 48.68; H, 6.69; N, 17.74. Found: C, 48.90; H, 6.74; N, 17.60.

5-Chloro-8-(dimethylaminoethylamino)pyrido[2,3-*d*]pyridazine (VId).

Three g. of 5,8-dichloropyrido[2,3-*d*]pyridazine (IV) (0.015 mole) and 2.34 g. of 3-dimethylaminoethylamine (0.03 mole) were allowed to react under conditions similar to those described for VIa. The product was separated from its isomer by a similar procedure except that a 5% solution of ethyl acetate in benzene was used as the eluent. Recrystallization by dissolving it in hot benzene and adding ligroin (90-120° B.P.) until the hot solution became turbid and then cooling yielded 1.4 g. (38%) of white needles, m.p. 112-113°; U.V. λ max (95% ethanol), 208 (ε, 36,300), 220 (Sh), (ε, 24,400), 257 (ε, 10,700), 342 mμ (ε, 5,400).

*Anal.* Calcd. for $C_{11}H_{14}ClN_5$: C, 52.49; H, 5.61; N, 27.82. Found: C, 52.80; H, 5.81; N, 28.11.

8-Chloro-5-(dimethylaminoethylamino)pyrido[2,3-*d*]pyridazine (Vd).

8-Chloro-5-(dimethylaminoethylamino)pyrido[2,3-*d*]pyridazine (Vd) was obtained as the second eluate by the procedure described for VId. Recrystallization by dissolving it in hot benzene then adding ligroin (90-120° B.P.) until the hot solution became turbid and cooling yielded 1.1 g. (30%) of white needles, m.p. 172-172.5°; U.V. λ max (95% ethanol), 208 (ε, 27,600), 220 (Sh) (ε, 13,700), 257 (ε, 6,100), 350 mμ (ε, 5,100).

*Anal.* Calcd. for $C_{11}H_{14}ClN_5$: C, 52.49; H, 5.61; N, 27.82. Found: C, 52.67; H, 5.86; N, 27.58.

5-Chloro-8-(diethylaminoethylamino)pyrido[2,3-*d*]pyridazine Dihydrochloride (VIe).

Three g. of 5,8-dichloropyrido[2,3-*d*]pyridazine (IV) (0.015 mole) and 3.48 g. of 3-diethylaminoethylamine (0.03 mole) were allowed to react under conditions similar to those described for VIa. The product was separated from its isomer by a similar procedure except that benzene was used as the eluent. It was isolated as the dihydrochloride salt. The yield was 1.6 g. (30%), m.p. 237-238°; U.V. λ max (95% ethanol) 206 (ε, 25,900) 218 (Sh) (ε, 13,600), 258 (ε, 7,850), 334 mμ (ε, 5,800).

*Anal.* Calcd. for $C_{13}H_{18}ClN_5 \cdot 2HCl$: C, 44.27; H, 5.71; N, 19.86. Found: C, 44.01; H, 6.05; N, 19.60.

8-Chloro-5-(diethylaminoethylamino)pyrido[2,3-*d*]pyridazine Dihydrochloride (Ve).

8-Chloro-5-(diethylaminoethylamino)pyrido[2,3-*d*]pyridazine (Ve) was obtained as the second eluate by the procedure described for VIe. It was isolated as the dihydrochloride salt. The yield was 0.89 g. (15%), m.p. 235-237°; U.V. λ max (95% ethanol), 208 (ε, 31,600), 220 (Sh) (ε, 14,200), 256 (ε, 7,900), 335 mμ (ε, 5,800).

*Anal.* Calcd. for $C_{13}H_{18}ClN_5 \cdot 2HCl$: C, 44.27; H, 5.71; N, 19.86. Found: C, 44.50; H, 6.08; N, 19.59.

5-Chloro-8-(3-di-*n*-butylaminopropylamino)pyrido[2,3-*d*]pyridazine Dihydrochloride (VIf).

Three g. of 5,8-dichloropyrido[2,3-*d*]pyridazine (IV) (0.015 mole) was allowed to react with 5.6 g. of 3-di-*n*-butylaminopropylamine (0.03 mole) under conditions similar to those described for VIa. The product was separated from its isomer by a similar procedure except that a 4% solution of ethyl acetate in ligroin (90-120° B.P.) was used as the eluent. The product was isolated as the dihydrochloride salt. The yield was 1.2 g. (23%), m.p. 160-162°; U.V. λ max (water), 203 (ε, 31,300), 225 (Sh), (ε, 13,100), 257 (ε, 7,600), 333 mμ (ε, 5,400).

*Anal.* Calcd. for $C_{18}H_{28}ClN_5 \cdot 2HCl$: C, 51.13; H, 7.13; N, 16.56. Found: C, 51.24; H, 7.38; N, 16.85.

8-Chloro-5-(3-di-*n*-butylaminopropylamino)pyrido[2,3-*d*]pyridazine Dihydrochloride (Vf).

8-Chloro-5-(3-di-*n*-butylaminopropylamino)pyrido[2,3-*d*]pyridazine (Vf) was obtained as the second eluate by the procedure described for VIf. It was isolated as the dihydrochloride salt. The yield was 1.4 g. (27%), m.p. 157-158°; U.V. λ max (water), 206 (ε, 28,950), 225 (Sh) (ε, 12,000), 257 (ε, 6,400), 340 mμ (ε, 4,950).

*Anal.* Calcd. for $C_{18}H_{28}ClN_5 \cdot 2HCl$: C, 51.13; H, 7.13; N, 16.56. Found: C, 51.42; H, 7.21; N, 16.75.

5-Ethoxy-8-(3-diethylaminopropylamino)pyrido[2,3-*d*]pyridazine Dihydrochloride (VIII).

To a solution of 0.45 g. of 5-chloro-8-(3-diethylaminopropylamino)pyrido[2,3-*d*]pyridazine (VIb) (0.0015 mole) in 3 ml. of absolute ethanol was added dropwise, under anhydrous conditions, a solution of 10 ml. of absolute ethanol in which a slight molar excess of sodium metal had been dissolved. The reaction mixture was refluxed on the steam bath for forty-two hours then the solvent was removed by evaporation under reduced pressure. The residue was dissolved in water and extracted with chloroform. The chloroform solution was dried with magnesium sulfate, filtered, and evaporated under reduced pressure to give a heavy syrup. The product was isolated as the dihydrochloride salt by dissolving the

syrup in anhydrous ether and passing dry hydrogen chloride through the solution. It was purified by solution in absolute ethanol and precipitation by the addition of anhydrous ether. The yield was 0.30 g. (57%) of white amorphous crystals, m.p. 130-131°; U.V. λ max (water), 203 (ε, 29,350), 233 (Sh) (ε, 7,200), 260 (ε, 6,350), 323 mμ (ε, 1,650); infrared $cm^{-1}$, 3420(s), 3100-2600 broad absorption(s), 2500(m), 2100(w), 1660(s), 1620(s), 1590(s), 1560(m), 1520(m), 1498(s), 1460(s), 1410(s), 1375(s), 1360(s), 1340(s), 1315(m), 1260(w), 1235(m), 1222(s), 1155(s), 1122(s), 1098(w), 1084(s), 1078(s), 1060(m), 1038(m), 1015(m), 1000(w), 980(w), 932(w), 890(w), 868(w), 830(m), 800(s), 778(m), 768(m), 740(m), 710(w), 670(m), 652(m), 637(m), 605(w), 553(w), 500(m), (potassium bromide); NMR (deuterium oxide) 9.37 δ ($C_2$-H doublet of doublet $J_{23}$ = 5, $J_{24}$ = 1.5 cps), 8.68 δ ($C_4$-H doublet of doublet $J_{43}$ = 8, $J_{42}$ = 1.5 cps), 8.21 δ ($C_3$-H two doublets J = 5 cps), 4.58 δ (-O-$CH_2$-quartet), 3.90 δ (-N-$CH_2$-triplet), 3.45 δ (-$CH_2$-N-($CH_2$)$_2$-multiplet), 2.45 δ (-C-$CH_2$-C-multiplet), 1.50 δ (-C-$CH_3$-multiplet).

*Anal.* Calcd. for $C_{16}H_{25}N_5O$·2HCl: C, 51.07; H, 7.23; N, 18.61. Found: C, 51.15; H, 7.26; N, 18.93.

5-Hydroxy-8-(3-dimethylaminopropylamino)pyrido[2,3-*d*]pyridazine (Xa).

To a solution of 35 g. of 3-dimethylaminopropylamine and 100 ml. of absolute ethanol in a stainless steel rocking autoclave was added 2.0 g. of 8-chloro-5-hydroxypyrido[2,3-*d*]pyridazine (IX) (0.011 mole). The solution was heated at 200° for sixteen hours, cooled, filtered and evaporated under reduced pressure to a dark syrup. The residue was dissolved in a 10% sodium hydroxide solution and extracted with ether. The aqueous layer was neutralized with concentrated hydrochloric acid then made basic with sodium bicarbonate and extracted with chloroform. The chloroform solution was dried with magnesium sulfate, filtered, and evaporated under reduced pressure to a thick syrup which slowly crystallized on standing. The product was purified by recrystallization from benzene, then recrystallized again from ligroin (90-120° B.P.) to yield 0.7 g. (28%) of yellowish needles, m.p. 124-125°; U.V. λ max (95% ethanol) 207 (ε, 22,300), 269 mμ (ε, 4,600); infrared $cm^{-1}$, 3410(s), 3260(s), 3020(s), 2925(s), 2860(s), 2820(s), 2760(s), 1670(s), 1610(s), 1590(s), 1530(s), 1480(s), 1460(s), 1430(s), 1380(m), 1360(m), 1340(m), 1315(s), 1290(w), 1265(w), 1220(s), 1185(w), 1160(m), 1135(m), 1100(w), 1082(m), 1040(w), 972(w), 870(m), 835(m), 802(s), 790(s), 754(m), 709 (m), 648(s), 592(w), 555(w), 482(m), (potassium bromide); NMR (deuteriochloroform) 11.25-10.83 δ (-OH broad peak), 8.95 δ ($C_2$-H doublet of doublet $J_{23}$ = 5, $J_{24}$ = 1.5 cps), 8.72 δ ($C_4$-H doublet of doublet $J_{43}$ = 8, $J_{42}$ = 2 cps), 7.67 δ ($C_3$-H two doublets J = 4 cps), 6.46 δ (-N-H triplet), 3.50 δ ($C_1'$-H quartet), 2.47 δ ($C_3'$-H triplet), 2.30 δ (-N-($CH_3$)$_2$ singlet), 1.88 δ ($C_2'$-H quintuplet).

*Anal.* Calcd. for $C_{12}H_{17}N_5O$: C, 58.30; H, 6.88; N, 28.34. Found: C, 58.41; H, 6.84; N, 28.49.

5-Hydroxy-8-(3-diethylaminopropylamino)pyrido[2,3-*d*]pyridazine (Xb).

To 1.8 g. of 8-chloro-5-hydroxypyrido[2,3-*d*]pyridazine (IX) (0.01 mole) in a glass pressure flask was added 20 ml. of 3-diethylaminopropylamine. The mixture was heated in an oil bath at 170° for twenty-one hours, cooled, and the excess 3-diethylaminopropylamine removed by evaporation under reduced pressure. The product was collected by suspending the solid residue in water and filtering. Recrystallization from ligroin (90-120° B.P.) yielded 1.5 g. (51%) of yellow crystals, m.p. 121-123°; U.V. λ max (95% ethanol), 210 (ε, 20,950), 269 (ε, 4,600), 345 mμ (ε, 3,200).

*Anal.* Calcd. for $C_{14}H_{21}N_5O$: C, 61.06; H, 7.69; N, 25.43. Found: C, 61.20; H, 7.93; N, 25.18.

4,7-Dihydroxyimidazo[4,5-*d*]pyridazine (XI).

Imidazole-4,5-dicarboxylic acid bishydrazide (4 g., 0.0227 mole) and 8 ml. of anhydrous hydrazine were mixed and refluxed for 4 hours. The mixture gave a clear solution after about one hour. The solution was cooled and 100 ml. of water was added and acidified with concentrated hydrochloric acid to *p*H 2. The white precipitates were filtered, washed with water followed by alcohol and dried to give 2.9 g. (yield 88%) of white powder m.p. >400°. (This compound was chlorinated as such without further purification); U.V. λ max (95% ethanol) 209 (ε, 14,950), 268 mμ (ε, 8,100); infrared $cm^{-1}$, 3130(m), 3025(s), 2900(s), 2825(s), 2550(m), 2425(m), 1900(m), 1675(m), 1652(s), 1580(m), 1525(s), 1460(m), 1430(m), 1400(w), 1300(m), 1255(s), 1165(s), 1120(m), 1090(w), 1077(w), 975(s), 900(m), 810(m), 800(s), 650(m), 640(m), 520(w), 505(m), (potassium bromide).

4,7-Dichloroimidazo[4,5-*d*]pyridazine (XII).

4,7-Dihydroxyimidazo[4,5-*d*]pyridazine (XI) (2.26 g., 0.015 mole) 2.26 ml. of dimethylaniline and 63 ml. of phosphorus oxychloride were mixed together and refluxed with magnetic stirring (condenser fitted with calcium chloride drying tube) for 12 hours at which time a clear reddish solution was obtained. The excess of phosphorus oxychloride was removed under reduced pressure and the syrupy residue was cooled and poured in 100 ml. of ice water with stirring while maintaining the temperature 0-5°. After a few minutes a buff-colored precipitate formed in the aqueous acidic solution. It was filtered, washed with cold water and dried to give a buff-colored compound. The compound was recrystallized from ethanol (charcoal) to give white crystals 2.0 g. (yield 72%) m.p. 240-242°; U.V. λ max (90% ethanol) 212 (ε, 34,400), 251 mμ (ε, 5,200); infrared $cm^{-1}$, 3120(w), 3070(w), 3025(w), 2975(m), 2950(w), 2800(m), 2700(w), 2525(w), 1585(m), 1545(w), 1452(m), 1420(m), 1360(w), 1340(s), 1302(m), 1285(s), 1211(m), 1128(m), 1120(w), 1087(m), 1030(w), 988(m), 924(s), 863(w), 692(w), 648(m), 628(w), 585(m), 500(w), (potassium bromide).

4,7-bis(3-Dimethylaminopropylamino)imidazo[4,5-*d*]pyridazine (XIIIa).

Method A.

4,7-Dichloroimidazo[4,5-*d*]pyridazine (XII) (0.57 g., 0.003 mole) and 1.22 g. (0.012 mole) of 3-dimethylaminopropylamine were mixed and heated in an oil bath (150°) with stirring for 24 hours. The thick syrup was dissolved in about 5 ml. of water and extracted with 4 x 25 ml. portions of chloroform. The combined chloroform layer was dried over anhydrous magnesium sulfate and evaporated to dryness to give a whitish yellow compound. Recrystallization from benzene gave 0.5 g. of XIIIa (yield 52%) m.p. 175-176°; U.V. λ max (95% ethanol), 214 (ε, 13,700), 224 (Sh) (ε, 13,100), 243 (Sh) (ε, 16,450), 248 (ε, 16,840), 265 mμ (Sh) (ε, 7,025); infrared $cm^{-1}$, 3250(m), 3100(w), 2945(s), 2852(m), 2810(m), 2775(m), 1652(m), 1570(s), 1505(w), 1490(w), 1460(w), 1420(w), 1400(w), 1375(w), 1345(w), 1310(w), 1300(w), 1263(s), 1242(w), 1188(m), 1178(m), 1135(w), 1103(w), 1045(w), 1008(w), 960(w), 950(w), 870(w), 740(w), 700(w), 650(m); NMR (deuteriochloroform) 8.14 δ ($C_2$-H singlet), 7.45-8.0 δ (-N-H- broad peak), 3.51 δ ($C_1'$-H triplet), 2.15-2.55 δ ($C_3'$-H multiplet), 2.31 δ (-N($CH_3$)$_2$ singlet), 1.5-2.1 δ ($C_2'$-H multiplet), N-H proton from imidazole ring was not located.

*Anal.* Calcd. for $C_{15}H_{28}N_8$: C, 56.23; H, 8.81; N, 34.98. Found: C, 56.45; H, 8.84; N, 35.08.

4,7-bis(3-Diethylaminopropylamino)imidazo[4,5-*d*]pyridazine (XIIIb).

The procedure was the same as for XIIIa except that reaction time was 3 hours. The product was recrystallized from ligroin (90-120° B.P.) to give a whitish product, m.p. 143-144° (yield 65%); U.V. λ max (95% ethanol), 214 (ε, 16,800), 224 (Sh) (ε, 13,100), 243 (Sh) (ε, 16,600) 248 (ε, 17,700), 264 (Sh) mμ (ε, 6,200).

*Anal.* Calcd. for $C_{19}H_{36}N_8$: C, 60.60; H, 9.64; N, 29.77. Found: C, 60.54; H, 9.53; N, 29.81.

4(7)-Chloro7(4)-ethoxyimidazo[4,5-*d*]pyridazine (XIV).

To a solution of 0.5 g. (0.022 mole) of sodium in 15 ml. of absolute ethanol in a pressure bottle, 1.89 g. (0.01 mole) of 4,7-dichloroimidazo[4,5-*d*]pyridazine (XII) was added. The reaction mixture was heated under pressure at 140° with stirring for 14 hours. After some time it gave a clear solution and sodium chloride started to precipitate. The reaction mixture was cooled, evaporated to dryness and dissolved in 25 ml. of water. The aqueous solution was treated with charcoal, filtered and acidified to ~pH 4, whereupon a white precipitate was obtained. The mixture was cooled, filtered and washed with cold water. The compound after drying weighed 1.65 g. (yield 83%) and the analytical sample was recrystallized from ethyl acetate to give white crystals, m.p. 200°, shrinks with decomposition, then melts at 275°; U.V. λ max (95% ethanol), 212 (ε, 32,350), 245 mμ (ε, 5,100); infrared $cm^{-1}$, 3145(w), 3090(w), 3045(w), 2995(m), 2940(w), 2795(m), 2690(w), 2580(w), 1620(m), 1610(m), 1550(m), 1485(m), 1475(m), 1450(m), 1440(m), 1420(s), 1405(m), 1380(s), 1353(m), 1345(m), 1303(s), 1240(w), 1159(s), 1142(w), 1135(m), 1090(w), 1030(m), 990(w), 930(m), 885(m), 850(w), 755(m), 610(s), 537(m), (potassium bromide); NMR (deuterium oxide, base) 8.3 δ ($C_2$-H singlet), 4.62 δ (-O-$CH_2$- quartet), 1.65 δ (-C-$CH_3$ triplet).

*Anal.* Calcd. for $C_7H_7ClN_4O$: C, 42.34; H, 3.55; N, 28.21. Found: C, 42.67; H, 3.81; N, 27.99.

4,7-bis(3-Dimethylaminopropylamino)imidazo[4,5-*d*]pyridazine (XIIIa).

Method B.

To 5 ml. of 3-dimethylaminopropylamine 0.5 g. (0.0252 mole) of XIV was added and the mixture was refluxed for 3.5 hours. Within a few minutes a clear solution was obtained. The reaction solution was cooled and a white precipitate was obtained. The precipitate was filtered, washed with ligroin (90-120° B.P.) and dried to give 0.5 g. of the compound. The filtrate was evaporated to dryness *in vacuo* followed by addition of a few milliliters of water and evaporated to give a yellow residue. The yellow residue was dissolved in 5 ml. of water and the aqueous solution was extracted twice with 25 ml. of chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and evaporated to dryness to give 0.1 g. of the product (yield 74%). The product was recrystallized from benzene to give white crystals, m.p. 175-176°. This compound was shown to be identical to the one prepared by Method A by TLC, infrared (potassium bromide) and NMR.

4,7-Dichloro-1-(tetrahydro-2′-pyranyl)imidazo[4,5-*d*]pyridazine (XV).

In 45 ml. of dry ethyl acetate (18) 4.4 g. (0.0232 mole) of XII was placed in a three-neck flask fitted with a condenser, drying tube and addition funnel. The suspension was stirred magnetically and 90 mg. of *p*-toluenesulfonic acid was added. The suspension was heated to 38° and after 20 minutes with continuous stirring under anhydrous conditions, 4.5 ml. of 2,3-dihydro-4*H*-pyran (dried over potassium hydroxide and distilled) was added dropwise during 20 minutes. The temperature of the reaction mixture rose 4°. The reaction mixture was then heated to 55° for 2 hours and cooled to room temperature. To this mixture 5 ml. of 10% ammonium hydroxide was added and stirred for 2 to 3 minutes and then transferred to a separatory funnel with the aid of 50 ml. of ethyl acetate. The ethyl acetate layer was extracted twice with 25 ml. of water and each water layer was extracted with 25 ml. of ethyl acetate. The combined ethyl acetate layer was dried over anhydrous magnesium sulfate and evaporated to dryness to give pale yellow product. Recrystallization from benzene and cyclohexane gave 4.75 g. (yield 75%) of XV. The analytical sample was recrystallized from ligroin (90-120° B.P.) to give colorless flakes, m.p. 129-130°; U.V. λ max (95% ethanol), 213 (ε, 38,400), 252 mμ (ε, 5,600); infrared $cm^{-1}$, 3100(m), 2945(m), 2847(w), 1565(m), 1530(w), 1450(s), 1435(w), 1415(m), 1400(s), 1335(s), 1300(m), 1290(s), 1240(s), 1205(m), 1190(s), 1153(m), 1120(w), 1090(s), 1060(w), 1045(s), 1018(w), 990(m), 950(s), 914(m), 900(w), 870(w), 848(w), 822(w), 681(m), 648(m), 582(m), 568(w), 548(w), 520(w), 450(w), (potassium bromide); NMR (deuteriochloroform) 8.56 δ ($C_2$-H singlet), 6.0-6.3 δ ($C_2$′-H multiplet), 3.7-4.5 δ ($C_6$′-H broad peak), 1.5-2.5 δ ($C_3$′, $C_4$′, and $C_5$′-H broad peak).

*Anal.* Calcd. for $C_{10}H_{10}Cl_2N_4O$: C, 43.96; H, 3.69; N, 20.51. Found: C, 44.22; H, 3.87; N, 20.32.

4-(3-Dimethylaminopropylamino)-7-chloro-1-(tetrahydro-2′-pyranyl)imidazo[4,5-*d*]pyridazine (XVI).

To 4 ml. of dry dimethylsulfoxide (19) 0.092 g. (0.004 mole) of XV and 0.82 g. (0.008 mole) of 3-dimethylaminopropylamine were added and the solution was stirred at 50° for 24 hours under anhydrous conditions. Upon cooling to room temperature, the solution solidified. This was dissolved in 50 ml. of dichloromethane and extracted twice with 25 ml. and 15 ml. of water, respectively. The aqueous layers were extracted with 25 ml. of dichloromethane. The combined organic layer was dried over anhydrous magnesium sulfate and evaporated to dryness to give 0.9 g. of a whitish-yellow product. Recrystallization from benzene and ligroin (90-120° B.P.) gave 0.5 g. (yield 37%) of XVI. The analytical sample was recrystallized from ligroin (90-120° B.P.) to give colorless flakes, m.p. 164-165°; U.V. λ max (95% ethanol), 221 (ε, 17,300), 274 mμ (ε, 6,400); infrared $cm^{-1}$, 3350(s), 3055(m), 2945(s), 2852(m), 2815(m), 2765(m), 1600(s), 1550(w), 1515(w), 1452(s), 1430(s), 1380(w), 1347(m), 1325(w), 1300(w), 1275(m), 1240(m), 1217(m), 1185(w), 1157(m), 1148(m), 1112(w), 1082(m), 1057(m), 1043(s), 997(w), 942(w), 912(m), 882(w), 842(w), 773(w), 695(w), 628(m), 565(w), (potassium bromide).

*Anal.* Calcd. for $C_{15}H_{23}ClN_6O$: C, 53.18; H, 6.84; N, 24.80. Found: C, 53.39; H, 7.13; N, 24.81.

4-(3-Dimethylaminopropylamino)-7-chloroimidazo[4,5-*d*]pyridazine Dihydrochloride (XVIIa).

In 50 ml. of 95% ethanol, 0.47 g. (0.00138 mole) of XVI was dissolved and 0.5 ml. of concentrated hydrochloric acid was added and the solution was allowed to stand at room temperature for 1-2 hours with occasional shaking. The solution was then evaporated to dryness under reduced pressure followed by addition of benzene and ethanol and evaporated to remove excess acid and water. The white residue was dissolved in absolute ethanol and treated with charcoal. To the filtrate anhydrous ether was added until it became slightly turbid and cooled to give 0.37 g. (yield 82%). The analytical sample was prepared from absolute ethanol and anhydrous ether to give white crystals, m.p. 249-251°; U.V. λ

max (95% ethanol), 220 ($\epsilon$, 17,500), 263 ($\epsilon$, 8,100), 284 (Sh) m$\mu$ ($\epsilon$, 4,100); infrared cm$^{-1}$, 3124(m), 3000(m), 2950(m), 2900(m), 2850(m), 2550(m), 2465(w), 1650(s), 1545(w), 1500(w), 1470(w), 1400(w), 1370(w), 1355(m), 1300(w), 1220(m), 1190(w), 1180(w), 1118(w), 1045(w), 1035(w), 1005(w), 990(w), 965(w), 935(m), 790(w), 770(w), 760(w), 678(w), 660(w), 610(m), 585(w), 545(w), (potassium bromide); NMR (deuterium oxide) 8.7 $\delta$ ($C_2$-H singlet), 3.91 $\delta$ ($C_1'$-H triplet), 3.3-3.65 $\delta$ ($C_3'$-H multiplet), 3.06 $\delta$ (-N-($CH_3$)$_2$singlet), 2.2-2.7 $\delta$ ($C_2'$-H multiplet).

*Anal.* Calcd. for $C_{10}H_{15}ClN_6 \cdot 2HCl$: C, 36.66; H, 5.23; N, 25.66. Found: C, 36.38; H, 5.61; N, 25.37.

4-(5-Diethylamino-2-pentylamino)-7-chloroimidazo[4,5-*d*]pyridazine Dihydrochloride (XVIIb).

To 4 ml. of dry dimethylsulfoxide, 1.092 g. (0.004 mole) of XV and 1.27 g. (0.008 mole) of 5-diethylamino-2-pentylamine was added and the solution was stirred at 60° under anhydrous conditions for 50 hours. The solution was cooled to room temperature and dissolved in 50 ml. of dichloromethane. The dichloromethane solution was extracted twice with 20 ml. of water and each water layer was extracted with 25 ml. of dichloromethane. The combined dichloromethane layer was dried over anhydrous sodium sulfate and evaporated to dryness to give a syrupy residue. The residue was swirled with 3 x 40 ml. portions of cold petroleum ether and decanted. The residue showed the presence of traces of XV on neutral alumina by TLC. The product was separated from XV on a neutral alumina column (Woelm grade I, 15 g.) prepared with benzene and the compound was eluted as follows:

| Fraction | Eluent | Volume | Product |
|---|---|---|---|
| 1-3 | Benzene | 20 ml. each | --- |
| 4-10 | " | " | Starting material (XV) |
| 11-14 | " | " | Mixture of XV + XVIIb |
| 15-above | Benzene + chloroform (1:1) | 300 ml. | XVIIb |

The product obtained after evaporation of fraction 15 and above was dissolved in 30 ml. of ethanol and 0.5 ml. of concentrated hydrochloric acid was added and evaporated to dryness. The residue was treated twice with 20 ml. of a mixture of benzene and ethanol (1:1) and evaporated to dryness to give a white powder, 0.4 g. (yield 26%). It was dissolved in absolute ethanol and treated with charcoal, filtered and anhydrous ether was added until it became turbid, then it was allowed to stand for 2-3 days to give a white product, m.p. 168-170°. The analytical sample was prepared by recrystallization from absolute ethanol and anhydrous ether; U.V. $\lambda$ max (95% ethanol), 220 ($\epsilon$, 16,450), 266 ($\epsilon$, 8,100), 288 (Sh) m$\mu$ ($\epsilon$, 3,600).

*Anal.* Calcd. for $C_{14}H_{23}ClN_6 \cdot 2HCl$: C, 43.83; H, 6.56; N, 21.92. Found: C, 43.94; H, 6.64; N, 21.66.

7-(3-Dimethylaminopropylamino)imidazo[4,5-*c*] pyridazine (XIXa).

To 15 ml. of ethanol in a pressure bottle was added 0.310 g. (0.002 mole) of 7-chloroimidazo[4,5-*c*]pyridazine (XVIII) and 0.6 ml. (0.004 mole) of 3-dimethylaminopropylamine. The solution was heated with stirring at 170° for 12 hours. The reaction mixture was cooled to give 0.1 g. of a brown precipitate. The mother liquor on concentration and cooling gave 0.08 g. of additional product (yield 41%). Recrystallization from ethanol-ethyl acetate gave a white product, m.p. 221-223°; U.V. $\lambda$ max (95% ethanol), 210 ($\epsilon$, 12,100), 224 (Sh) ($\epsilon$, 11,400), 267 ($\epsilon$, 5,200), 313 m$\mu$ ($\epsilon$, 9,800); infrared cm$^{-1}$, 3440(s), 3230(m), 3165(s), 2950(s), 2760(m), 2560(m), 1650(s), 1550(m), 1450(m), 1380(m), 1365(m), 1350(m), 1305(m), 1280(w), 1233(w), 1192(w), 1160(w), 1142(m), 1110(m), 1068(w), 1043(w), 1002(w), 930(m), 890(w), 840(m), 750(m), 685(m), 605(w), NMR (deuterium oxide) 8.21 $\delta$ ($C_2$-H and $C_6$-H singlet), 3.5 $\delta$ ($C_1'$-H triplet), 2.7-3.1 $\delta$ ($C_3'$-H multiplet), 2.61 $\delta$ (-N-($CH_3$)$_2$ singlet), 1.6-2.25 $\delta$ ($C_2'$-H multiplet).

*Anal.* Calcd. for $C_{10}H_{16}N_6$: C, 54.53; H, 7.32; N, 38.15. Found: C, 54.46; H, 7.37; N, 37.88.

7-(3-Diethylaminopropylamino)imidazo[4,5-*c*]pyridazine Dihydrochloride (XIXb).

To 5 ml. of absolute ethanol 0.54 g. (0.00225 mole) of XX and 0.63 g. (0.0045 mole) of 3-diethylaminopropylamine were added and refluxed for 60 hours. The solution was evaporated to dryness under reduced pressure and the residue was treated with 10 ml. of water and 50 ml. of chloroform and transferred to a separatory funnel. The aqueous solution was extracted with two more portions of 25 ml. of chloroform and the chloroform extracts were washed with 10 ml. of water. The combined chloroform extract was dried over anhydrous magnesium sulfate and evaporated to dryness to give a yellowish syrup. This was dissolved in 50 ml. of ethanol and 1.1 ml. of concentrated hydrochloric acid was added and the solution was allowed to stand for one hour at room temperature. The solution was then evaporated to dryness followed by addition of benzene and ethanol and evaporated under reduced pressure to give a yellow powder. The material was dissolved in absolute ethanol, treated with charcoal, filtered and anhydrous ether was added until it became slightly turbid, then cooled to give white crystals, 0.52 g. (yield 74%) of XIXb. The analytical sample was prepared by one more recrystallization from absolute ethanol and anhydrous ether, m.p. 257-259°; U.V. $\lambda$ max (95% ethanol), 215 ($\epsilon$, 12,650), 266 ($\epsilon$, 6,000), 312 m$\mu$ ($\epsilon$, 10,750); infrared cm$^{-1}$, 3175(w), 3095(m), 3000(s), 2800(m), 2750(m), 2680(w), 1655(s), 1540(w), 1445(m), 1425(m), 1345(m), 1295(m), 1210(w), 1165(w), 1140(w), 1065(w), 1030(w), 885(w), 830(w), 748(m), 653(w), 603(m), 545(w), (potassium bromide).

*Anal.* Calcd. for $C_{12}H_{20}N_6 \cdot 2HCl$: C, 44.86; H, 6.90; N, 26.17. Found: C, 44.91; H, 7.15; N, 25.98.

4-(5-Diethylamino-2-pentylamino)-7-chloroimidazo[4,5-*c*]pyridazine Dihydrochloride (XIXc).

The procedure used for the preparation of this compound was similar to XIXb except that the reaction time was increased to 9 days. The analytical sample was recrystallized from absolute ethanol and anhydrous ether to give a white hygroscopic compound, m.p. 102-105° (yield 23%); U.V. $\lambda$ max 213 ($\epsilon$, 16,200), 267 ($\epsilon$, 5,900), 314 m$\mu$ ($\epsilon$, 11,250).

*Anal.* Calcd. for $C_{14}H_{24}N_6 \cdot 2HCl \cdot H_2O$: C, 45.77; H, 7.68; N, 22.88. Found: C, 45.63; H, 8.05; N, 22.90.

7-Chloro-3-(tetrahydro-2'-pyranyl)imidazo[4,5-*c*]pyridazine (XX).

To 20 ml. of dry ethyl acetate, 0.77 g. (0.005 mole) of 7-chloroimidazo[4,5-*c*]pyridazine (XVII) was added under anhydrous conditions. The suspension was stirred magnetically and 30 mg. of *p*-toluenesulfonic acid was added and stirred for 15 minutes. To this continuously stirred suspension, 1 ml. of 2,3-dihydro-4*H*-pyran was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 16 hours and filtered. The brown residue was washed with ethyl acetate and dried to give 0.44 g. of the unreacted XVIII. The ethyl acetate filtrate was extracted once with 10 ml. of 10% ammonium hy-

droxide and once with 10 ml. of water. The combined aqueous layer was washed with 25 ml. of ethyl acetate. The combined ethyl acetate layer was dried over anhydrous sodium sulfate and evaporated to dryness to give a brown residue. This residue was boiled with excess petroleum ether and filtered. The petroleum ether extract was concentrated to a low volume and cooled to give 0.27 g. (yield 52% of the reacted material) of the crystals, m.p. 90°. The analytical sample was recrystallized from petroleum ether to give light amber-colored crystals, m.p. 90°; U.V. λ max (95% ethanol) 208 (ε, 21,800), 259 (ε, 6,800), 285 mμ (ε, 5,600); infrared $cm^{-1}$, 3105(m), 3052(m), 2955(m), 2945(s), 2860(m), 1840(w), 1600(s), 1545(w), 1495(s), 1460(m), 1450(m), 1425(m), 1400(m), 1380(s), 1350(m), 1335(m), 1320(m), 1290(m), 1270(s), 1255(w), 1243(w), 1230(s), 1210(m), 1190(s), 1183(s), 1152(m), 1122(m), 1090(s), 1065(s), 1045(s), 1003(m), 950(s), 945(m), 915(s), 887(w), 872(m), 847(w), 823(w), 790(w), 782(w), 660(w), 638(m), 623(w), 562(m), 542(w), 482(w), 450(w), (potassium bromide); NMR (carbon tetrachloride) 9.05 δ ($C_6$-H singlet), 8.45 δ ($C_2$-H singlet), 5.85-6.15 δ ($C_2'$-H broad peak), 3.6-4.4 δ ($C_6'$-H broad peak), 1.5-2.5 δ ($C_3'$, $C_4'$ and $C_5'$-H broad peak).

*Anal.* Calcd. for $C_{10}H_{11}ClN_4O$: C, 50.31; H, 4.65; N, 23.47. Found: C, 50.53; H, 4.81; N, 23.33.

6-Thioimidazo[4,5-*c*]pyridazine (XXIII) and 6-Thio-3,4-diaminopyridazine (XXIIIa).

To a solution of 1.12 g. of sodium hydrosulfide in 6 ml. of 50% ethanol, 1.54 g. (0.01 mole) of 6-chloroimidazo[4,5-*c*]-pyridazine (XXII) were added in a pressure bottle. The reaction mixture was heated under pressure with stirring at 140° for 8 hours, whereupon an orange precipitate separated. The reaction mixture was cooled, filtered, washed with cold water and dried to give 1.2 g. of crude product. The mother liquor was acidified to *p*H 3-4 with glacial acetic acid and cooled to give 0.1 g. of additional product. The product proved to be a mixture of two components by thin-layer chromatography on neutral alumina with methanol.

The compounds XXIII and XXIIIa were separated on neutral alumina (grade I, Woelm, 50 g.) column with methanol and purified as follows:

| Fraction | Volume | Compound |
|---|---|---|
| 1-5 | 25 ml. each (Colorless eluate) | 0.57 g. yellowish compound XXIIIa |
| 6-9 | " | 0.04 g. mixture of XXIII & XXIIIa |
| 10-20 | 25 ml. each (Yellow eluate) | 0.42 g. of orange compound XXIII |

The orange compound XXIII was recrystallized from methanol to give crystals, m.p. 210° dec.; U.V. λ max (95% ethanol) 209 (ε, 36,800), 256 (Sh) (ε, 14,250), 298 mμ (ε, 13,700); infrared $cm^{-1}$, 3175(w), 3045(m), 2900(w), 2600(w), 2550(w), 1640(m), 1580(m), 1480(w), 1450(m), 1380(s), 1325(w), 1300(m), 1260(w), 1222(w), 1208(w), 1152(w), 1122(w), 1059(s), 955(m), 878(w), 797(w), 720(m), 610(m), (potassium bromide).

*Anal.* Calcd. for $C_5H_4N_4S$: C, 39.47; H, 2.65; N, 36.82. Found: C, 39.36; H, 3.05; N, 36.57.

The yellowish compound (XXIIIa) was dissolved in methanol, treated with charcoal, filtered and cooled to give a whitish product, m.p. > 270° (dec.); U.V. λ max (95% ethanol) 231 (ε, 16,100), 240 (ε, 22,500), 238 mμ (ε, 3,400); infrared $cm^{-1}$, 3440(s), 3350(s), 3200(s), 3120(s), 2950(m), 2700(w), 1675(m), 1665(s), 1652(m), 1625(w), 1590(s), 1520(s), 1480(s), 1410(w), 1350(m), 1325(w), 1235(m), 1125(s), 1100(w), 1055(m), 975(w), 873(w), 850(m), 823(m), 771(w), 692(m), 630(w), 560(w), 500(w), (potassium bromide).

*Anal.* Calcd. for $C_4H_6N_4S \cdot 0.25H_2O$: C, 32.74; H, 4.46; N, 38.19. Found: C, 32.94; H, 4.34; N, 38.18.

6-Methylthioimidazo[4,5-*c*]pyridazine (XXV).

To a solution of 0.152 g. (0.001 mole) of XXIII in 2.2 ml. of 0.5 *N* aqueous potassium hydroxide, 0.212 g. (0.0015 mole) of methyl iodide were added with continuous stirring. The clear solution gave a white precipitate within a few minutes. The mixture was stirred at room temperature for 4 hours, filtered, washed with cold water and dried to give 0.14 g. (yield 51%) of white compound. The product was purified by recrystallization from ethanol to give white crystals, m.p. 276-277°; U.V. λ max (95% ethanol), 210 (ε, 8,150), 272 (ε, 35,500), 322 (Sh) mμ (ε, 3,100); infrared $cm^{-1}$, 3170(s), 2960(m), 2920(w), 2860(w), 2790(w), 2720(m), 2550(w), 1890(w), 1640(m), 1550(w), 1450(m), 1395(s), 1300(s), 1275(m), 1157(m), 1055(m), 967(w), 915(m), 875(m), 737(m), 710(w), 617(m), (potassium bromide).

*Anal.* Calcd. for $C_6H_6N_4S$: C, 43.36; H, 3.65; N, 33.71. Found: C, 43.45; H, 3.45; N, 34.00.

7-Thioimidazo[4,5-*c*]pyridazine (XXIV).

To a solution of 0.336 g. of sodium hydrosulfide in 2 ml. of 50% ethanol in a pressure bottle, 0.462 g. (0.003 mole) of 7-chloroimidazo[4,5-*c*]pyridazine (XVIII) was added. The reaction mixture was heated at 140° with stirring for 1 hour, during which time a yellow precipitate separated. The reaction mixture was cooled, filtered, washed with cold water and dried to give 0.25 g. (yield 55%) of a yellow compound. The compound was suspended in 10 ml. of 50% methanol and 5% aqueous sodium hydroxide solution was added until a clear solution was obtained. This solution was treated with charcoal, filtered and acidified with hydrochloric acid and then cooled to give yellow needles, m.p. 273-275° (dec.); U.V. λ max (95% ethanol) 206 (ε, 11,200), 229 (ε, 8,400), 264 (ε, 3,500), 377 mμ (ε, 15,600); infrared $cm^{-1}$, 3190(w), 3080(m), 2965(w), 2930(w), 2545(m), 2000(w), 1603(s), 1577(m), 1530(m), 1448(m), 1410(w), 1375(m), 1325(w), 1295(m), 1215(s), 1150(m), 1132(w), 1090(w), 1000(m), 942(w), 908(w), 867(s), 647(m), 611(m), 502(m), (potassium bromide).

*Anal.* Calcd. for $C_5H_4N_4S$: C, 39.48; H, 2.63; N, 36.82. Found: C, 39.39; H, 2.68; N, 36.68.

7-Methylthioimidazo[4,5-*c*]pyridazine (XXVI).

To a cold solution of 0.14 g. of 7-thioimidazo[4,5-*c*]pyridazine (XXIV) in 2.5 ml. of 0.5 *N* aqueous potassium hydroxide, 0.158 g. of methyl iodide was added. The solution was stirred at 10° for 1 hour and then at room temperature for 8 hours. The white precipitate was filtered, washed with cold water and dried to give 0.50 g. (yield 33%) of XXVI. The product was purified by recrystallization from ethanol, m.p. 240-242°; U.V. λ max (95% ethanol) 206 (ε, 10,600), 221 (ε, 14,200), 276 (ε, 6,700), 302 mμ (ε, 9,950); infrared $cm^{-1}$, 3180(w), 3000(w), 2920(w), 2765(m), 2680(m), 2610(m), 2550(m), 1780(w), 1565(s), 1485(w), 1460(m), 1450(m), 1425(m), 1380(s), 1320(w), 1295(m), 1248(s), 1150(w), 1108(m), 1000(m), 965(w), 945(m), 915(m), 890(m), 871(s), 858(m), 718(w), 670(m), 635(m), 627(m), 620(w), 502(w), (potassium bromide).

*Anal.* Calcd. for $C_6H_6N_4S$: C, 43.36; H, 3.61; N, 33.71. Found: C, 43.03; H, 3.52; N, 33.93.

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## REFERENCES

(1) Communications concerning this paper should be directed to Professor Raymond N. Castle.

(2) N. R. Patel and R. N. Castle, *J. Heterocyclic Chem.*, 3, 512 (1966).

(3) Y. Nitta, J. Matsuura and F. Yoneda, *Chem. Pharm. Bull.*, 13, 586 (1965).

(4) R. G. Shepherd and J. L. Fedrick, "Advances in Heterocyclic Chemistry," A. R. Katritzky, Ed., Vol. IV, Academic Press, New York, 1965, p. 314.

(5) R. N. Castle and W. S. Seese, *J. Org. Chem.*, 23, 1534 (1958).

(6) J. Nematollahi, W. Guiss and J. Autian, *J. Med. Chem.*, 9, 660 (1966).

(7) R. G. Jones, *J. Am. Chem. Soc.*, 78, 159 (1956).

(8) L. Erichomovitch and F. L. Chubb, *Can. J. Chem.*, 44, 2095 (1966).

(9) G. A. Gerhardt. D. L. Aldous and R. N. Castle, *J. Heterocyclic Chem.*, 2, 247 (1965).

(10) E. Y. Sutcliffe and R. K. Robins, *J. Org. Chem.*, 28, 1662 (1963).

(11) J. A. Carbon, *J. Am. Chem. Soc.*, 80, 6083 (1958).

(12) R. K. Robins, E. F. Godefroi, E. C. Taylor, L. R. Lewis and A. Jackson, *ibid.*, 83, 2574 (1961).

(13) T. Kuraishi and R. N. Castle, *J. Heterocyclic Chem.*, 1, 42 (1964).

(14) H. Murakami and R. N. Castle, *ibid.*,, 4, 555 (1967).

(15) T. Kuraishi and R. N. Castle, *ibid.*, 3, 218 (1966).

(16) T. Hori, K. Kinjo and T. Ueda, *Chem. Pharm. Bull.*, 10, 580 (1962).

(17) G. H. Elion, E. Burgi and J. H. Hitchings, *J. Am. Chem. Soc.*, 74, 411 (1952).

(18) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, p. 287.

(19) R. E. Dessy, T. Hieber and F. Paulik, *J. Am. Chem. Soc.*, 86, 29 (1964).

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