Synthesis of Some 6-Methoxyimidazo[1,2-*b*]pyridazines

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The synthesis of 6-methoxyimidazo[1,2-*b*]pyridazine and its 2-methyl analog is reported. Carboxylic acids, esters and quaternary salts derived from this ring system are described and the heterocyclic system is shown to undergo the Mannich reaction. A condensation reaction of the 2-methyl group is reported and nuclear magnetic resonance (nmr) spectra and acidity constants of some imidazo[1,2-*b*]pyridazines are recorded.

Since the first reported synthesis of an imidazo[1,2-*b*]-pyridazine (I) only a few further examples of this system have been described. 2-Aryl derivatives of I have been made from phenacyl halides and 2-aminopyridazines (1,2,3), while 6-chloro analogs of I have been prepared by condensation of 3-amino-6-chloropyridazine with either bromoacetaldehyde, bromoacetone or ethyl 2-bromo-acetoacetate (4,5a,b). A very low yield of I has been obtained (6) by oxidation of 2,3-dihydroimidazo[1,2-*b*]-pyridazine. The present report will deal with the preparation and reactions of 6-methoxyimidazo[1,2-*b*]pyridazine and its 2-methyl analog.

Preparative Methods.

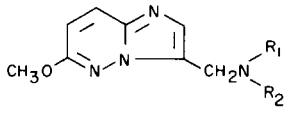
Condensation of 3-amino-6-methoxypyridazine (II) with chloroacetaldehyde proceeded smoothly to yield 6-methoxyimidazo[1,2-*b*]pyridazine (III). Reaction of II with chloro-2-propanone provided a good yield of 6-methoxy-2-methylimidazo[1,2-*b*]pyridazine (IV) (5b). Finally, by analogy with synthetic methods used for preparing some imidazo[1,2-*a*]pyridinecarboxylic acids (7), II was allowed to react with ethyl bromopyruvate or with ethyl 2-chloroacetoacetate to yield ethyl 6-methoxy-imidazo[1,2-*b*]pyridazine-2-carboxylate (V), and ethyl 6-methoxy-2-methylimidazo[1,2-*b*]pyridazine-3-carboxylate (VI), respectively. Base hydrolysis of the esters (V and VI) provided the corresponding carboxylic acid sodium salts (VII and VIII).

Reactions.

Structural analogy of imidazo[1,2-*b*]pyridazines such as III or IV with indole or with imidazo[1,2-*a*]pyridines

TABLE I

3-Dialkylaminomethyl-6-methoxyimidazo[1,2-*b*]pyridazines (IX)

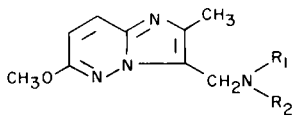


R_1	R_2	Recrystn. solvent	Yield, %	M.P., °C	Formula	Anal., % Calcd. C	H	N	Found C	H	N
CH_3	CH_3	a	8	94-96	$C_{10}H_{14}N_4O$	58.20	6.84	27.15	58.16	6.77	27.44
—$(CH_2)_5$—		b	57	202-205 dec.	$C_{13}H_{18}N_4O \cdot 2HCl \cdot 0.5H_2O$	47.57	6.45	17.07	47.43	6.35	16.98
-$(CH_2)_2$-O-$(CH_2)_2$-		c	64	213-215 dec.	$C_{12}H_{16}N_4O_2 \cdot 2HCl \cdot H_2O$	42.49	5.99	16.52	42.76	6.04	16.60
-$(CH_2)_2$-N-$(CH_2)_2$-	CH_3	c	88	204-206 dec.	$C_{13}H_{19}N_5O \cdot 3HCl \cdot H_2O$	40.16	6.22	18.02	40.24	6.32	18.22
CH_3	$CH_2C_6H_5$	b	72	166-169 dec.	$C_{16}H_{18}N_4O \cdot 2HCl \cdot 0.5H_2O$	52.75	5.81	15.38	52.46	5.69	14.98

(a) Hexane. (b) Ethanol-ether. (c) Methanol-ether.

TABLE II

3-Dialkylaminomethyl-6-methoxy-2-methylimidazo[1,2-*b*]pyridazines (X)



R_1	R_2	Recrystn. solvent	Yield, %	M.P., °C	Formula	Anal., % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	CH_3	a	71	202-206 dec.	$C_{11}H_{16}N_4O \cdot 2HCl$	45.06	6.19	19.11	44.73	5.98	19.09
CH_2CH_2OH	CH_2CH_2OH	b	37	130-131	$C_{13}H_{20}N_4O_3$	55.70	7.19	19.99	55.49	7.19	19.59
——$(CH_2)_5$——		a	38	211-212 dec.	$C_{14}H_{20}N_4O \cdot 2HCl \cdot 0.5H_2O$	49.12	6.73	16.37	49.41	6.78	16.30
n-C_4H_9	n-C_4H_9	a	56	168-170 dec.	$C_{17}H_{28}N_4O \cdot 2HCl \cdot 0.5H_2O$	52.84	8.05	14.50	52.58	8.01	14.32
$-(CH_2)_2-O-(CH_2)_2-$		d	54	77-79	$C_{13}H_{18}N_4O_2$	59.52	6.92	21.36	59.30	6.73	20.97
CH_3	$CH_2C_6H_5$	c	83	206-207 dec.	$C_{17}H_{20}N_4O \cdot 2HCl \cdot 0.5H_2O$	53.97	6.12	14.81	54.23	6.08	14.63
$-(CH_2)_2-N(C_6H_5)-(CH_2)_2-$		a	39	213-214 dec.	$C_{19}H_{23}N_5O \cdot 3HCl$	51.07	5.87	15.68	51.27	6.15	15.94

(a) Ethanol-ether. (b) Hexane-ethanol. (c) Methanol-ether. (d) Hexane.

(7) suggested that III might undergo the Mannich reaction at the 3-position. In fact, combination of III or IV with formaldehyde and secondary amines readily provided some 3-dialkylaminomethylimidazo[1,2-*b*]pyridazines (IX and X, see Tables I and II, respectively). The base X, (R_1R_2 = CH_3) was converted to a side-chain methiodide (XI) under mild conditions with no evidence of nuclear alkylation. Forcing conditions were found necessary to cause IV to react with *p*-chlorobenzyl chloride producing a compound assigned the structure of 1-(*p*-chlorobenzyl)-6-methoxy-2-methylimidazo[1,2-*b*]pyridazinium chloride (XII). Alkylation at N^1 appears most likely since protonation occurs at N^1 (6) and structure XII contains a conjugated, aromatic pyridazinium ring which could not arise from alkylation of either N^4 or N^5. Aqueous hydrobromic acid smoothly cleaved the methoxyl function of IV to produce 6-hydroxy-2-methylimidazo[1,2-*b*]pyridazine (XIII). The 2-methyl group in IV was condensed with chloral in a manner previously applied to 2-methylimidazo[1,2-*a*]pyridines (7), 2-picolines, methylpyrazines and methylpyrimidines (8) to produce the alcohol XIV.

EXPERIMENTAL (9)

6-Methoxyimidazo[1,2-*b*]pyridazine (III).

To a solution of 120.0 g. (0.6 mole) of chloroacetaldehyde (40% aqueous solution) in 400 ml. of ethanol and 100 ml. of water was added 62.6 g. (0.5 mole) of 3-amino-6-methoxypyridazine in 100 ml. of ethanol. To this clear red solution was slowly added 50.4 g. (0.6 mole) of sodium bicarbonate. Vigorous gas evolution proceeded during a 2 hour reflux period after which time the reaction was concentrated *in vacuo* to approximately 250 ml., partitioned between water-ether and the ether extracts dried over sodium sulfate. Evaporation of all solvent, and recrystallization from ethanol (charcoal treatment) yielded in 3 crops 38.6 g. (52%) of III, m.p. 106-108°.

Titration in aqueous sodium hydroxide gave a neutralization equivalent 154 (calc. 149), $pH_{1/2}$ 4.97; nmr (deuteriochloroform); τ 2.19 (d, J = 9.5 cps, 1-H, the 8-proton); 3.32 (d, J = 9.5 cps, 1-H, the 7-proton); 2.24 (d, J = 1 cps, 1-H, the 2 or 3-proton); 2.36 (d, J = 1 cps, 1-H, the 2 or 3-proton) 6.03 (s, 3-H, methoxyl); ultraviolet spectrum; λ max (EtOH), 311, ϵ 5,670; infrared spectrum: 6.15, 6.43, 6.65, 7.70, 8.70, 9.82 μ.

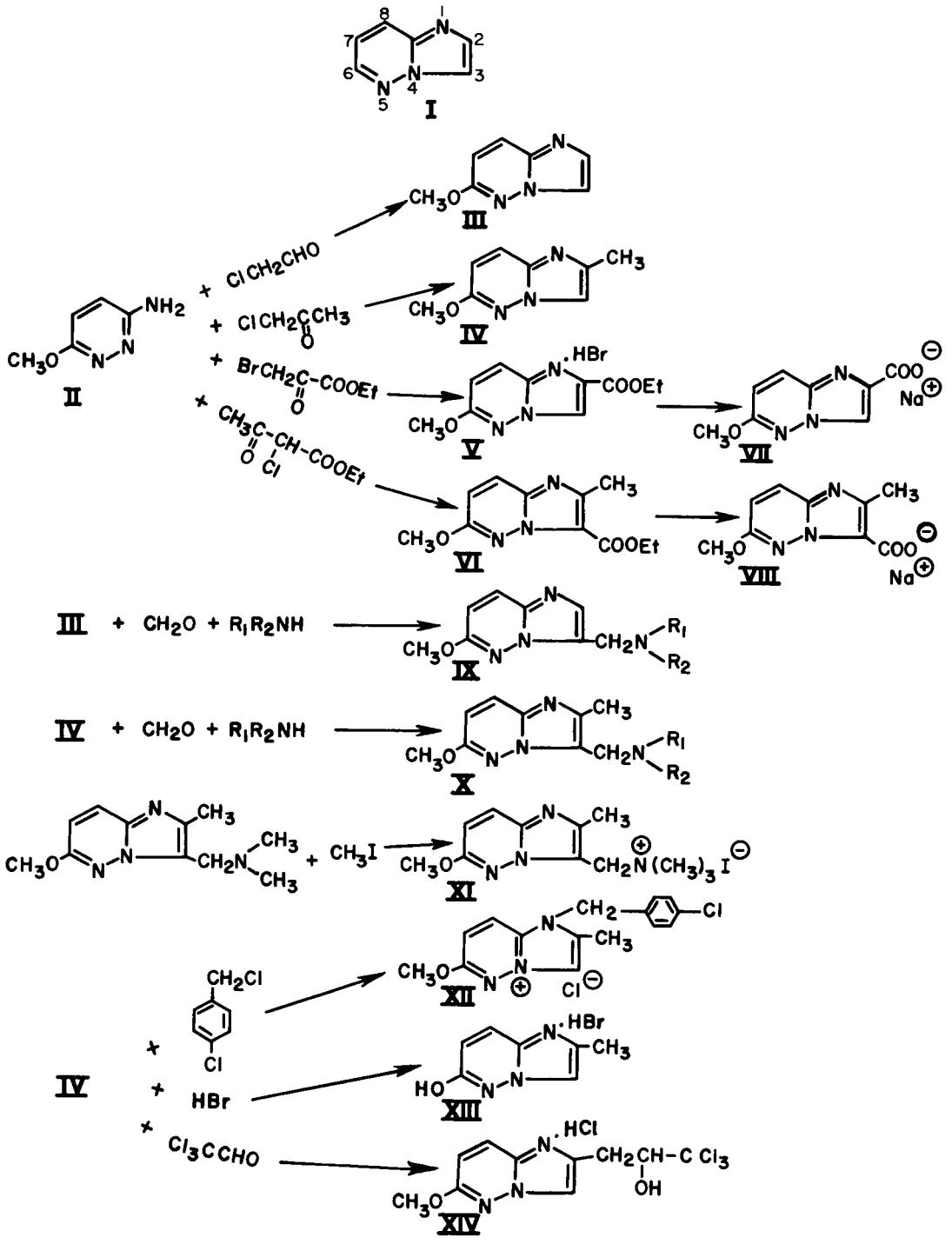
Anal. Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.71. Found: C, 56.54; H, 4.71; N, 28.90.

6-Methoxy-2-methylimidazo[1,2-*b*]pyridazine (IV).

A solution obtained from 76 g. (0.60 mole) of 3-amino-6-methoxypyridazine, 61.4 g. (0.66 mole) of freshly distilled chloro-2-propanone and 500 ml. of ethanol was refluxed for 2 hours. After cooling, 55.4 g. (0.33 mole) of sodium bicarbonate in 350 ml. of water was slowly added resulting in very vigorous gas evolution. After a further 23 hours of reflux the reaction was concentrated to dryness *in vacuo* and partitioned between water and chloroform. The chloroform extracts were dried over sodium sulfate, treated with charcoal, and evaporated to dryness producing a residual oil which was dissolved in water containing some ethanol and allowed to stand in the cold. Filtration gave a light tan solid 54.0 g. (56%), m.p. 87-88°; nmr spectrum (deuteriochloroform); τ 2.33 (d, J = 9.5 cps, 1-H, the 8-proton); 3.40 (d, J = 9.5 cps, 1-H, the 7-proton); 2.47 (s, 1-H, the 3-proton); 6.06 (s, 3-H, methoxyl); 7.56 (s, 3-H, methyl).

Anal. Calcd. for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.63; H, 5.38; N, 25.74.

Ethyl 6-Methoxyimidazo[1,2-*b*]pyridazine-2-carboxylate Hydrobromide (V).



To a solution of 12.5 g. (0.10 mole) of 3-amino-6-methoxypyridazine in 75 ml. of 1,2-dimethoxyethane was slowly added a solution of 19.5 g. (0.10 mole) of ethyl bromopyruvate in 25 ml. of 1,2-dimethoxyethane. An initial exothermic reaction was controlled with an ice bath after which stirring for 2 hours at room temperature produced a solid, 21.3 g. (71%), m.p. 115-117°. This intermediate salt was cyclized by refluxing for 2 hours in 500 ml. of ethanol, and evaporating to dryness. After recrystallization from ethanol-ether a white solid resulted, 17.3 g. (57%), m.p. 154-155°; infrared; 3.2-4.0 (NH^+), 5.79, 6.4, 7.05, 7.65, 7.94 μ; nmr spectrum (deuteriochloroform): τ 1.14 (d, J = 10 cps, 1-H, the 8-proton); 1.64 (s, 1-H, the 3-proton); 2.52 (d, J = 10 cps, 1-H, the 7-proton); 5.48 (q, J = 7 cps, 2-H, CH_2); 8.54 (t, J = 7 cps, 3-H, CH_3); 5.85 (s, 3-H, methoxyl); -2.22 (s, acidic, NH).

Anal. Calcd. for $C_{10}H_{11}N_3O_3 \cdot HBr$: C, 39.75; H, 4.00; N, 13.91. Found: C, 39.55; H, 4.10; N, 13.78.

Sodium 6-Methoxyimidazo[1,2-*b*]pyridazine-2-carboxylate (VII).

A combination of 2.0 g. (0.0066 mole) of V, 50 ml. of ethanol and 5 ml. of water and 10 ml. of 10% sodium hydroxide was refluxed for 18 hours. Cooling to room temperature produced 1.29 g. (91%) of a solid which did not melt below 320°. infrared; strong absorption at 6.25 μ (carboxylate anion).

Anal. Calcd. for $C_8H_6N_3O_3Na \cdot 0.5H_2O$: C, 42.86; H, 3.15; N, 18.75. Found: C, 42.85; H, 3.08; N, 18.87.

Ethyl 6-Methoxy-2-methylimidazo[1,2-*b*]pyridazine-3-carboxylate (VI).

A combination of 6.25 g. (0.050 mole) of 3-amino-6-methoxypyridazine, 8.3 g. (0.050 mole) of ethyl 2-chloroacetoacetate, and 70 ml. of 1,2-dimethoxyethane was refluxed for 2 hours. Filtration of the crude, tan solids followed by recrystallization from 40 ml. of 3:1 ethanol-ether produced a solid, m.p. 155-161° which was not identified. On further standing, a second crop precipitated, 0.80 g. (7%), m.p. 110-112°; infrared; 5.91, 6.45, 7.04, 7.88, 8.45, 12.1, 13.1 μ; nmr spectrum (deuteriochloroform); τ 2.22 (d, J = 9.5 cps, 1-H, the 8-proton); 3.18 (d, J = 9.5 cps, 1-H, the 7-proton); 5.53 (q, J = 7 cps, 2-H, CH_2); 5.94 (s, 3-H, methoxyl); 7.31 (s, 3-H, the 2-CH_3 group); 8.54 (t, J = 7 cps, 3-H, CH_3).

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.47; H, 5.64; N, 17.55.

Sodium 6-Methoxy-2-methylimidazo[1,2-*b*]pyridazine-3-carboxylate (VIII).

A solution of 1.2 g. (0.051 mole) of VI, 50 ml. of ethanol and 63 ml. of 0.1 *N* sodium hydroxide was stirred overnight at room temperature. After heating for 0.5 hour (steam bath) the reaction was evaporated to dryness. The residue after recrystallization from ethanol containing a trace of water produced a solid, 0.59 g. (49%), m.p. 315° dec.; infrared spectrum; strong absorption at 6.20 μ (carboxylate anion).

Anal. Calcd. for $C_9H_8N_3O_3Na \cdot H_2O$: C, 43.73; H, 4.08; N, 17.00. Found: C, 43.92; H, 4.22; N, 16.86.

The series of compounds obtained by application of the Mannich reaction to III are summarized in Table I. The following will serve as a typical example of the procedure used to prepare members of this series.

3-Piperidinomethyl-6-methoxyimidazo[1,2-*b*]pyridazine (IX, $R_1R_2 = (CH_2)_5$).

A pale yellow solution of 3.7 g. (0.025 mole) of III in 10 g. of glacial acetic acid was cooled to 0° and 2.1 g. (0.025 mole) of piperidine was added. After stirring a few minutes, 2.2 g. (0.025 mole) of 37% formalin was added and the solution stirred for 5 hours at room temperature and then heated (steam bath) for 1 hour. An additional 2.1 g. of piperidine and 2.2 g. of 37% formalin was added, and the reaction was stirred for another 42 hours. After steaming for 2 hours the reaction was strongly basified with 10% sodium hydroxide and extracted exhaustively with ether. Drying (sodium sulfate) and evaporating the ether extracts produced an oil which was dissolved in methanol and a solution of gaseous hydrochloric acid in methanol added. After evaporation to dryness the residue was recrystallized from ethanol-ether yielding 4.6 g. (57%) of dihydrochloride, m.p. 202-205° dec.

As a representative spectrum of this structural type, an nmr (deuteriochloroform) was determined on the *free base* of IX, $R_1R_2 = CH_3$ (m.p. 94-96°); τ 2.24 (d, J = 9.5 cps, 1-H, the 8-proton); 2.45 (s, 1-H, the 2-proton); 3.32 (d, J = 9.5, 1-H, the 7-proton); 5.98 (s, 3-H, methoxyl); 6.14 (s, 2-H, CH_2); 7.66 (s, 6-H, $N(CH_3)_2$).

Analyses and other physical data are recorded in Table I. Many of these salts formed hydrated crystals which could not be dehydrated under high vacuum over phosphoric pentoxide at 57°.

The following will serve as a typical example of the Mannich reaction applied to IV. Table II summarizes compounds of this type.

3-Dimethylaminomethyl-6-methoxy-2-methylimidazo[1,2-*b*]pyridazine Dihydrochloride (X, $R_1R_2 = CH_3$).

To a solution of 1.6 g. (0.010 mole) of IV in 2.4 g. of glacial acetic acid was added 0.90 g. (0.010 mole) of 50% aqueous dimethylamine and 0.82 g. (0.010 mole) of 37% formalin. A precipitate formed which was redissolved with an additional 2.4 g. of acetic acid. After 47 hours at room temperature another 0.90 g. (0.010 mole) of 50% aqueous dimethylamine and 0.82 g. (0.010 mole) of 37% formalin was added. After an additional 24 hours the solution was strongly basified with 10% sodium hydroxide and exhaustively extracted with ether. Drying and evaporation of the extracts produced a crude semi-solid. A dihydrochloride salt was prepared in methanol solution and recrystallized from ethanol-ether, m.p. 202-206° dec. Nmr (deuteriochloroform) was determined on the *free base* of X, $R_1R_2 = CH_3$ (m.p. 68-70°); τ 2.36 (d, J = 9.5 cps, 1-H, the 8-proton); 3.41 (d, J = 9.5 cps, 1-H, the 7-proton); 6.0 (s, 3-H, methoxyl); 6.2 (s, 2-H, CH_2); 7.53 (s, 3-H, the 2-CH_3 group); 7.68 (s, 6-H, $N(CH_3)_2$). Analyses and other physical data are recorded in Table II.

6-Methoxy-2-methylimidazo[1,2-*b*]pyridazinylmeth-3-yl-trimethylammonium Iodide (XI).

To 1.1 g. (0.005 mole) of X ($R_1R_2 = CH_3$) in 15 ml. of ethanol was added 0.78 g. (0.0055 mole) of iodomethane. After stirring for 20 hours the white suspension was cooled to 0° and filtered yielding 1.3 g. (72%) of XI, m.p. 260-267° dec.; infrared; 3.5 (broad), 6.45, 7.74, 11.35, 12.25 μ; nmr (deuterium oxide); τ 1.82 (d, J = 10 cps, 1-H, the 8-proton); 2.70 (d, J = 10 cps, 1-H, the 7-proton); 4.69 (s, 2-H, CH_2); 5.35 (s, 3-H, methoxyl); 6.32 (s, 9-H, $(CH_3)_3$), 7.08 (s, 3-H, CH_3).

An analytical sample was prepared by recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{19}IN_4O$: C, 39.79; H, 5.29; N, 15.47. Found: C, 39.73; H, 5.19; N, 15.08.

1-(*p*-Chlorobenzyl)-6-methoxy-2-methylimidazo[1,2-*b*]pyridazinium Chloride (XII).

A combination of 4.9 g. (0.030 mole) of IV and 9.6 g. (0.060 mole) of *p*-chlorobenzyl chloride was placed under a nitrogen atmosphere and heated at 100° (oil bath) for 3 hours. Trituration of the semi-solid residue with ether yielded in two crops 7.0 g. (72%) of white solid (XII), m.p. 189.5-190.5° dec. Under milder reaction conditions, in solution at lower temperatures, this reaction failed completely. Infrared spectrum; 3.39, 6.25, 6.31, 7.16, 7.5, 8.22, 9.85, 12.0 μ; nmr (D_6-DMSO); τ 1.06 (d, J = 10 cps, 1-H, the 8-proton); 1.46 (s, 1-H, the 3-proton); 2.40 (d, J = 10 cps, 1-H, the 7-proton); 2.62 (s, 4-H, aromatic protons); 4.06 (s, 2-H, CH_2); 5.96 (s, 3-H, methoxyl); 6.56 (s, 3-H, the 2-CH_3 group).

An analytical sample was prepared from hot ethanol, m.p. 194-195° dec.

Anal. Calcd. for $C_{15}H_{15}Cl_2N_3O$: C, 55.57; H, 4.66; N, 12.96. Found: C, 55.82; H, 4.69; N, 12.69.

6-Hydroxy-2-methylimidazo[1,2-*b*]pyridazine Hydrobromide (XIII).

A combination of 1.0 g. (0.0061 mole) of IV and 25 ml. of 48%

aqueous hydrogen bromide was refluxed for 7 hours. Cooling to room temperature precipitated a solid which was recrystallized from ethanol-ether to yield 0.90 g. (64%) of tan crystals, m.p. 188° dec.; infrared; 2.96, 3.4 (broad), 6.2, 6.65, 8.3, 12.5 μ.

An analytical sample was prepared from hot ethanol, m.p. 204° dec.

Anal. Calcd. for $C_7H_7N_3O \cdot HBr \cdot 0.5H_2O$: C, 35.16; H, 3.79. N, 17.58. Found: C, 35.53; H, 3.59; N, 17.48.

2-(3,3,3-Trichloro-2-hydroxypropyl)-6-methoxyimidazo[1,2-*b*]-pyridazine Hydrochloride (XIV).

A solution of 3.3 g. (0.02 mole) of IV and 20 ml. of chloral was refluxed (steam bath) for 58 hours. The dark brown suspension was filtered yielding 3.5 g. (56%) of a dark brown solid. Recrystallization from ethanol yielded a solid, m.p. 228-230° dec. A sample of this solid precipitated silver chloride when mixed with a solution of silver nitrate.

Anal. Calcd. for $C_{10}H_{10}Cl_3N_3O_2 \cdot HCl$: C, 34.61; H, 3.20; N, 12.11. Found: C, 34.75; H, 3.23; N, 11.99.

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(9) Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are corrected. A Varian A-60 spectrometer, using tetramethylsilane as an internal standard, was used to measure the nmr spectra. Chemical shifts are reported in τ (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Infrared spectra were determined in potassium bromide pellets.

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