1*H*-Imidazo[4,5-*b*]pyrazines. 1. 2-Alkyl Derivatives (1)

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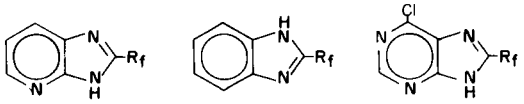
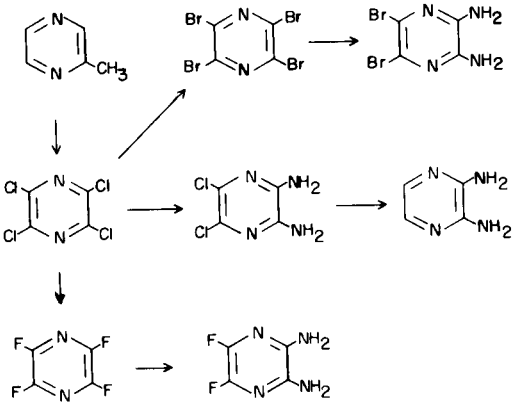
A group of 2-alkyl-1*H*-imidazo[4,5-*b*]pyrazines were prepared by condensing diaminopyrazines with acid, acid chloride or acid anhydride.

Newhold and co-workers noted the pesticidal activity of 3*H*-imidazo[4,5-*b*]pyridines (2) and benzimidazoles (3), with fluoroalkyl groups at the 2-position. We noticed the herbicidal activity of 6-chloro-8-trifluoromethylpurine. These compounds have in common an imidazole fused to a six-numbered ring with a fluoroalkyl group at the 2-position.



We set out to prepare 2-alkyl-1*H*-imidazo[4,5-*b*]pyrazines for our own pesticide screenings and antitumor screening at the National Cancer Institute.

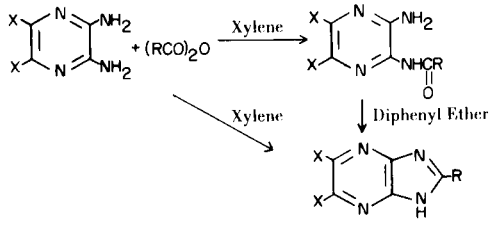
Preparation of the starting diamines are summarized in the following scheme.



Schipper and Day (4) in 1952 first reported imidazo[4,5-*b*]-pyrazine, Palamidessi and Luini (5) prepared 2,3-diamino-5,6-dichloropyrazine and converted it into imidazo[4,5-*b*]-pyrazine.

There are generally three mehtods for the preparation of 2-alkyl-1*H*-imidazo[4,5-*b*]pyrazines.

Method I. Reaction of Diamine with Acid Anhydride.



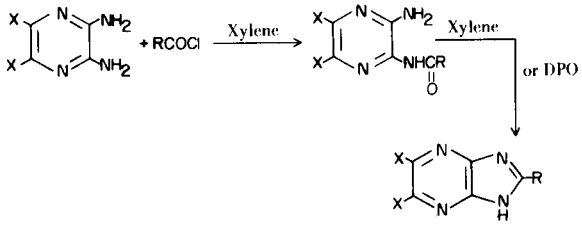
The compounds prepared are summarized in Table I.

Table I

2-Alkyl-1*H*-imidazo[4,5-*b*]pyrazines Prepared from 2,3-Diaminopyrazines and Acid Anhydrides

Compound	X	R	Ratio of diamine-anhydride	Hours in refluxing Xylene	Hours in refluxing DPO
I	Cl	CH_3	1:2.4	22	3
II	Cl	CF_3	1:2.2	9	1
III	H	CF_3	1:2.2	22	3
IV	H	CH_3	1:2.4	21	--
V	Cl	C_2F_5	1:1.0	20	--
VI	Br	CF_3	1:1.1	24	--
VII	Br	C_2F_5	1:1.0	24	--
VIII	F	CF_3	1:1.0	6	--
IX	Cl	CH_2Cl	1:1.0	20	--
X	Cl	Et	1:2.0	20	--

Method II. Reaction of Diamine with Acid Chloride.

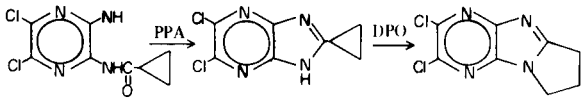


Compounds prepared were summarized in Table II.

Table II

2-Alkyl, Aryl-1*H*-imidazo[4,5-*b*]pyrazines Prepared from 2,3-Diaminopyrazines and Acid Chlorides

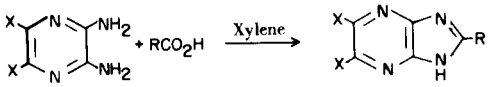
Compound	X	R	Ratio of diamine-acid chloride	Hours in refluxing Xyplene	Hours in refluxing DPO
XI	Cl	*n*-Propyl	1:1	20	4
XII	Cl	*iso*-Propyl	1:1	20	2
XIII	Cl	*iso*-Butyl	1:1	20	8
XIV	Cl	*t*-Butyl	1:1	20	2
XV	Cl	Adamantyl	1:1	24	10
XVI	Cl	$CClF_2$	1:1	2	1.5
V	Cl	C_2F_5	1:1	2	1.5
XVII	Cl	n-C_3F_7	1:1	15	---
XVIII	Cl	p-F-C_6H_4	1:1	8	25
XIX	Cl	m-$CF_3C_6H_4$	1:1	8	24
XX	H		1:1	2.5	1
XXI	Cl	$C_{17}H_{35}$	1:1	24	6



XXII XXIII

When R was cyclopropyl, the ring closure was carried out in PPA. Heating in boiling DPO gave the arranged product.

Method III. Reaction of Diamine with Acid.

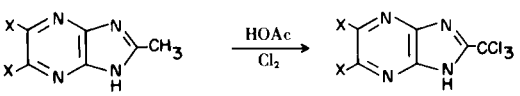


This method may have wider application than the few examples indicate. We started using this method rather late in the program and intend to use it more.

Table III

2-Alkyl-1*H*-imidazo[4,5-*b*]pyrazines Prepared from 2,3-Diaminopyrazines and Acids

Compound	X	R	Ratio of Diamine-acid	Hours in Refluxing Xylene
II	Cl	CF_3	1:2	20
XXIV	Cl	CHF_2	1:2	20
XXV	Br	CHF_2	1:2	20
XXVI	Cl	CH_2OH	1:2	20
XXVII	Cl	CH_2F	1:3	20



X = Cl I
X = H VI

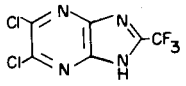
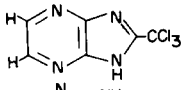
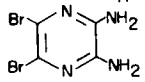
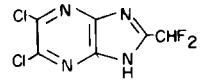
X = Cl XXVIII
X = H XXIX

Attempts to form the imidazole ring with trichloroacetylchloride and dichloropropionic acid resulted in tar. The trichloromethyl compounds were prepared by chlorination in acetic acid.

These compounds showed different degrees of pesticidal activities and antitumor activity. The more outstanding examples of the latter are summarized in Table IV.

Table IV

Antitumor Activity of 1*H*-imidazo[4,5-*b*]pyrazines

NSC No.	Structure	Tumors L-1210 OD	L-1210 T/C	P-388 OD	P-388 T/C	KB ED_{50}
150,436		100	176	100	150	
153,402				100	145	
165,920						2.2
167,059		50	145	75	140	

OD Optimum dosage. T/C Mean life span of test animals over control animals expressed in percentage. ED_{50} Effective dosage for 50% control.

EXPERIMENTAL

Tetrachloropyrazine was prepared by vapor phase chlorination of methylpyrazine in carbontetrachloride (10% w/w) at 545° in 15 times the molar ratio of chlorine for 13 seconds (6). Tetrabromo-

pyrazine was prepared by the procedure of Gulbenk (7). Tetrafluoropyrazine was prepared by the procedure of Musgrave, *et al.*, (8). 2,3-Diamino-5,6-dichloropyrazine and 2,3-diaminopyrazine were prepared according to the method of Palamidessi and Luini (5).

2,3-Diamino-5,6-dibromopyrazine and 2,6-Diamino-3,5-dibromopyrazine.

Tetrabromopyrazine was aminated in concentrated ammonium hydroxide (200 ml./0.1 mole) at 120° for 14 hours. The solid obtained was stirred in acetone and filtered. The acetone insoluble material was dried under vacuum and recrystallized from alcohol to give 2,3-diamino-5,6-dibromopyrazine, m.p. 252°.

Anal. Calcd. for $C_4H_4Br_2N_4$: C, 17.9; H, 1.5; N, 20.9. Found: C, 18.1; H, 1.5; N, 21.1.

From the acetone filtrate was isolated 2,6-diamino-3,5-dibromopyrazine, m.p. 160-165°.

Anal. Calcd. for $C_4H_4Br_2N_4$: C, 17.9; H, 1.5; N, 20.9. Found: C, 18.3 ; H, 1.5; N, 20.6.

The isomers can be separated on tlc (alumina-ethanol).

2,3-Diamino-5,6-difluoropyrazine.

Tetrachloropyrazine, 85 g. (0.39 mole) was mixed with 545 g. of anhydrous potassium fluoride and heated in a bomb at 315° for 15 hours. The tetrafluoropyrazine produced was collected in concentrated ammonium hydroxide trap. The content of the trap was then stirred at room temperature for 4 days. Filtration gave 3 g. of product. From the filtrate was obtained another 4.1 g. of product, m.p. 237-239°.

Anal. Calcd. for $C_4H_4F_2N_4$: C, 32.9; H, 2.8; N, 38.4. Found: C, 32.6; H, 2.5; N, 37.4.

5,6-Dichloro-2-methyl-1*H*-imidazo[4,5-*b*]pyrazine (I) (5).

2,3-Diamino-5,6-dichloropyrazine, 17.9 g. (0.1 mole), and 12.3 g. (0.12 mole) of acetic anhydride were mixed in 200 ml. of xylene and heated to boiling under reflux for 7 hours. Another 12.3 g. (0.12 mole) of acetic anhydride was added and heating was continued for another 15 hours. The reaction mixture was evaporated to dryness under reduced pressure and washed with hexane. The solid was mixed with 150 ml. of DPO and heated to boiling under reflux for 3 hours, cooled and diluted with 1 liter of hexane, filtered, and dried to give 15.7 g. of product (77%), m.p. 299-302°, (reported (5), m.p. 295-297°).

5,6-Dichloro-2-trifluoromethyl-1*H*-imidazo[4,5-*b*]pyrazine (II).

A. From 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine, 2 x 8 ml. of trifluoroacetic anhydride in 100 ml. of xylene, using the same procedure as in I, 9.5 g. (74%) of II was obtained, m.p. 168-170°.

Anal. Calcd. for $C_6HCl_2F_3N_4$: C, 28.0; H, 0.4; N, 21.8. Found: C, 28.3; H, 0.7; N, 21.3.

B. 2,3-Diamino-5,6-dichloropyrazine, 9.0 g. (0.05 mole) and 11.4 g. (0.1 mole) of trifluoroacetic acid were mixed in 100 ml. of xylene and heated to boiling under reflux for 20 hours. The reaction mixture was evaporated to dryness under reduced pressure. The residue was washed with hexane and filtered to give 13.9 g. of material. Infrared spectrum indicated the desired compound.

2-Trifluoromethyl-1*H*-imidazo[4,5-*b*]pyrazine (III).

By method for compound I, 5.5 g. (0.05 mole) of 2,3-diaminopyrazine and 16 ml. of trifluoroacetic anhydride gave 2.0 g. (21%) of the desired compound, purified from 2-propanol/hexane mixture, m.p. 220-222°.

Anal. Calcd. for $C_6H_3F_3N_4$: C, 38.3; H, 1.61; N, 29.8. Found: C, 38.5; H, 2.0; N, 29.4.

2-Methyl-1*H*-imidazo[4,5-*b*]pyrazine (IV).

By method for Compound I, 11.0 g. (0.1 mole) of 2,3-diaminopyrazine and 2 x 12.3 g. (0.12 mole) of acetic acid anhydride in 200 ml. of xylene gave IV. It was dissolved in 150 ml. of sodium hydroxide, treated with charcoal and filtered. The filtrate was acidified with 15 g. of acetic acid, the precipitate was collected by filtration, washed with water, alcohol and dried under vacuum to give 8.3 g. (62%) of desired compound, m.p. 365° subl., reported (9) m.p. 370°.

5,6-Dichloro-2-pentafluoroethyl-1*H*-imidazo[4,5-*b*]pyrazine (V).

A. Using the method for the preparation of Compound XIV, 4.4 g. (0.025 mole) of 2,3-diamino-5,6-dichloropyrazine and 4.5 g. (0.025 mole) of pentafluoropropionyl chloride in 50 ml. of xylene gave 2.6 g. (34%) of the titled compound, m.p. 178-179° from 2-propanol/hexane.

Anal. Calcd. for $C_7HCl_2F_5N_4$: C, 27.4; H, 0.3; N, 18.3. Found: C, 27.7; H, 0.5; N, 17.9.

B. 2,3-Diamino-5,6-dichloropyrazine, 9.0 g. (0.05 mole) and 15.5 g. (0.05 mole) of pentafluoropropionic anhydride were mixed in 120 ml. of xylene and heated to boiling under reflux for 20 hours. The reaction mixture was evaporated to dryness and the residue was extracted with benzene. Upon cooling, 7.8 g. (51%) of product was obtained, identified by ir spectrum.

5,6-Dibromo-2-trifluoromethyl-1*H*-imidazo[4,5-*b*]pyrazine (VI).

2,3-Diamino-5,6-dibromopyrazine, 13.4 g. (0.1 mole) was mixed with 100 ml. of xylene. The whole was heated to boiling under reflux. To this mixture was added slowly 8 ml. of trifluoroacetic anhydride followed by 20 ml. of xylene. Heating was continued under reflux for 24 hours. The reaction mixture was evaporated to dryness under reduced pressure and the residue extracted with benzene and sublimed to give 12.7 g. (37%) of product, m.p. 191-192°.

Anal. Calcd. for $C_6HBr_2F_3N_4$: C, 20.8; H, 0.3; N, 16.2. Found: C, 21.3; H, 0.7; N, 16.4.

5,6-Dibromo-2-pentafluoroethyl-1*H*-imidazo[4,5-*b*]pyrazine (VII).

Using the method given above, 13.4 g. (0.05 mole) of 2,3-diamino-5,6-dibromopyrazine was caused to react with 15.5 g. (0.05 mole) of pentafluoropropionic anhydride in 120 ml. of xylene. After sublimation, 5.2 g. (26%) of the desired product was obtained, m.p. 193-194°.

Anal. Calcd. for $C_7HBr_2F_5N_4$: C, 21.2; H, 0.3; N, 14.2. Found: C, 21.6; H, 0.5; N, 14.4.

5,6-Difluoro-2-trifluoromethyl-1*H*-imidazo[4,5-*b*]pyrazine (VIII).

Using the method B for Compound V, 7.3 g. (0.05 mole) of 2,3-diamino-5,6-difluoropyrazine and 8 ml. of trifluoroacetic anhydride in 120 ml. of xylene gave 6.7 g. (60%) of product, from benzene-methylcyclohexane, m.p. 150-152°.

Anal. Calcd. for $C_6HF_5N_4$: C, 32.2; H, 0.5; N, 25.0. Found: C, 32.6; H, 0.5; N, 24.6.

2-Chloromethyl-5,6-dichloro-1*H*-imidazo[4,5-*b*]pyrazine (IX).

Using method B for the preparation of V, 7.5 g. (0.042 mole) of 2,3-diamino-5,6-dichloropyrazine was caused to react with 6.7 g. (0.042 mole) of chloroacetic anhydride in 100 ml. of xylene to give 2.8 g. (28%) of material, m.p. 204°.

Anal. Calcd. for $C_6H_3Cl_3N_4$: C, 30.4; H, 1.3; N, 23.6. Found: C, 30.7; H, 0.8; N, 23.3.

5,6-Dichloro-2-ethyl-1*H*-imidazo[4,5-*b*]pyrazine (X).

Using the method for IV, 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine and 2 x 7.5 g. (0.05 mole) of propionic anhydride in 100 ml. of xylene (0.05 mole) yielded 8.5 g. (79%) of product, m.p. 286-290°.

Anal. Calcd. for $C_7H_6Cl_2N_4$: C, 38.7; H, 2.8; N, 25.8. Found: C, 38.8; H, 2.8; N, 26.0.

5,6-Dichloro-2-propyl-1*H*-imidazo[4,5-*b*]pyrazine (XI).

Using the method for I, 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine in 100 ml. of xylene and 5.3 g. (0.05 mole) of butyryl chloride, gave a crude product. The solid was boiled in 300 ml. of 2-propanol and filtered. It was then dissolved in 0.5*N* sodium hydroxide, treated with charcoal and filtered. The filtrate was acidified with acetic acid to give 4.0 g. (35%) of white powder, m.p. 278-281°.

Anal. Calcd. for $C_8H_8Cl_2N_4$: C, 41.6; H, 3.5; N, 24.3. Found: C, 41.8; H, 3.5; N, 24.9.

5,6-Dichloro-2-isopropyl-1*H*-imidazo[4,5-*b*]pyrazine (XII).

The reaction of 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine and 5.3 g. (0.05 mole) of isobutyryl chloride in 100 ml. of xylene was carried out as described in preparation of XI. After heating under reflux for 2 hours in diphenyl ether, the solid obtained was dissolved in warm 1*N* sodium hydroxide, treated with charcoal, and filtered. Upon acidification, 9.0 g. of material was obtained. The solid was washed repeatedly with dichloromethane until the ir spectrum was free of carbonyl and amino absorptions. The final product weighed 2.8 g. (24%), m.p. 145-146°.

Anal. Calcd. for $C_8H_8Cl_2N_4$: C, 41.6; H, 3.5; N, 24.2. Found: C, 41.8; H, 3.8; N, 24.2.

5,6-Dichloro-2-isobutyl-1*H*-imidazo[4,5-*b*]pyrazine (XIII).

The reaction of 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine and 6.0 g. (0.05 mole) of isovaleryl chloride in 100 ml. of xylene was carried out as described in the preparation of XI. The intermediate was heated under reflux for 8 hours in diphenyl ether, and worked up as before. Recrystallization from 2-propanol yielded 1.8 g. (15%) of product, m.p. 252-255°.

Anal. Calcd. for $C_9H_{10}Cl_2N_4$: C, 44.1; H, 4.1; N, 22.8. Found: C, 44.3; H, 3.8; N, 23.9.

2-*t*-Butyl-5,6-dichloro-1*H*-imidazo[4,5-*b*]pyrazine (XIV).

The reaction of 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine and 6.0 g. (0.05 mole) of pivaloyl chloride in 100 ml. of xylene was carried out as described in the preparation of XI. After heating for 2 hours in 150 ml. of refluxing diphenyl ether, the product obtained was recrystallized from 2-propanol/hexane mixture to give 5.6 g. of product containing diphenyl ether, as indicated by ir and mass-spectral analyses. Attempts to isolate a pure sample failed. The nmr spectrum indicated a 9:1 mixture of the desired compound and diphenyl ether.

2-Adamantyl-5,6-dichloro-1*H*-imidazo[4,5-*b*]pyrazine (XV).

Using the method A for Compound V, 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine, 10.0 g. (0.05 mole) of adamantanecarbonyl chloride in 120 ml. of xylene was added. Yield after recrystallization from 2-propanol followed by sublimation was 0.9 g. (5.6%) of product m.p. 315-317°.

Anal. Calcd. for $C_{15}H_{16}Cl_2N_4$: C, 55.7; H, 5.0; N, 17.3. Found: C, 55.9; H, 5.2; N, 17.5.

5,6-Dichloro-2-chlorodifluoromethyl-1*H*-imidazo[4,5-*b*]pyrazine (XVI).

In a flask equipped with Dewar condenser filled with dry ice, thermometer, magnetic stirrer and gas inlet tube was placed 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine in 100 ml. of xylene. While stirring at 10-15°, chlorodifluoroacetyl chloride was bubbled in until the weight loss of the small cylinder amounted to 7.5 g. (0.05 mole). The whole was stirred at room temperature for 4 hours followed by heating under reflux for 2 hours. The reaction mixture was evaporated to dryness and the residue mixed with 135 ml. of diphenyloxide and heated to 260° for 1½ hours. Work up as for Compound II gave 1.9 g. (14%) of desired product, m.p. 187-188°.

Anal. Calcd. for $C_6HCl_3F_2N_4$: C, 26.4; H, 0.4; N, 20.5. Found: C, 26.3; H, 0.6; N, 20.2.

5,6-Dichloro-2-(*n*-heptafluoropropyl)-1*H*-imidazo[4,5-*b*]pyrazine (XVII).

Using method A for Compound V, 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine in 150 ml. of xylene and 11.6 g. (0.05 mole) of heptafluorobutryl chloride yielded 3.3 g. (22%) of product m.p. 158-160° (from benzene-hexane).

Anal. Calcd. for $C_8HCl_2F_7N_4$: C, 26.9; H, 0.3; N, 15.7. Found: C, 27.0; H, 0.6; N, 15.6.

5,6-Dichloro-2-(*p*-fluorophenyl)-1*H*-imidazo[4,5-*b*]pyrazine (XVIII).

2,3-Diamino-5,6-dichloropyrazine, 9.0 g. (0.05 mole) and 7.9 g. (0.05 mole) of *p*-fluorobenzoyl chloride were mixed in 100 ml. of xylene, stirred at room temperature for 4 hours, and heated under reflux for 8 hours. The reaction mixture was evaporated to dryenss under reduced pressure; the residue was mixed with 150 ml. of DPO and heated to boiling under reflux for 25 hours. After cooling, the DPO solution was diluted with hexane and filtered. The solid was boiled in 200 ml. of 2-propanol and filtered. The insoluble material was sublimated and recrystallized from DMF-acetonitrile to give 2.7 g. (19%) of the desired compound, m.p. 377°.

Anal. Calcd. for $C_{11}H_5Cl_2FN_4$: C, 46.7; H, 1.8; N, 19.8. Found: C, 46.4; H, 2.1; N, 20.0.

5,6-Dichloro-2-(α,α,α-trifluoro-*m*-tolyl)-1*H*-imidazo[4,5-*b*]pyrazine (XIX).

Using the same procedure as reported in XVIII, 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine was caused to react with 10.4 g. (0.05 mole) of *m*-trifluoromethylbenzoyl chloride in 100 ml. of xylene. The solid from DPO-hexane was boiled in 200 ml. of alcohol and filtered. The filtrate was concentrated and recrystallized from 2-propanol twice to give 1.7 g. (11%) of desired compound, m.p. 173-174°.

Anal. Calcd. for $C_{12}H_5Cl_2F_3N_4$: C, 43.3; H, 1.5; N, 16.8. Found: C, 42.9; H, 1.4; N, 17.0.

2-(4-Thiazolyl)-1*H*-imidazo[4,5-*b*]pyrazine (XX).

Using the method for I, 5.5 g. (0.05 mole) of 2,3-diaminopyrazine and 7.4 g. (0.05 mole) of 4-thiazolecarbonyl chloride in 100 ml. of xylene yielded crude XX. The solid was washed with hot alcohol. The alcohol insoluble material was placed in a Soxhlet Extractor and extracted with alcohol for 24 hours to give 1.7 g. (17%) of product, m.p. 333° (by DTA).

Anal. Calcd. for $C_8H_5N_5S$: C, 47.3; H, 2.5; N, 34.5. Found: C, 47.7; H, 2.5; N, 34.5.

5,6-Dichloro-2-heptadecyl-1*H*-imidazo[4,5-*b*]pyrazine (XXI).

Using the method for I, 3.6 g. (0.02 mole) of 2,3-diamino-5,6-dichloropyrazine and 6.06 g. (0.02 mole) of stearoyl chloride in 200 ml. xylene yielded 5.1 g. (61%) of product, m.p. 162-164° (recrystallized from xylene).

Anal. Calcd. for $C_{22}H_{36}Cl_2N_4$: C, 62.0; H, 8.3; N, 13.1. Found: C, 61.8; H, 8.4; N, 13.6.

5,6-Dichloro-2-difluoromethyl-1*H*-imidazo[4,5-*b*]pyrazine (XXIV).

Using the method B reported for II, 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine and 9.6 g. (0.1 mole) of difluoroacetic acid in 100 ml. of xylene gave 4.8 g. (40%) of product, m.p. 173-174° from dichloromethane.

Anal. Calcd. for $C_6H_2Cl_2F_2N_4$: C, 30.2; H, 0.8; N, 23.4. Found: C, 30.4; H, 1.0; N, 23.0.

5,6-Dibromo-2-difluoromethyl-1*H*-imidazo[4,5-*b*]pyrazine (XXV).

Using method B reported in II, 13.4 g. (0.05 mole) of 2,3-diamino-5,6-dibromopyrazine was caused to react with 9.6 g. (0.1 mole) of difluoroacetic acid in 100 ml. of xylene. The product was purified by benzene extraction and sublimation to yield 6.0 g. (31%) m.p. 170-173°.

Anal. Calcd. for $C_6H_2Br_2F_2N_4$: C, 22.0; H, 0.6; N, 17.1. Found: C, 22.4; H, 1.0; N, 17.4.

5,6-Dichloro-2-hydroxymethyl-1*H*-imidazo[4,5-*b*]pyrazine (XXVI).

2,3-Diamino-5,6-dichloropyrazine, 9.0 g. (0.05 mole) and 7.6 g. (0.1 mole) of glycolic acid were mixed into 100 ml. of xylene. The mixture was heated to reflux for 20 hours. Evaporation under reduced pressure gave a tarry residue which was dissolved in 150 ml. of 1*N* sodium hydroxide treated with charcoal and then filtered. The filtrate was acidified with acetic acid and filtered again. The solid was boiled in 275 ml. of 2-propanol and filtered. The insoluble material, 8.8 g. (80%) was the desired product as indicated by ir, nmr and MS analyses, m.p. 280-281°.

Anal. Calcd. for $C_6H_4Cl_2N_4O$: C, 32.9; H, 1.8; N, 25.6. Found: C, 32.8; H, 1.9; N, 24.8.

5,6-Dichloro-2-fluoromethyl-1*H*-imidazo[4,5-*b*]pyrazine (XXVII).

A mixture of 18.0 g. (0.1 mole) of 2,3-diamino-5,6-dichloropyrazine, 23.4 g. (0.3 mole) of fluoroacetic acid and 0.5 g. of *p*-toluenesulfonic acid monohydrate in 300 ml. of xylene was heated to boiling under reflux for 20 hours. The clear solution was then decanted into a round flask and evaporated to dryness under reduced pressure. The solid, 25 g. was dissolved in 250 ml. of 1*N* sodium hydroxide solution and filtered. The alkaline filtrate was acidified with acetic acid and the precipitate was collected by filtration. The solid was stirred in 1600 ml. of dichloromethane at room temperature, decolorized with charcoal, and dried over magnesium sulfate. The organic mixture was concentrated to 150 ml. of give 5.8 g. (26%) of product.

Anal. Calcd. for $C_6H_3Cl_2FN_4$: C, 32.62; H, 1.37; Cl, 32.07; F, 8.60; N, 25.33. Found: C, 32.44; H, 1.27; Cl, 32.27; F, 8.81; N, 25.25.

5,6-Dichloro-2-trichloromethyl-1*H*-imidazo[4,5-*b*]pyrazine (XXVIII).

5,6-Dichloro-2-methyl-1*H*-imidazo[4,5-*b*]pyrazine, 100.0 g. (0.495 mole) was placed in 100 ml. of acetic acid and heated to 100°. The solution was irradiated with uv light while chlorine was bubbled in for 8 hours. The acetic acid solution was filtered hot and the filtrate was poured into 2 liters of ice water. The solid was filtered and dried to give 87.7 g. (58%) of desired product. A small sample was sublimated and sent for analysis, m.p. 247-248°.

Anal. Calcd. for $C_6HCl_5N_4$: C, 23.5; H, 0.3; N, 18.3. Found: C, 23.8; H, 0.6; N, 18.6.

2-Trichloromethyl-1*H*-imidazo[4,5-*b*]pyrazine (XXIX).

Using the above procedure, 13 g. (0.1 mole) of 2-methyl-1*H*-imidazo[4,5-*b*]pyrazine in 130 ml. of glacial acetic acid was chlorinated to give 14.1 g. (61.2%) of crystalline product, m.p. 275° dec., from 4:1 mixture of methanol and dichloromethane.

Anal. Calcd. for $C_6H_3Cl_3N_4$: C, 30.3; H, 1.3; N, 23.6. Found: C, 30.2; H, 1.4; N, 23.3.

2-Cyclopropyl-5,6-dichloro-1*H*-imidazo[4,5-*b*]pyrazine (XXII).

The reaction of 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine and 5.2 g. (0.05 mole) of cyclopropanecarbonyl chloride in 100 ml. of xylene was carried out as in XX. The intermediate so obtained was mixed with 150 g. of polyphosphoric acid and heated at 125° for 16 hours. At the end, the reaction mixture was poured into 1 kg. of ice and stirred until all tarry material dissolved. The precipitate was filtered, dried, placed in a Soxhlet Extractor and extracted with 2-propanol. From the 2-propanol solution was obtained 5.2 g. (45%) of product, m.p. 276-280°.

Anal. Calcd. for $C_8H_6Cl_2N_4$: C, 42.0; H, 2.6; N, 24.5. Found: C, 42.2; H, 3.0; N, 24.9.

Rearrangement of 2-Cyclopropyl-1*H*-imidazo[4,5-*b*]pyrazine, 2,3-Dichloro-7,8-dihydro-6*H*-pyrrolo[1′,2′:1,2]imidazo[4,5-*b*]pyrazine (XXIII).

A mixture of 11.5 g. (0.05 mole) 2-cyclopropyl-5,6-dichloro-1*H*-imidazo[4,5-*b*]pyrazine in 130 ml. of DPO with a trace of *p*-toluenesulfonic acid monohydrate present, was heated at reflux for 2 hours. The reaction mixture was cooled to 100°, poured into 900 ml. of hexane and filtered. The filter cake was placed in 300 ml. of dichloromethane with decolorizing charcoal. The mixture was stirred, filtered and concentrated to 100 ml. Upon addition of 100 ml. of hexane, 6.0 g. (52%) of product precipitated, m.p. 228-230°. The structure was confirmed by the disappearance of the NH in ir spectrum, and the appearance of three methylene groups in the nmr spectrum.

Anal. Calcd. for $C_8H_6Cl_2N_4$: C, 42.0; H, 2.6; N, 24.5. Found: C, 41.8; H, 2.8; N, 24.8.

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