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Novel 1-aryl-1*H*- and 1-aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxalines (flavazoles) **9a-c**, **12**, **13** were synthesized from 3-methyl-2-oxo-1,2-dihydroquinoxaline **5** and the 3-triazolylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **6**, respectively, *via* a facile hydrazone synthesis using aryl diazonium salts. Some of the above flavazoles and their related compounds exhibited the antifungal activity in some extent. The above results are described.

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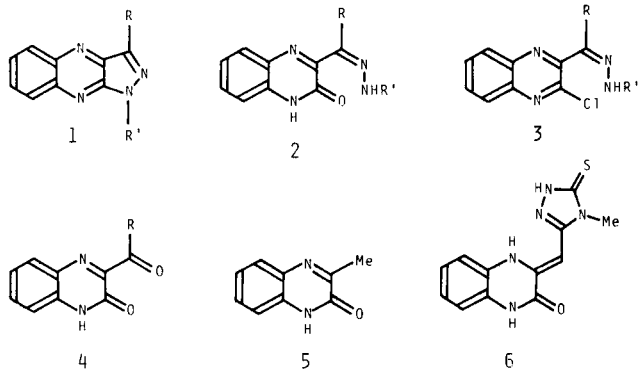
Various 1*H*-pyrazolo[3,4-*b*]quinoxalines (flavazoles) **1** have been synthesized by the direct dehydrative cyclization of the hydrazones **2** in a diluted base or acetic acid under reflux [2-5] or the dehydrochlorination of the 2-chlorinated hydrazones **3** [6,7], wherein the 3-acyl or 3-formyl (R = H) quinoxalines **4** have been required for the synthesis of the hydrazones **2** and **3**. However, we have found a facile method for the direct synthesis of the hydrazones **2** from the compounds such as the quinoxalines **5** [8] and **6** [9]. This method utilizes aryl diazonium salts in the hydrazone syntheses and needs no oxidation procedures for the methyl and methylene groups in the side-chains of **5** and **6**. This paper describes a convenient synthesis of the 1-aryl-1*H*- and 1-aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxalines **9a-c**, **10**, **12**, **13** (Schemes 1 and 2). Moreover, some of these compounds have been clarified to possess the antifungal activity in some extent by our screening tests, and hence the results are shown in Table 2.



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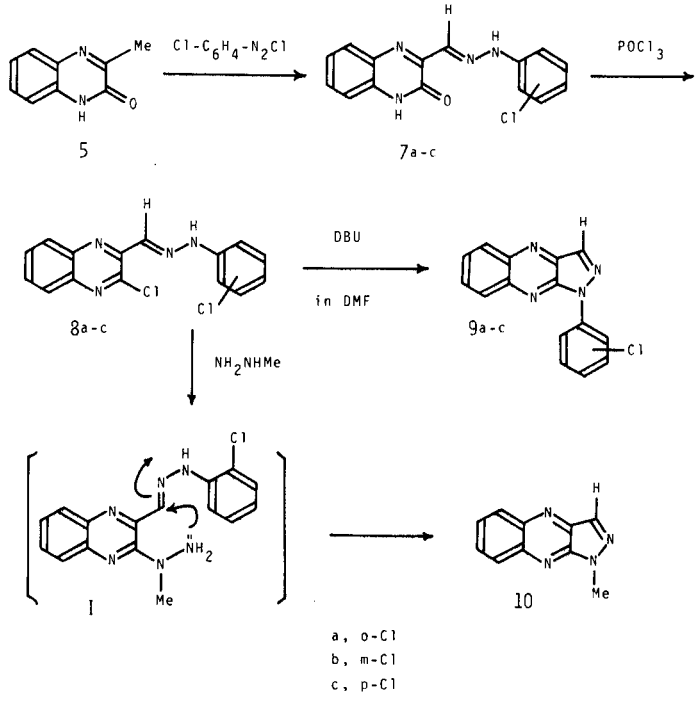
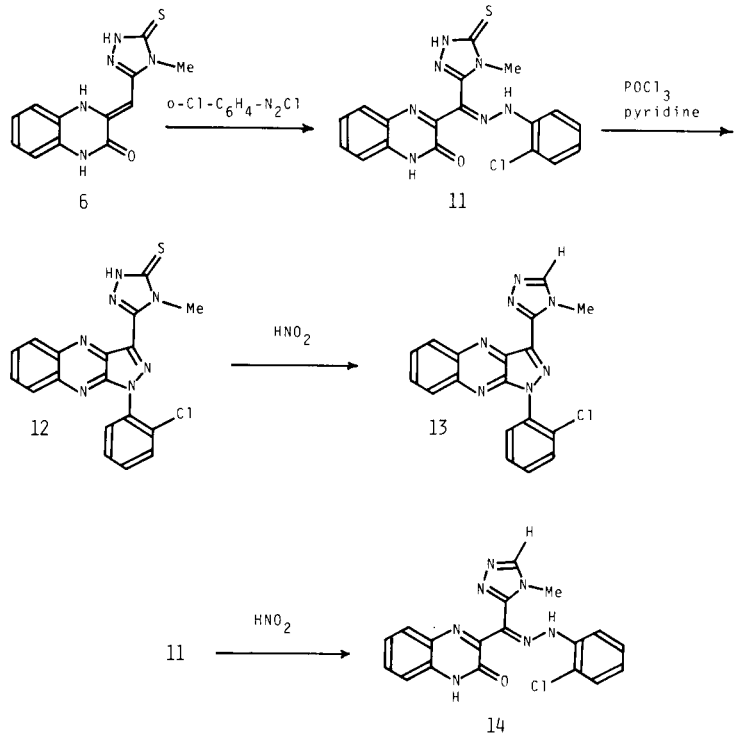


SCHEME 1

Synthesis of 1-Aryl-1*H*-pyrazolo[3,4-*b*]quinoxalines.

The reactions of **5** with chlorophenyl diazonium salts (*o*-, *m*-, *p*-Cl) gave 3-(chlorophenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines **7a-c**, whose chlorinations with phosphoryl chloride provided 2-chloro-3- (chlorophenylhydrazono)methylquinoxalines **8a-c**, respectively. Refluxing of **8a-c** and 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) in *N*,*N*-dimethylformamide resulted in dehydrochlorinative cyclization to afford 1-chlorophenyl-1*H*-pyrazolo[3,4-*b*]quinoxalines **9a-c**, respectively. On the other hand, the reaction of **8a** with an excess of methyl hydrazine produced 1-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline **10** [10], presumably *via* an intermediate I.



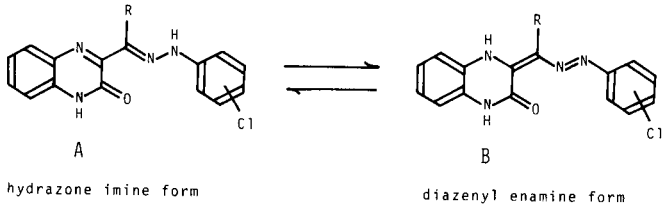
SCHEME 2

Synthesis of 1-Aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxalines.

The reaction of **6** with *o*-chlorophenyl diazonium salt gave 3-[α-(*o*-chlorophenylhydrazono)-2,3-dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-ylmethyl]-2-oxo-1,2-dihydroquinoxaline **11**, whose refluxing in phosphoryl chloride/pyridine effected one-step dehydrative cyclization to afford 1-(*o*-chlorophenyl)-3-(2,3-dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **12**. The reaction of **12** with nitrous acid resulted in sulfur extrusion to produce 1-(*o*-chlorophenyl)-3-(4-methyl-4*H*-1,2,4-triazol-5-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **13**. Similarly, the reaction of **11** with nitrous acid effected sulfur extrusion to provide 3-[α-(*o*-chlorophenylhydrazono)-4-methyl-4*H*-1,2,4-triazol-5- ylmethyl]-2-oxo-1,2-dihydroquinoxaline **14**.

Spectroscopic Property.

The pmr spectra of **7b** and **7c** in deuteriodimethylsulfoxide exhibited the tautomeric equilibria between the hydrazone imine form **A** and the diazenyl enamine form **B** (Scheme 3), as shown in our previous papers [11,12]. Namely, their pmr spectra represented the hydrazone CH and hydrazone NH proton signals due to the tautomer **A** together with the N_4-H and vinyl CH proton signals due to the tautomer **B**. However, **7a**, **11** and **14** predominated as the tautomer **A**. The tautomer ratios are shown in Table 1.



SCHEME 3

Table 1

Tautomer Ratios for **7**, **11** and **14**

Compound	Tautomer Ratio A	B
7a	100	---
7b	67	33
7c	67	33
11	100	---
14	100	---

Antifungal Activity.

Some of the compounds synthesized above exhibited the antifungal activity against *Pathium debaryanum*, *Pyriclaria oryzae* and *Rhizoctonia solani* in some extent, as shown in Table 2. In addition, compound **7c** showed the bactericidal activity against *Xanthomonas oryzae* (100% growth inhibition in a concentration of 100 ppm).

Table 2

Antifungal Activities of Compounds **7a-c**, **9a-c**, **11-14**

Compound	Concentration (ppm)	Activity [a] P.d.	P.o.	R.s. [b]
7a	100	37	7	48
	10	10	6	34
7b	100	35	9	45
	10	2	6	27
7c	100	100	10	56
	10	11	6	33
9a	100	96	59	79
	10	6	34	52
9b	100	58	9	31
	10	12	5	6
9c	100	58	10	15
	10	27	5	5
11	100	47	34	27
	10	4	16	0
12	100	62	42	51
	10	5	5	1
13	100	70	48	47
	10	5	11	10
14	100	65	35	46
	10	9	13	2

[a] Growth inhibition (%). [b] P.d.: *Pythium debaryanum*, P.o.: *Pyriclaria oryzae*, R.s.: *Rhizoctonia solani*.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded from potassium bromide discs on a JASCO IRA-1 spectrophotometer. The pmr spectra were measured with an EM-390 spectrometer at 90 MHz using tetramethylsilane as an internal standard. Chemical shifts are given in the δ scale, relative to the internal standard. Mass spectra (ms) were determined with a JMS-01S spectrometer (JEOL).

3-(Chlorophenylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines **7a-c**.

A solution of sodium nitrite (5.18 g, 0.075 mole) in water (60 ml) was added dropwise to a suspension of the appropriate chloroaniline hydrochloride (12.3 g, 0.075 mole) in 5% hydrochloric acid (200 ml) with stirring in an ice-water bath to give a clear solution, which was added to a suspension of compound **5** (10 g, 0.0625 mole) in acetic acid (60 ml)/water (40 ml). The whole reaction mixture was stirred in an ice-water bath for 30 minutes, and then heated on a boiling water bath for 1 hour to precipitate orange crystals **7**. Recrystallization from *N,N*-dimethylformamide/ethanol afforded orange needles [**7a**, 18.35 g (98%); **7b**, 18.10 g (97%); **7c**, 15.10 g (81%)]; mp 318-319° (**7a**), 304-305° (**7b**), 310-311° (**7c**); ms: m/z 298 (M^+), 300 ($M^+ + 2$); ir: ν cm^{-1} 1670 (C=O) (**7a-c**); pmr (deuteriodimethylsulfoxide): 14.73 (s, 1H, =N-NH-), 12.60 (brs, 1H, N_1-H), 7.87 (s, 1H, -CH=N-N), 7.87-6.87 (m, 8H, aromatic) (**7a**); (deuteriodimethylsulfoxide): 14.45 (s, ⅔ H, =N-NH-), 12.53 (brs, 1H, N_1-H), 11.33 (s, ⅓ H, N_4-H), 8.40 (s, ⅓ H, =CH-N=N), 7.78 (s, ⅔ H, -CH=N-N), 8.20-6.80 (m, 8H, aromatic) (**7b**); (deuteriodimethylsulfoxide): 14.53 (s, ⅔ H, =N-NH-), 12.53 (brs, 1H, N_1-H), 11.26 (s, ⅓ H, N_4-H), 8.37 (s, ⅓ H, =CH-N=N), 7.73 (s, ⅔ H, -CH=N-N), 8.13-7.00 (m, 8H, aromatic) (**7c**).

Anal. Calcd. for $C_{15}H_{11}ClN_4O$: C, 60.31; H, 3.71; Cl, 11.87; N, 18.76. Found: C, 60.40; H, 3.66; Cl, 11.65; N, 19.04 (**7a**); C, 60.32; H, 3.65; Cl, 11.96; N, 18.83 (**7b**); C, 60.19; H, 3.66; Cl, 11.66; N, 18.76 (**7c**).

2-Chloro-3-(chlorophenylhydrazono)methylquinoxaline **8a-c**.

A solution of **7a** (20 g) in phosphoryl chloride (300 ml) was refluxed in an oil bath for 9 hours. Phosphoryl chloride was evaporated *in vacuo* to precipitate yellow needles **8a**, to which 1,4-dioxane (300 ml) was added. The mixture was poured onto crushed ice to precipitate the yellow needles **8a**, which were collected by suction filtration (19.76 g, 90%).

Compounds **8b,c** were obtained by a similar manner to the above [**8b** (85%), **8c** (86%)].

Recrystallization from *N,N*-dimethylformamide/ethanol gave orange needles, mp 182-183° (**8a**), 163-164° (**8b**), 211-212° (**8c**); ms: m/z 316 (M^+), 318 ($M^+ + 2$) (**8a-c**); ir: ν cm^{-1} 3060, 3020, 1602, 1590, 1550, 1510 (**8a**), 3060, 3030, 1600, 1560, 1510 (**8b**), 3060, 3040, 1600, 1555, 1515, 1510 (**8c**); pmr (trifluoroacetic acid): 8.52 (s, 1H, hydrazone CH), 8.40-7.80 (m, 8H, aromatic) (**8a**); (trifluoroacetic acid): 8.47-7.27 (m, hydrazone CH and aromatic) (**8b**); (trifluoroacetic acid): 8.40-7.00 (m, hydrazone CH and aromatic) (**8c**); NH proton signals of **8a-c** were unobservable.

Anal. Calcd. for $C_{15}H_{10}Cl_2N_4$: C, 56.80; H, 3.18; Cl, 22.36; N, 17.66. Found: C, 56.83; H, 2.97; Cl, 22.13; N, 17.90 (**8a**); C, 56.72; H, 3.09; Cl, 22.18; N, 17.42 (**8b**); C, 56.93; H, 3.31; Cl, 22.54; N, 17.91 (**8c**).

1-Aryl-1*H*-pyrazolo[3,4-*b*]quinoxalines **9a-c**.

A solution of **8a** (2 g, 0.0063 mole) and DBU (0.96 g, 0.0076 mole) in *N,N*-dimethylformamide (100 ml) was refluxed in an oil bath for 3 hours. Removal of the solvent by evaporation *in vacuo* left an oily residue, which was triturated with water to give yellow crystals **9a** (1.46 g, 83%).

Compounds **9b,c** were obtained by a similar manner to the above [**9b** (81%), **9c** (79%)].

Recrystallization from ethanol afforded yellow needles, mp 108-109° (**9a**), 151-152° (**9b**), 199-200° (**9c**); ms: m/z 280 (M^+), 282 ($M^+ + 2$) (**9a-c**); ir: ν cm^{-1} 3080, 3055, 1585, 1575, 1565, 1490, 1470 (**9a**); 3120, 3080, 1600, 1590, 1570, 1560, 1540, 1520 (**9b**); 3110, 3060, 1600, 1580, 1570, 1560, 1540, 1500 (**9c**); pmr (deuteriodimethylsulfoxide): 9.10 (s, 1H, C_3-H), 8.47-7.57 (m, 8H, aromatic) (**9a**); (trifluoroacetic acid): 9.07 (s, 1H, C_3-H), 8.80-7.50 (m, 8H, aromatic) (**9b**); (trifluoroacetic acid): 9.07 (s, 1H, C_3-H), 8.80-7.50 (m, 8H, aromatic) (**9c**).

Anal. Calcd. for $C_{15}H_9ClN_4$: C, 64.18; H, 3.23; Cl, 12.63; N, 19.96. Found: C, 63.95; H, 3.50; Cl, 12.77; N, 19.74 (**9a**); C, 64.08; H, 3.30; Cl, 12.33; N, 19.72 (**9b**); C, 63.90; H, 3.16; Cl, 12.38; N, 19.97 (**9c**).

1-Methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline **10**.

A solution of **8a** (5 g, 0.0158 mole) and methylhydrazine (3.63 g, 0.0789 mole) in ethanol (500 ml) was refluxed for 3 hours. Removal of the solvent *in vacuo* gave yellow crystals **10** (1.20 g, 40%). Recrystallization from ethanol afforded analytically pure prisms, mp 113-114° [10]; pmr: (deuteriodimethylsulfoxide) 8.67 (s, 1H, C_3-H), 8.33-7.67 (m, 4H, aromatic), 4.18 (s, 3H, Me). The ir spectrum of this sample was identical with that of an authentic sample [10].

3-[α-(*o*-Chlorophenylhydrazono)-2,3-dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-ylmethyl]-2-oxo-1,2-dihydroquinoxaline **11**.

A solution of sodium nitrite (8.28 g, 0.12 mole) in water (100 ml) was added to a suspension of *o*-chloroaniline hydrochloride (18.1 g, 0.11 mole) in 10% hydrochloric acid (200 ml) with stirring in an ice-water bath to give a clear solution, which was successively added to a suspension of **6** (25.0 g, 0.092 mole) in acetic acid (300 ml) and water (100 ml) with stirring in an ice-water bath to afford a yellow suspension. The suspension was heated on a boiling water bath for 2 hours with an initial stirring to provide orange crystals **11** (36.73 g, 97%). Recrystallization from *N,N*-dimethylformamide/ethanol gave orange needles, mp 314-315°; ms: m/z 411 (M^+), 413 ($M^+ + 2$); ir: ν cm^{-1} 1663; pmr (deuteriodimethylsulfoxide): 14.47 (s, 1H, NH), 13.72 (s, 1H, NH), 12.72 (s, 1H, NH), 8.00-6.80 (m, 8H, aromatic), 3.49 (s, 3H, Me).

Anal. Calcd. for $C_{18}H_{14}ClN_7OS$: C, 52.49; H, 3.42; Cl, 8.51; N, 23.80; S, 7.78. Found: C, 52.22; H, 3.45; Cl, 8.62; N, 23.90; S, 7.65.

1-Aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxaline **12**.

A solution of the hydrazone **11** (20 g) in phosphoryl chloride (200 ml) and pyridine (20 ml) was refluxed in an oil bath for 3 hours. The solution was evaporated *in vacuo* to leave an oily residue, which was dissolved in dioxane. The solution was poured onto crushed ice to give yellow

crystals, which were collected by suction filtration. (These yellow crystals were confirmed to include no open-chained 2-chloro compound when checked by mass spectroscopy). A solution of the above whole yellow crystals and DBU (6.4 g) in *N,N*-dimethylformamide (400 ml) was refluxed in an oil bath for 3 hours. Evaporation of the solvent *in vacuo* followed by trituration with water furnished yellow crystals **12**, which were collected by suction filtration (17.94 g, 94%). Recrystallization from *N,N*-dimethylformamide/ethanol gave orange needles, mp 344-345°; ms: m/z 393 (M^+), 395 ($M^+ + 2$); ir: ν cm^{-1} 1570, 1510, 1490, 1475, 1460; pmr (deuteriodimethylsulfoxide): 14.37 (brs, 1H, NH), 8.67-7.60 (m, 8H, aromatic), 3.91 (s, 3H, Me).

Anal. Calcd. for $C_{16}H_{12}ClN_7S$: C, 54.89; H, 3.06; Cl, 9.00; N, 24.89; S, 8.14. Found: C, 54.92; H, 3.15; Cl, 9.30; N, 25.09; S, 8.12.

1-Aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxaline **13**.

A solution of sodium nitrite (3.51 g, 0.0509 mole) in water (20 ml) was added to a suspension of **12** (5 g, 0.0127 mole) in acetic acid (300 ml) with stirring in an ice-water bath. The whole mixture was heated on a boiling water bath for 2 hours to give a clear solution. The solvent was evaporated *in vacuo* to afford yellow crystals, which were triturated with hot water, and the residual yellow crystals **13** were collected by suction filtration (4.49 g, 98%). Recrystallization from *N,N*-dimethylformamide/-ethanol afforded yellow needles, mp 319-320°; ms: m/z 361 (M^+), 363 ($M^+ + 2$); ir: ν cm^{-1} 3080, 1585, 1560, 1515, 1490, 1470; pmr (trifluoroactic acid): 9.81 (s, 1H, $C_{3'}$-H), 9.00-7.57 (m, 8H, aromatic), 4.63 (s, 3H, Me).

Anal. Calcd. for $C_{16}H_{12}ClN_7$: C, 59.76; H, 3.34; Cl, 9.80; N, 27.10. Found: C, 59.65; H, 3.21; Cl, 9.71; N, 27.31.

3-[α-(*o*-Chlorophenylhydrazono)-4-methyl-4*H*-1,2,4-triazol-5-ylmethyl]-2-oxo-1,2-dihydroquinoxaline **14**.

A solution of sodium nitrite (10.07 g, 0.146 mole) in water (50 ml) was added to a suspension of the hydrazone **11** (20 g, 0.0486 mole) in acetic acid (500 ml) and water (50 ml) with stirring in an ice-water bath. The whole mixture was heated on a boiling water bath for 3 hours. After yellow crystals precipitated were filtered off, the solvent was evaporated *in vacuo* to provide crystals, which were triturated with hot water, and residual yellow crystals **14** were collected by suction filtration (14.85 g, 81%). Recrystallization from *N,N*-dimethylformamide/ethanol gave yellow needles as 1:1 complex of **14** and *N,N*-dimethylformamide, mp 316-317°; ms: m/z 379 (M^+), 381 ($M^+ + 2$); ir: ν cm^{-1} 1680, 1645, 1610; pmr (trifluoroacetic acid): 9.28 (s, 1H, $C_{3'}$-H), 8.67-7.13 (m, 9H, aromatic and CH of $HCONMe_2$), 4.16 (s, 3H, $N_{4'}$-Me), 3.38 (s, 3H, Me of $HCONMe_2$), 3.27 (s, 3H, Me of $HCONMe_2$).

Anal. Calcd. for $C_{21}H_{21}ClN_8O_2$: C, 55.69; H, 4.67; Cl, 7.83; N, 24.74. Found: C, 55.57; H, 4.39; Cl, 7.92; N, 24.58.

Acknowledgement.

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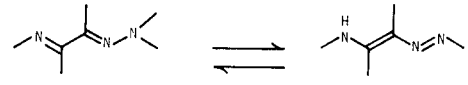

A hydrazone imine form ⇌ B diazenyl enamine form