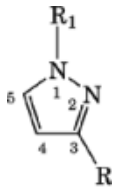
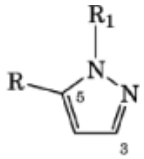
Kirk-Othmer Encyclopedia of Chemical Technology.

PYRAZOLES, PYRAZOLINES, AND PYRAZOLONES

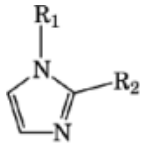
The compounds of this article, ie, five-membered heterocycles containing two adjacent nitrogen atoms, can best be discussed according to the number of double bonds present. Pyrazoles contain two double bonds within the nucleus, imparting an aromatic character to these molecules. They are stable compounds and can display the isomeric forms, **(1)** and **(2)**, when properly substituted. Pyrazoles are scarce in nature when compared to the imidazoles **(3)**, which are widespread and have a central role in many biological processes.



(**1**)

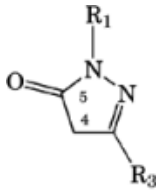


(**2**)

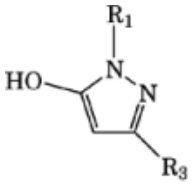


(**3**)

Pyrazolones, also containing two double bonds, are predominantly in the keto form **(4)**, although they can also exist in the enol form **(5)**.



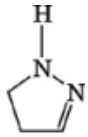
(**4**)



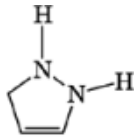
(**5**)

Pyrazolines have only one double bond within the nucleus and, depending on the position of the double bond, can exist in three separate forms: 1-pyrazoline [2721-43-9] **(6)**, 2-pyrazoline [109-98-8] **(7)**, and 3-pyrazoline [6569-23-9] **(8)**.

(**6**)

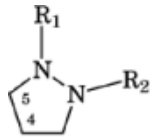


(**7**)

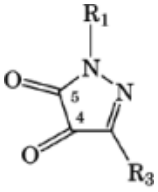


(**8**)

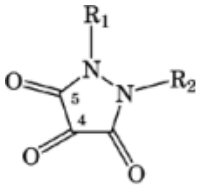
Neither pyrazolidines **(9)**, which have no double bonds, nor pyrazoline diones **(10)**, with two double bonds, and pyrazolidine triones **(11)**, which have three double bonds, are covered in this article.



(**9**)



(**10**)



(**11**)

Despite their scarcity in nature, the title compounds have found use in many applications, including pharmaceuticals, agricultural chemicals, and dyes.

Extensive reviews have been published, covering the literature to about 1967 (1–3). Pyrazoles and the benzopyrazoles have been well reviewed in References 4 and 5. More up-to-date reviews, though much narrower in scope, have been published on pyrazole oxides (6), dihydropyrazoles as insecticides (7), the anticancer drugs anthrapyrazoles (8, 9), and pyrazole sulfonylureas as herbicides (10).

1. Theoretical Methods

A number of theoretical studies on the reactivity of pyrazoles have been published (11). However, due to the difficulties involving these calculations, the studies often only approximate the actual reactions occurring in the laboratory. A summary of the calculated electron densities of the pyrazole molecule is available (11). Using the Dewar modified intermediate neglect of differential overlap (MINDO) method, optimized geometries have been obtained that approximate those observed from microwave spectroscopy and neutron diffraction experiments. Localization of the π-system has been established by Hückel molecular orbital (HMO) calculations. In accordance with experimental results, total electronic density values suggest electrophilic substitution at position 4. Pyrazole has a binding energy of 0.309 atomic units. It is less basic than imidazole due to greater destabilization of bonding after protonation as found by the MINDO method. Electron densities and bond orders of *N*-substituted pyrazoles have been calculated by the HMO method (12). The complete neglect of differential overlap (CNDO/2) procedure has been used to calculate π- and σ-electron densities on protonated and neutral *N*-methylpyrazole (13). Also, the energy required to localize π-electrons at the position where substitution takes place has been determined (12). Calculations for the electrophiles NO^+_2 and Br^+ include the electrostatic energy required to move the electrophile to the position where substitution takes place.

2. Structural Elucidation

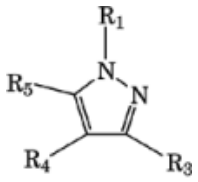
Among the modern procedures utilized to establish the chemical structure of a molecule, nuclear magnetic resonance (nmr) is the most widely used technique. Mass spectrometry is distinguished by its ability to determine molecular formulas on minute amounts, but provides no information on stereochemistry. The third most important technique is x-ray diffraction crystallography, used to establish the relative and absolute configuration of any molecule that forms suitable crystals. Other physical techniques, although useful, provide less information on structural problems.

2.1. Nuclear Magnetic Resonance Spectroscopy

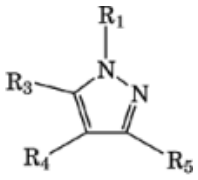
The literature up to 1984 has been reviewed (14).

2.1.1. ^{1}*H-Nmr*

This topic is best discussed in terms of the formulas **(12)** and **(13)**. In symmetrical pyrazoles with no substituents on N_1, ie, **(12)**, where $R_1 = H$ and $R_3 = R_5$, the peaks attributed to the R_3 and R_5 positions are the same on account of tautomerism; the peak due to R_4 is generally at a higher field. In *N*-substituted nonsymmetrical pyrazoles, ie, **(12)** and **(13)**, where $R_3 \neq R_5$, nmr has been widely used to distinguish between the two possible isomeric structures.



(12)



(13)

The following generalizations have been useful in determining the structures of isomeric pyrazoles. In compounds of type **(12)**, where $R_3 \neq R_5$ and $R_1 \neq H$, the coupling constant, $J_{4,5}$, is larger than $J_{3,4}$ and increases with an increase in the electron-withdrawing property of the substituent on N_1. The peak due to hydrogen at C_3 is normally broad because of the nuclear quadrupole relaxation effect of nitrogen. When R_4 is not hydrogen, the signal for the proton at C_3 is smaller than that for the proton at C_5; when R_4 is hydrogen, the signal at C_3 shows poorer resolution than that at C_5. The absorptions due to substituents at C_5 display solvent shifts that are greater than the solvent shifts displayed by substituents at C_3 (14). Table 1 summarizes the chemical shifts of some representative pyrazoles.

The main application of nmr in the field of pyrazolines is to determine the stereochemistry of the substituents and the conformation of the ring. For pyrazolones, nmr is useful in establishing the structure of the various tautomeric forms. Table 2 summarizes the chemical shifts of a few representative derivatives.

Table 1. ^{1}H-Nmr Chemical Shifts for Selected Pyrazoles (12)[a]

					$\delta(^1H)^b$, ppm			
Compound	R_1	R_3	R_4	R_5	R_1	R_3	R_4	R_5
pyrazole	H	H	H	H	12.64	7.61	6.31	7.61
3-methyl	H	CH_3	H	H		2.32	6.06	7.48
4-methyl	H	H	CH_3	H		7.36	2.09	7.36
3,5-dimethyl	H	CH_3	H	CH_3		2.21	5.76	2.21
3-phenyl	H	C_6H_5	H	H		7.77	6.53	7.52
4-fluoro	H	H	F	H	12.40	7.49		7.49
4-ethoxy	H	H	OC_2H_5	H	10.96	7.25	3.92; 1.36	7.25
3-cyano	H	CN	H	H	12.37		6.80	7.81
1-methyl	CH_3	H	H	H	3.88	7.49	6.22	7.35
1-phenyl	C_6H_5	H	H	H	7.2–7.6	7.72	6.46	7.87
1-acetyl	CH_3CO	H	H	H	2.70	7.71	6.44	8.25
1–amino	NH_2	H	H	H	6.30	7.30	6.06	7.30
1,3-dimethyl	CH_3	CH_3	H	H	3.80	2.23	5.95	7.22
1,5-dimethyl	CH_3	H	H	CH_3	3.73	7.36	5.98	2.22
1,3,4,5-tetra-methyl	CH_3	CH_3	CH_3	CH_3	3.68	2.14	1.89	2.12
1,3-dimethyl-5-phenyl	CH_3	CH_3	H	C_6H_5	3.80	2.30	6.09	7.43
1,5-dimethyl-3-phenyl	CH_3	C_6H_5	H	CH_3	3.80	7.78	6.30	2.30

[a]Ref. 15.
[b]Solvent is $CDCl_3$.

Table 2. ^{1}H-Nmr Chemical Shifts for Selected Pyrazolones and Pyrazolines[a]

	$\delta(^1H)^b$, ppm			
Compound	R_1	R_3	R_4	R_5
Pyrazolone				
3-methyl-1-phenyl-2-pyrazolin-5-one	7.3–7.8	2.12	3.37	
5-ethoxy-3-methyl-1-phenylpyrazole	7.0–7.9	2.26	5.50	4.14; 1.41
2,3-dimethyl-1-phenyl-3-pyrazolin-5-one	7.30	2.20	5.37	
Pyrazoline				
unsubstituted-Δ^2	5.33	6.88	2.65	3.31
1,3-dimethyl-Δ^2	2.74	1.95	2.96	3.58
1-formyl-3-methyl-Δ^2	8.81	2.05	2.88	3.90
1,2,3-trimethyl-Δ^3	2.55	1.71	4.60	3.65
1,2,3,5,5-pentamethyl-Δ^3	2.47	1.80	4.53	1.17

[a]Ref. 16.
[b]Solvent is $CDCl_3$.

2.1.2. ^{13}C-Nmr

The availability of superconducting magnets combined with spectrometers operating at up to 600 MHz has led to great advancements in ^{13}C-nmr spectroscopy. Pyrazole [288-13-1] itself shows one or two peaks for C_3 and C_5 depending on solvent and temperature, illustrating the similarity of the tautomers present in solution. When a substituent at N_1 is present, the chemical shifts at C_3 and C_5 move to higher (ppm) values (deshielded, lower fields) as the electron-withdrawing property of the N_1 substituent increases. Compared to ^{1}H-nmr, ^{13}C-nmr is much more precise in distinguishing between two isomers, eg, 3-CH_3 vs 5-CH_3 or *N*-CH_3. Table 3 presents the chemical shifts for a number of representative pyrazoles.

Table 3. ^{13}C-Nmr Chemical Shifts for Pyrazoles (1)[a]

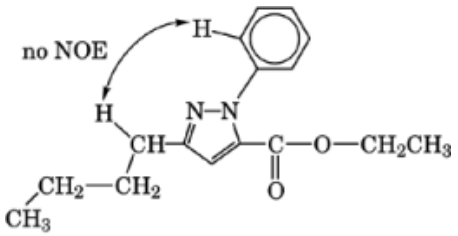
		$\delta(^{13}C)$, ppm from TMS[b]			
Compound	Solvent	C-1	C-3	C-4	C-5
pyrazole	CH_2Cl_2		134.6	105.8	134.6
	HMPT (−17°C)		138.1	103.9	127.6
	DMSO-d_6 (29°C)		138.6	104.5	128.2
3(5)-methylpyrazole	CH_2Cl_2		144.4 (CCH_3)	105.3	135.8
3(5)-nitropyrazole	acetone-d_6			102.4	132.6
3(5)-aminopyrazole	DMSO-d_6		154.0 (CNH_2)	91.5	132.0
1-methylpyrazole	$CDCl_3$	38.4	138.7	105.1	129.3
1-benzylpyrazole	$CDCl_3$	55.8 (CH_2)	139.4	105.7	129.1
1-phenylpyrazole	$CDCl_3$		140.7	107.3	126.2
1-acetylpyrazole	$CDCl_3$	21.3[c]; 169.2[d]	143.6	109.3	127.8
1-nitropyrazole	DMSO-d_6		141.6	109.8	126.8
1,3,5-trimethylpyrazole	CH_2Cl_2	36.3	147.5	105.4	139.8
3-amino-1-methylpyrazole	DMSO-d_6	38.0	155.7	92.2	131.5
5-bromo-1-phenylpyrazole	$CDCl_3$		141.1	110.2	112.5

[a] Ref. 17.
[b] TMS = tetramethylsilane.
[c] CH_3.
[d] CO.

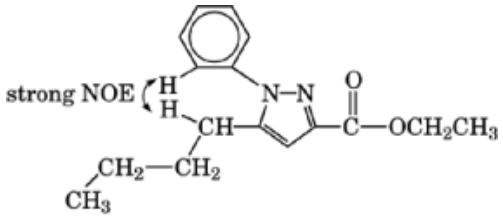
2.1.3. Newer Developments

The nmr spectra of four pyrazole derivatives using 98% sulfuric acid as the solvent has been recorded (18); proton chemical shifts, ^{1}H–^{1}H coupling constants, ^{13}C chemical shifts, and ^{1}H–^{13}C coupling constants of the pyrazolium derivatives were determined. Ten pyrazoles bearing a formyl or hydrazone group at C_4 and a benzyl, *p*-methoxybenzyl, or phenyl group attached to N_1, have been prepared. The ^{13}C signals of these derivatives were compared to pyrazoles unsubstituted at C_4 (19), and it was concluded that a formyl group produces a large effect on C_4 and lesser effect on C_5 and C_3 (19).

Nuclear Overhauser enhancement (NOE) spectroscopy has been used to measure the through-space interaction between protons at C_5 and the protons associated with the substituents at N_1 (20). The method is also useful for distinguishing between isomers with different groups at C_3 and C_5. Reference 21 contains the chemical shifts and coupling constants of a considerable number of pyrazoles with substituents at N_1 and C_4. NOE difference spectroscopy (^{1}H) has been employed to differentiate between the two regioisomers [153076-45-0] **(14)** and [153076-46-1] **(15)** (22). ^{15}N-nmr spectroscopy also has some utility in the field of pyrazoles and derivatives.



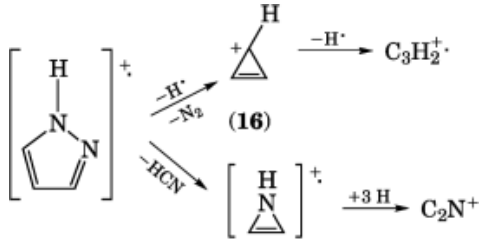
(14)



(15)

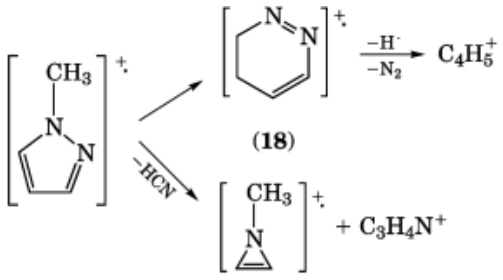
2.2. Mass Spectrometry

As of 1996, ms characteristics of pyrazoles and derivatives had not been described in depth. The fate of unsubstituted pyrazole (23) in the mass spectrometer operated in the electron ionization mode may be depicted as follows:



(17)

Loss of nitrogen occurs to give the cyclopropene **(16)**, which loses a proton to yield the charged species $C_3H^+{}_2$. Loss of HCN leads to the unsaturated aziridine **(17)**, which further decays to the C_2N^+ fragment. In the presence of a methyl group at N_1, ring enlargement can occur to give **(18)**, which degrades to the charged species $C_4H^+{}_5$, or degradation proceeds to a mixture of *N*-methylaziridine **(19)** and the charged species $C_3H_4N^+$.

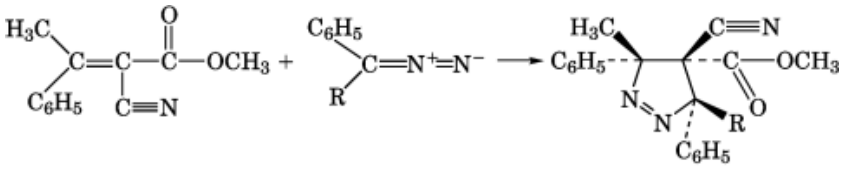


(19)

2.3. X-Ray Diffraction

Because of the rapid advancement of computer technology (qv), this technique has become almost routine and the structures of moderately complex molecules can be established sometimes in as little as 24 hours. An example illustrating the method is offered by Reference 24. The reaction of the acrylate **(20)** with

phenyldiazo derivatives results in the formation of pyrazoline **(21)**. The stereochemistry of the substituents and the conformation of the ring can only be established by single crystal x-ray diffraction.



(20) **(21)**

2.4. Miscellaneous Techniques

The use of ultraviolet (uv) and infrared (ir) spectroscopy has diminished drastically as newer and more powerful procedures have been introduced. However, uv is still useful in studying the tautomeric structures and ionization constants of pyrazoles. Studies of the effect of substituents on the absorption and fluorescence properties of di- and triphenyl-substituted pyrazolines showed that electron-withdrawing groups attached to phenyl groups such as –CN, $–SO_2CH_3$, and $–OCOCH_3$ cause a profound quenching of fluorescence (25). Infrared spectroscopy was used in theoretical studies on pyrazoles and deuterated pyrazoles, and also to facilitate structure determination. Infrared was also used to characterize in solution the various tautomeric forms of pyrazolones (double bond within or outside the ring). The three isomeric pyrazolines could be distinguished by their characteristic N═N and C═N vibrations (26). Other methods useful in structural elucidation are microwave spectroscopy and dipole moment measurements, but these are seldom used in the field of pyrazoles.

3. Physical Properties

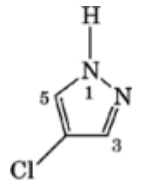
Pyrazoles in general are stable compounds, as demonstrated by pyrazole itself, which distills at 186°C at atmospheric pressure. The boiling point (bp) increases with an increase in the number of alkyl substituents on carbon. *N*-Methylation decreases both the bp and the melting point (mp) as a result of the elimination of hydrogen bonding. Thus 3-methylpyrazole [1453-58-3] has a bp of 205°C and the isomeric *N*-methylpyrazole [930-36-9] has a bp of 127°C. Pyrazoles with substituents at C_3 (C_5) are tautomeric mixtures and form azeotropes. The solubility of pyrazole in H_2O is about 1 g/mL, but it is much less soluble in organic solvents. Pyrazole is a weak base ($pK_a = 2.5$) and can be protonated by strong acids; strong bases yield metal salts. The pyrazolines resemble the pyrazoles in their physical properties. They are liquids with a high bp or low mp. Pyrazolines are basic and the ease of protonation is dependent on the position of the double bond. Most pyrazolones are solids and the mp usually decreases in the presence of substituents at N_1. Simple low molecular weight pyrazolones are soluble in hot water and the higher mol wt materials are soluble in most organic solvents. Hydrogen bonding has strong influence on the predominant tautomeric form. 3-Pyrazolones are more basic than the isomeric 5-pyrazolones.

4. Chemical Reactivity

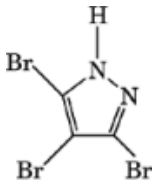
4.1. Pyrazoles

The chemical reactivity of the pyrazole molecule can be explained by the effect of individual atoms. The N-atom at position 2 with two electrons is basic and therefore reacts with electrophiles. The N-atom at position 1 is

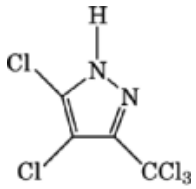
unreactive, but loses its proton in the presence of base. The combined two N-atoms reduce the charge density at C_3 and C_5, making C_4 available for electrophilic attack. Deprotonation at C_3 can occur in the presence of strong base, leading to ring opening. Protonation of pyrazoles leads to pyrazolium cations that are less likely to undergo electrophilic attack at C_4, but attack at C_3 is facilitated. The pyrazole anion is much less reactive toward nucleophiles, but the reactivity to electrophiles is increased. Some of the more general chemical properties of the pyrazole molecule are as follows. Chlorination of pyrazole yields 4-chloropyrazole [15878-00-4] **(22)** and bromination can produce mono-, di-, or tribromo pyrazoles [17635-44-8] **(23)**. 3-Methylpyrazole on treatment with chlorine in acetic acid yields the pentachloropyrazole derivative **(24)** [80294-32-2].



(22)

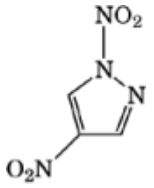


(23)

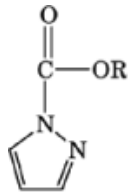


(24)

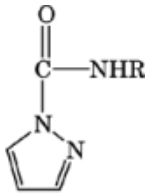
1,4-Dinitropyrazole [35852-77-8] **(25)** can be reduced, or can react with amines to give 5-substituted pyrazoles. Friedel-Craft reactions introduce acyl groups at C_4. Halogens at C_3 or C_5 can be displaced only if there is an activating group at C_4; bromine at C_4 can be replaced by hydrogen or a carboxyl group after treatment with butyllithium. In the presence of base, alkyl and acyl halides react at N_1 to yield alkyl and acyl derivatives, respectively. Treatment with alkyl chloroformate leads to **(26)** and reaction with isocyanates yields **(27)**.



(25)

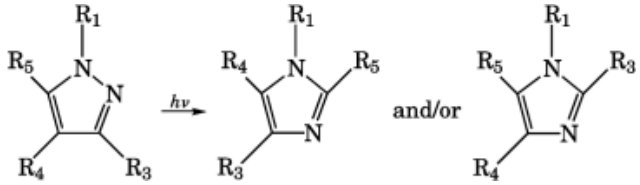


(26)

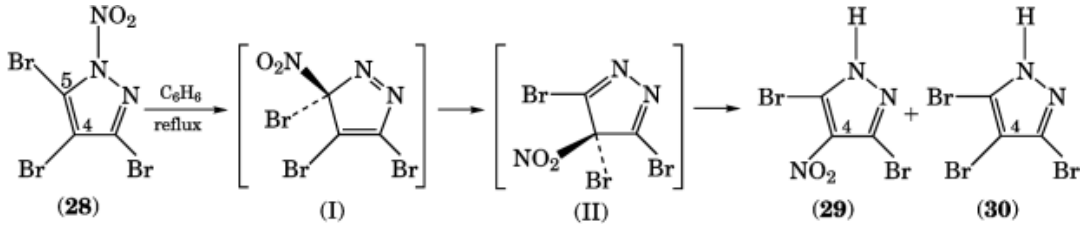


(27)

The pyrazole ring is resistant to oxidation and reduction. Only ozonolysis, electrolytic oxidations, or strong base can cause ring fission. On photolysis, pyrazoles undergo an unusual rearrangement to yield imidazoles via cleavage of the N_1–N_2 bond, followed by cyclization of the radical intermediate to azirine (27).



1-Nitropyrazoles undergo a thermal intramolecular rearrangement leading to the migration of the nitro group from nitrogen (N_1) to carbon (C_3 and C_4) (28). Thermolysis of 1-nitro-3,4,5-tribromopyrazole [104599-40-8] **(28)** in boiling benzene gives a mixture consisting of di- and tribromopyrazole derivatives, **(29)** and **(30)**, with the nitro group having migrated from N_1 to C_4.



This reaction probably proceeds via the bromo nitro intermediate (I), which under certain conditions rearranges to intermediate (II) by a second migration of the nitro group from C_5 to C_4. Loss of Br or NO_2 can lead to a neutral pyrazolyl radical, followed by phenylation on nitrogen to yield 1-phenylpyrazole derivatives such as 1-phenyl-3,5-dibromo-4-nitropyrazole [104599-39-5] or 1-phenyl-3,4,5-tribromopyrazole.

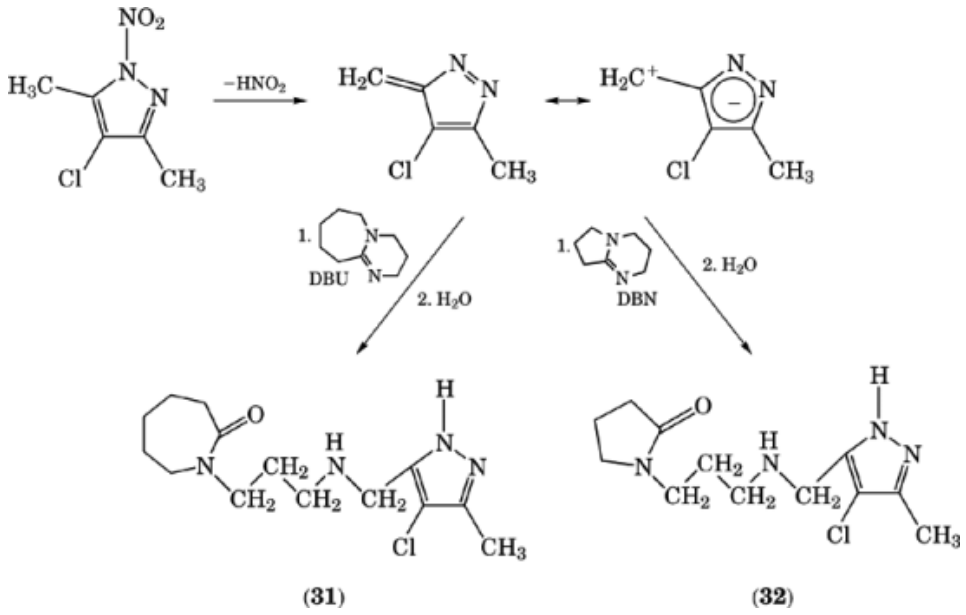


Fig. 1. Intermediary of diazafulvene in reactions of 1-nitropyrazoles.

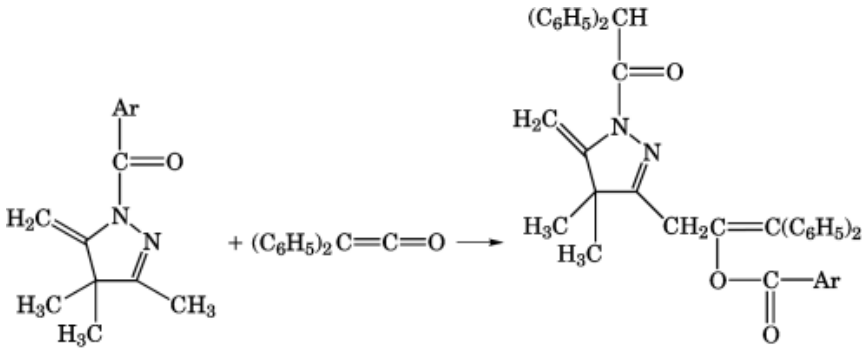
On changing solvents from benzene to acetonitrile, besides the previously identified compounds 3,5-dibromo-4-nitropyrazole [104599-36-2] **(29)** and 3,4,5-tribromopyrazole [17635-44-8] **(30)**, 3,4-dibromo-5-nitropyrazole [104599-37-3] is also isolated, further indicating the presence of (I) as an intermediate. Reaction of 4-chloro-3,5-dimethyl-1-nitropyrazole [153813-97-9] with three equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in acetonitrile leads to two unexpected compounds, 1 and 1, respectively (29). Their formation takes place via the nucleophilic attack of DBU or DBN on the diazafulvene intermediate, which in turn arises by the elimination of HNO_2 from the starting pyrazole (Fig. 1).

Oxidation of N_1-substituted pyrazoles to 2-substituted pyrazole-1-oxides using various peracids (30) facilitates the introduction of halogen at C_3, followed by selective nitration at C_4. The halogen atom at C_3 or C_5 is easily removed by sodium sulfite and acts as a protecting group. Formaldehyde was used to direct the selective introduction of electrophiles at C_5 in a simple one-pot procedure (31). The SO_2NH_2 moiety has been introduced selectively at C_5 by treating ethyl 1-methylpyrazole-4-carboxylate with lithium diisopropylamide (LDA), followed by SO_2, *N*-chlorosuccinimide, and 28% aqueous ammonium hydroxide (32).

4.2. Pyrazolines

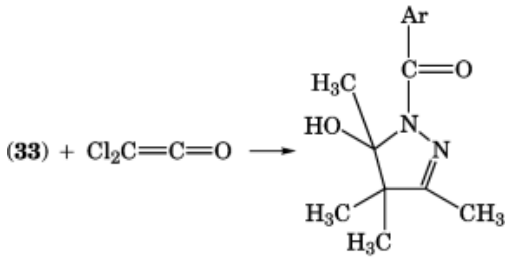
The chemical properties of pyrazolines are governed by their relative instability. They readily undergo ring cleavage, and are easily reduced and oxidized. Loss of nitrogen occurs in pyrazolines lacking a substituent at N_1 to give a mixture of olefins and cyclopropanes, the latter being predominant. This elimination occurs near the mp and can be catalyzed by uv light, aluminum oxide, and many other substances. Mild reduction of pyrazolines leads to pyrazolidines. Sodium–alcohol, tin–HCl, or Raney nickel cause ring cleavage, yielding diamines or aminonitrile derivatives. Pyrazolines are easily oxidized to pyrazoles by many reagents, such as bromine, permanganate, and lead tetraacetate. Besides pyrazole formation, rearrangements or side-chain oxidations may also occur. Oxidation with peracids produce N-oxides. Pyrazolines lacking a substituent at N_1 undergo reactions typical of secondary amines, such as acylation, benzoylation, nitrosation, carbamate, and urea formation. An interesting reaction of pyrazoline has been described (33). Reaction of **(33)** with excess

diphenylketene gives a 60% yield of the rearranged **(34)**; the structure of **(34)** has been determined by x-ray crystallography.



(33) **(34)**

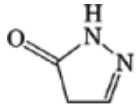
With dichloroketene, the reaction takes a different path leading to the hydroxypyrazoline **(35)**. A mechanism to explain these results has been proposed (33).



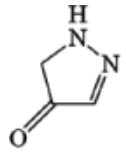
(35)

4.3. Pyrazolones

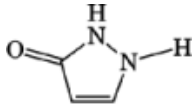
The oxo derivatives of pyrazolines, known as pyrazolones, are best classified as follows: 5-pyrazolone, also called 2-pyrazolin-5-one [137-44-0] **(36)**; 4-pyrazolone, also called 2-pyrazolin-4-one [27662-65-3] **(37)**; and 3-pyrazolone, also called 3-pyrazolin-5-one [137-45-1] **(38)**. Within each class of pyrazolones many tautomeric forms are possible; for simplicity only one form is shown.



(36)

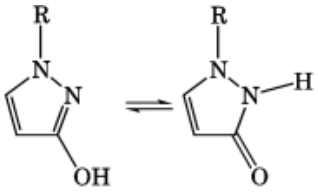


(37)



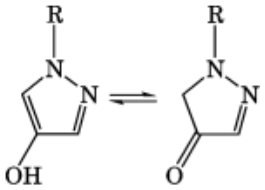
(38)

Substitution at N_1 decreases the possible number of tautomers: for 3-pyrazolones, two tautomeric forms are possible, **(39)** and **(40)**, which in nonpolar solvents are both present in about the same ratio. 5-Pyrazolones exhibit similar behavior.



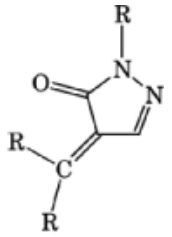
(39) (40)

In 4-pyrazolones, the enol form predominates, although the keto form has also been observed.

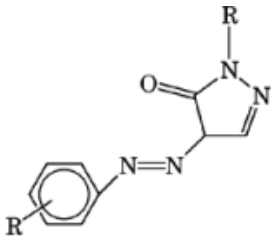


enol keto

The tautomeric character of the pyrazolones is also illustrated by the mixture of products isolated after certain reactions. Thus alkylation normally takes place at C_4, but on occasion it is accompanied by alkylation on O and N. Similar problems can arise during acylation and carbamoylation reactions, which also favor C_4. Pyrazolones react with aldehydes and ketones at C_4 to form a carbon–carbon double bond, eg **(41)**. Coupling takes place when pyrazolones react with diazonium salts to produce azo compounds, eg **(42)**.

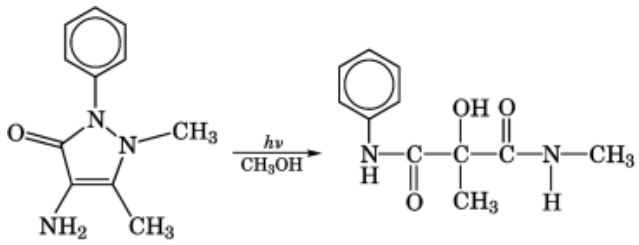


(41)



(42)

Compounds of type **(42)** are widely used in the dye industry (see Azo dyes). The Mannich reaction also takes place at C_4, as does halogenation and nitration. The important analgesic aminoantipyrine [83-07-8] **(43)** on photolysis in methanol undergoes ring fission to yield **(44)** (27).



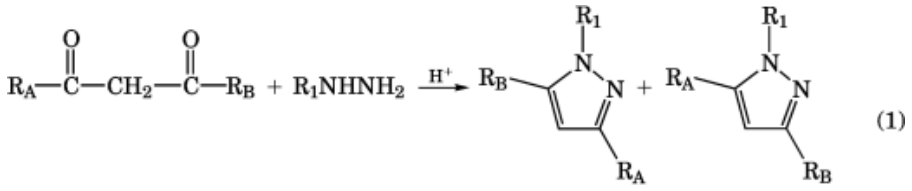
(43) (44)

5. Synthesis

Although there are many publications devoted to the synthesis of pyrazoles and related compounds, most can be classified into one of four principal categories, with the first class being by far the most important: (*1*) from the reaction of hydrazine or its derivatives with β-bifunctional compounds, or compounds that give rise to such functionality; (*2*) by 1,3-dipolar cycloaddition, usually involving diazo compounds; (*3*) by ring-opening of more complex systems already containing the pyrazole nucleus; and (*4*) by chemical, thermal, or photochemical rearrangement of other monocyclic heterocycles. Examples from each class follow.

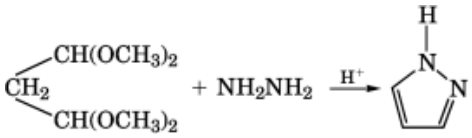
5.1. From Hydrazines and β-Bifunctional Compounds

One of the oldest examples in this class is the reaction of a β-diketone with a substituted hydrazine to give a pyrazole (eq. **1**).



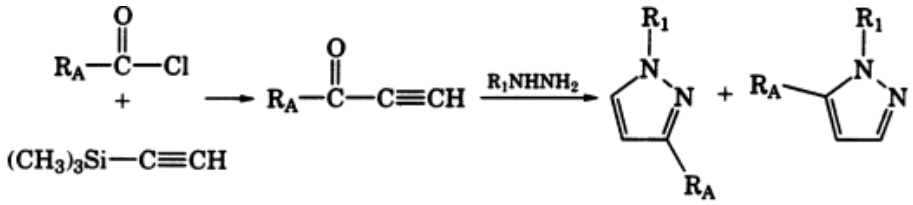
(1)

If $R_A \neq R_B$, a mixture of the two isomeric pyrazoles is obtained. An excellent method to prepare pyrazole [288-13-1] consists in treating 1,1,3,3-tetramethoxypropane (masked malondialdehyde) with hydrazine (eq. **2**).



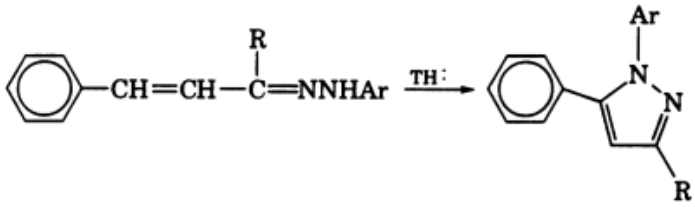
(2)

Reaction of an acid chloride with trimethylsilylacetylene produces an α,β-ethynyl ketone, which on treatment with substituted hydrazines yields a mixture of 1,5- and 1,3-substituted pyrazoles (34). The ratio is dependent on the reaction conditions (eq. **3**).



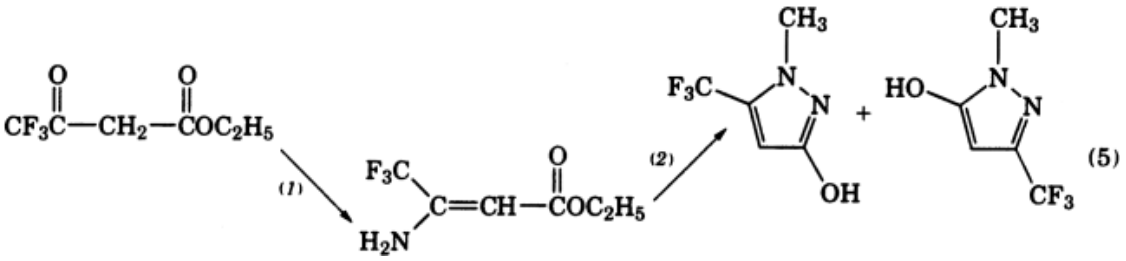
(3)

Unsaturated ketones react with phenylhydrazines to form hydrazones, which under acidic conditions cyclize to pyrazolines (35). Oxidation, instead of acid treatment, of the hydrazone with thianthrene radical cation ($TH^{\cdot+}$) perchlorate yields pyrazoles; this oxidative cyclization does not proceed via the pyrazoline (eq. **4**).

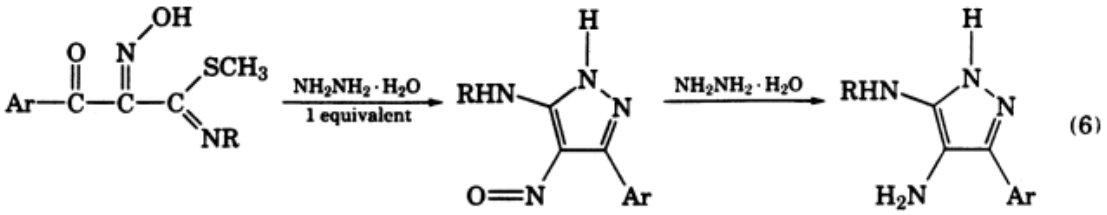


(4)

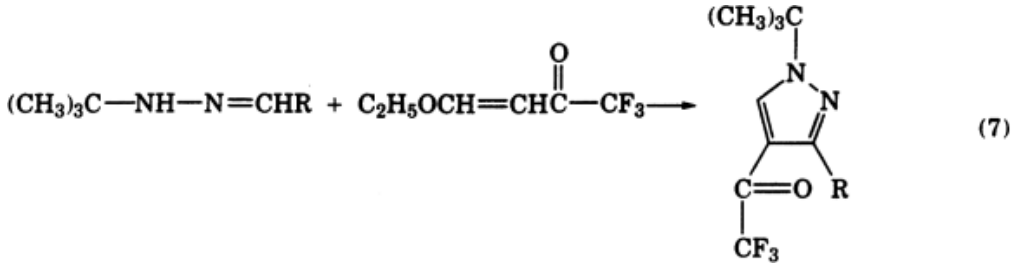
Reaction of a β-ketoester with gaseous ammonia (*1*) gives an enamine, which on treatment with methylhydrazine (*2*) yields an 85:15 mixture of 3-hydroxy- and 5-hydroxy-1-substituted pyrazoles (36) (eq. **5**). Previously β-ketoesters furnished mainly the 5-hydroxy isomer.



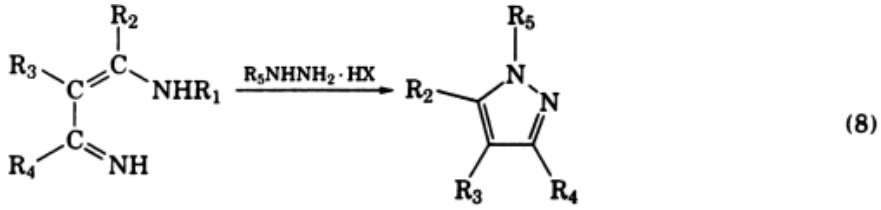
Treatment of a hydroxyiminoimine with one equivalent of hydrazine hydrate gave a nitrosopyrazole, which on addition of excess hydrazine hydrate yielded a 4-aminopyrazole derivative (eq. **6**) (37).



The need for pyrazoles substituted with the trifluoroacetyl group led to the reaction of ethoxyvinyl ether with trifluoroacetic anhydride, yielding 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (38); this further reacted with aldehyde *tert*-butylhydrazones, and after cyclization at room temperature under mildly acidic conditions the pyrazoles were obtained in satisfactory yields (eq. **7**). Further treatment with H_2SO_4 removed the *tert*-butyl group, thus providing an opportunity for further derivatization at N_1.

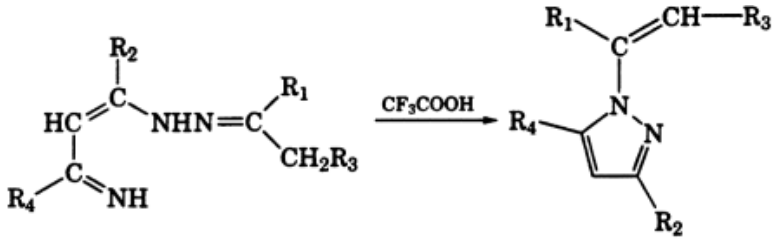


Reaction of 4-amino-1-azabutadienes **(45)** with various hydrazine salts at 60°C leads to the expected pyrazoles **(46)** without isolation of the hydrazone intermediate (eq. **8**) (39).



(45) **(46)**

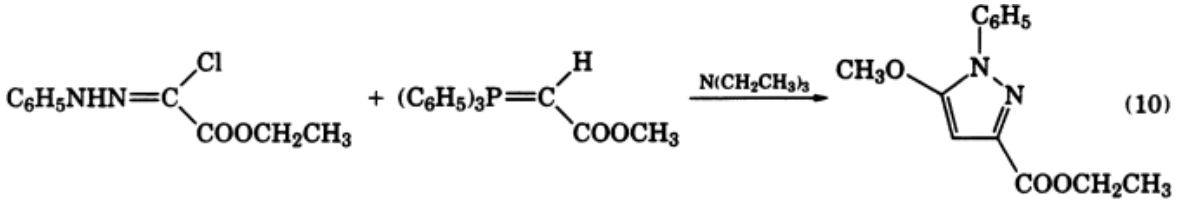
On reaction with *N*-methyl-*N*-phenylhydrazine, however, the hydrazone **(47)** can be isolated, which on further treatment with anhydrous trifluoroacetic acid gives an *N*-alkenylpyrazole **(48)** (eq. **9**).



(9)

(47) **(48)**

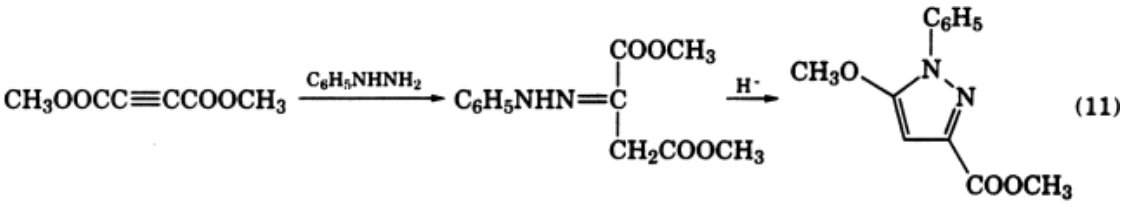
Instead of a β-dicarbonyl compound, triphenylphosphorane derivatives have been used to synthesize 5-alkoxy-substituted pyrazoles (40). Thus, reaction of ethyl chloroglyoxalate phenylhydrazone **(49)** with carbomethoxymethylene triphenylphosphorane **(50)** furnishes the 5-methoxypyrazole **(51)** in an 84% yield (eq. **10**).



(10)

(49) **(50)** **(51)**

Structure proof is based on spectroscopic means and an independent synthesis of **(51)**. Reaction of phenylhydrazine with dimethyl acetylenedicarboxylate gives a hydrazone, which is then cyclized to 1-phenyl-3-methoxycarbonyl-5-methoxypyrazole [113246-37-0] **(52)** (eq. **11**). This is followed by transesterification with ethanol, yielding **(51)**. A second synthesis utilizing phosphorus has also been developed (41). 1,4-Addition of triphenylphosphine to conjugated azoalkenes gives rise to 3-hydrazono-2-triphenylphosphoranylidenebutanoates **(53)**. The latter, on treatment with acid chlorides or anhydrides, leads to the intermediate **(54)**, which cyclizes spontaneously to the phosphonium betaine **(55)**. Loss of triphenylphosphine oxide produces the desired pyrazoles **(56)** in good to excellent yields.

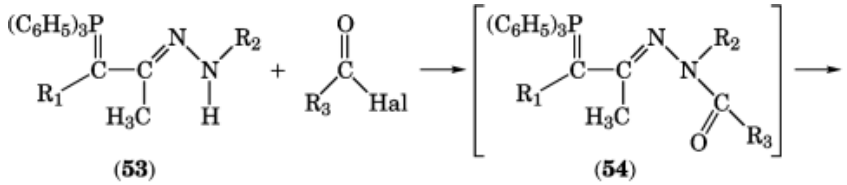


(11)

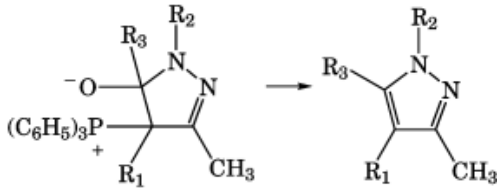
(52)

5.2. From Diazo Compounds via 1,3-Dipolar Cycloaddition

This method has been utilized widely in heterocyclic chemistry. Pyrazoline **(57)** has been synthesized by reaction of ethyl diazoacetate **(58)** with α,β-unsaturated ester in the presence of pyridine (eq. **12**) (42).

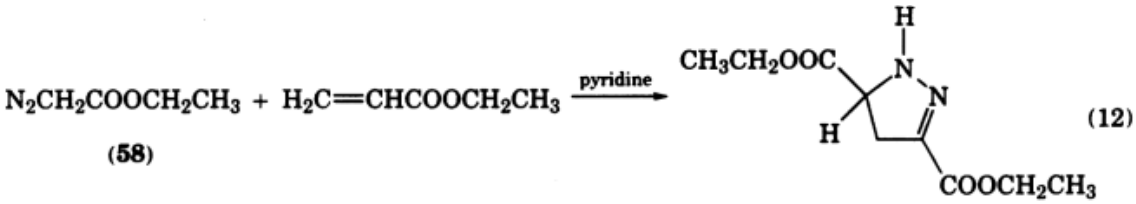


(53) **(54)**



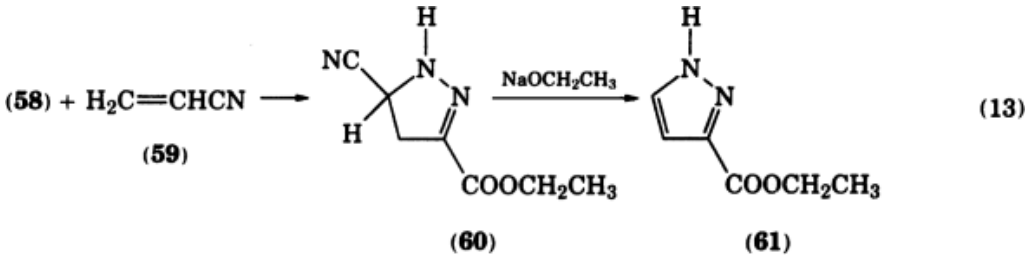
(55) **(56)**

Reaction of **(58)** with unsaturated nitrile **(59)** produces 5-cyanopyrazoline **(60)**, which on treatment with sodium ethoxide eliminates hydrogen cyanide to provide the pyrazole **(61)** in high yield (eq. **13**).



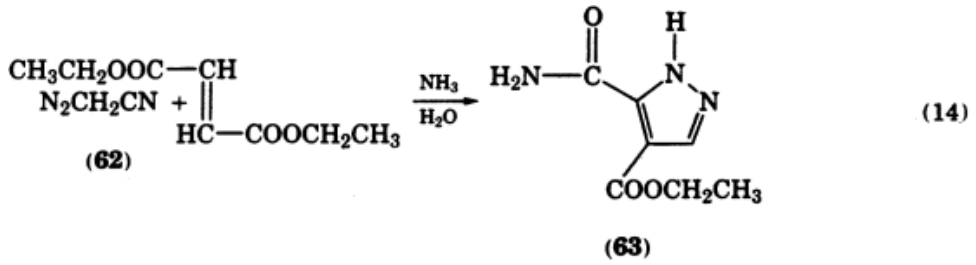
(58) **(57)** **(12)**

Reaction of aminoacetonitrile hydrochloride with sodium nitrite provides diazoacetonitrile **(62)**. The product undergoes a 1,3-dipolar cycloaddition with diethyl fumarate to yield a pyrazoline intermediate, which without isolation reacts with ammonia in water to furnish the pyrazole [119741-54-7] **(63)** (eq. **14**) (43).



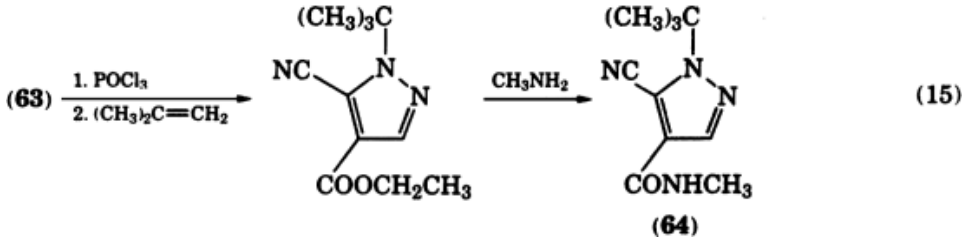
(58) **(59)** **(60)** **(61)** **(13)**

Dehydration with $POCl_3$, followed by *N*-alkylation with isobutylene, gives the cyano ester intermediate, which on treatment with methylamine yields **(64)**, a compound having good herbicidal activity (eq. **15**).



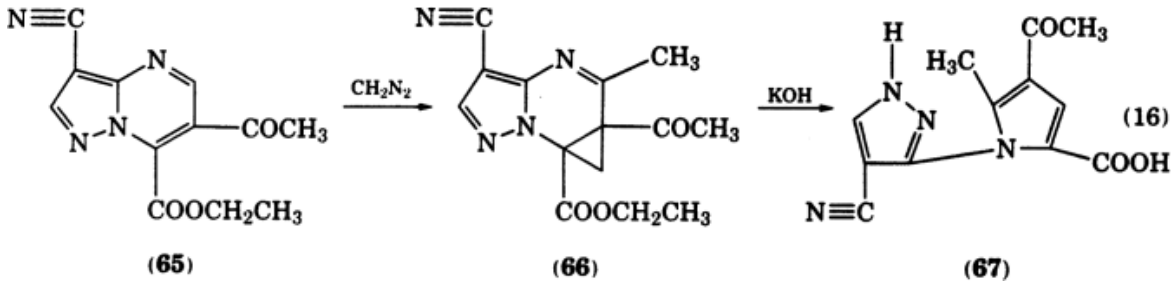
5.3. From Multiring Systems Containing Pyrazoles

The pyrazolopyrimidine **(65)** on treatment with diazomethane forms the cyclopropane **(66)**, which undergoes a ring-opening reaction with potassium hydroxide to yield the pyrazole **(67)** (eq. **16**) (44).

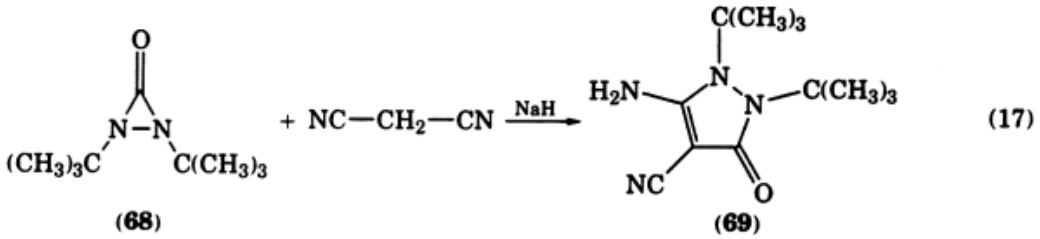


5.4. From Other Heterocycles by Rearrangement

Although there are numerous examples of pyrazole syntheses from other monocyclic heterocycles by chemical, thermal, or photochemical means, such examples are only of limited practical value on account of high cost. Reaction of diaziridinone **(68)** with the sodium salt of malondinitrile yields the di-*t*-butylaminopyrazolinone **(69)** (eq. **17**) (45).

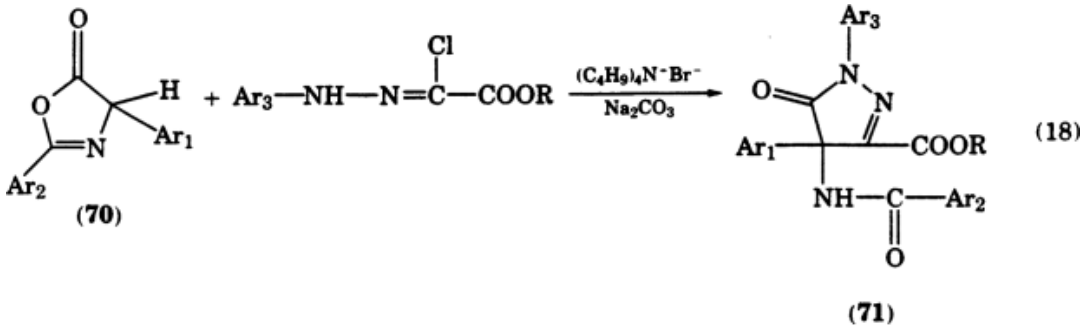


The pyrazolone-3-carboxylic acid **(71)** has been isolated by reaction of oxazolone **(70)** with hydrazonyl chloride (eq. **18**) (46).



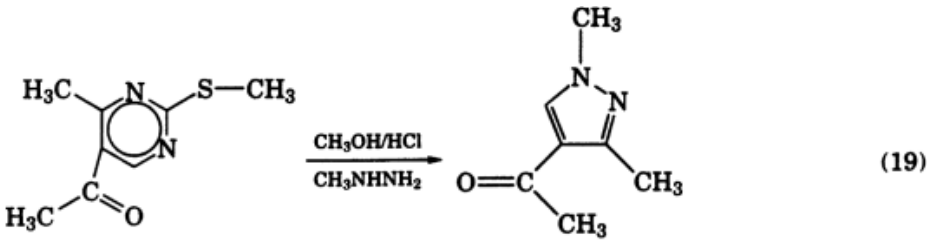
(68) (69) (17)

Heating methylhydrazine with an *S*-methylpyrimidine derivative **(72)** in an HCl methanolic solution produces in a yield of over 50% the 4-acetylpyrazole **(73)** (eq. **19**) (47).



(70) (71) (18)

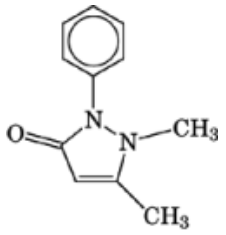
Another example is a claim of possible industrial application for preparing 1-cyclohexyl-3,5-dimethylpyrazole [79580-49-7] **(75)** and similar compounds from 1,2,6-thiadiazine-1,1-dioxide **(74)** by extrusion of SO_2 (eq. **20**) (48). This process has the added advantage of not requiring hydrazine derivatives as reactants.



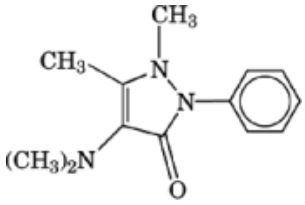
(72) (73) (19)

6. Health Factors

Pyrazole is considered a toxic material because in rats it causes hepatomegaly, anemia, and atrophy of the testis. It also inhibits the enzyme alcohol dehydrogenase, leading to severe hepatotoxic effects and liver necrosis when administered in combination with alcohol. Chronic administration of bromopyrazoles to rats, even in the absence of ethanol, causes significant increases in liver size. Pyrazolones with a free NH group are easily nitrosated and give rise to nitrosamines, which cause tumors in the liver of test animals. The analgesics antipyrine [60-80-0] **(76)** and aminopyrine [58-15-1] **(77)**, if admixed with nitrites, are mutagenic when tested *in vitro*; however, when tested in the absence of nitrites, negative results are obtained (49).



(76)

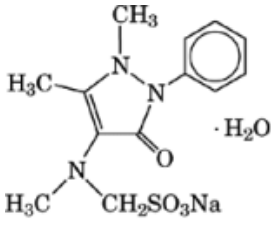


(77)

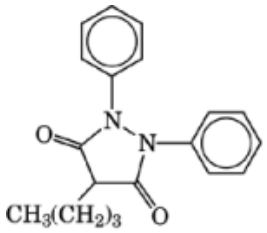
Pyrazolone-type drugs, such as phenylbutazone and sulfinpyrazone, are metabolized in the liver by microsomal enzymes, forming glucuronide metabolites that are easily excreted because of enhanced water solubility.

7. Applications

Pyrazoles, pyrazolines, and pyrazolones have all found wide use in many fields. Their greatest utility resides in pharmaceuticals, agrochemicals, dyes (textile and photography), and to a lesser extent in plastics. Figure 2 summarizes some of the pharmaceuticals that incorporate the pyrazole nucleus. Their main uses are as antipyretic, antiinflammatory, and analgesic agents. To a lesser extent, they have shown efficacy as antibacterial/antimicrobial, antipsychotic, antiemetic, and diuretic agents (50). The analgesic aminopyrine **(77)**, the antipyretic dipyrone [5907-38-0] **(78)**, and the antiinflammatory phenylbutazone [50-33-9] **(79)**, though once widely prescribed, are rarely used in the 1990s on account of their tendency to cause agranulocytosis.

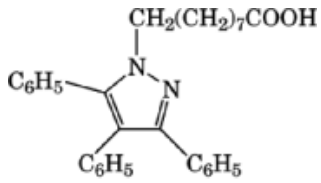


(78)



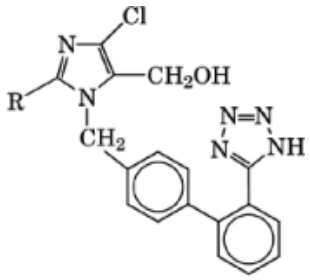
(**79**)

4-Methylpyrazole has been investigated as a possible treatment for alcoholism. The structure–activity relationship (SAR) associated with a series of pyrazoles has been examined in a 1992 study (51). These compounds were designed as nonprostanoid prostacyclin mimetics to inhibit human platelet aggregation. In this study, 3,4,5-triphenylpyrazole was linked to a number of alkanoic acids, esters, and amides. From the many compounds synthesized, triphenyl-1*H*-pyrazole-1-nonanoic acid **(80)** was found to be the most efficacious candidate (IC_{50} = 0.4 μM).



(**80**)

At Merck Research Laboratories, the imidazole ring in losartan (**81**, R = $n-$ butyl), a novel clinical candidate against hypertension, was replaced with a pyrazole ring (52). Some of the best compounds are represented by formula **(82)**, where R = $n-$ butyl and R' = 2,6-dichlorophenyl, 2-chlorophenyl, or 2-trifluoromethylphenyl.



(**81**)

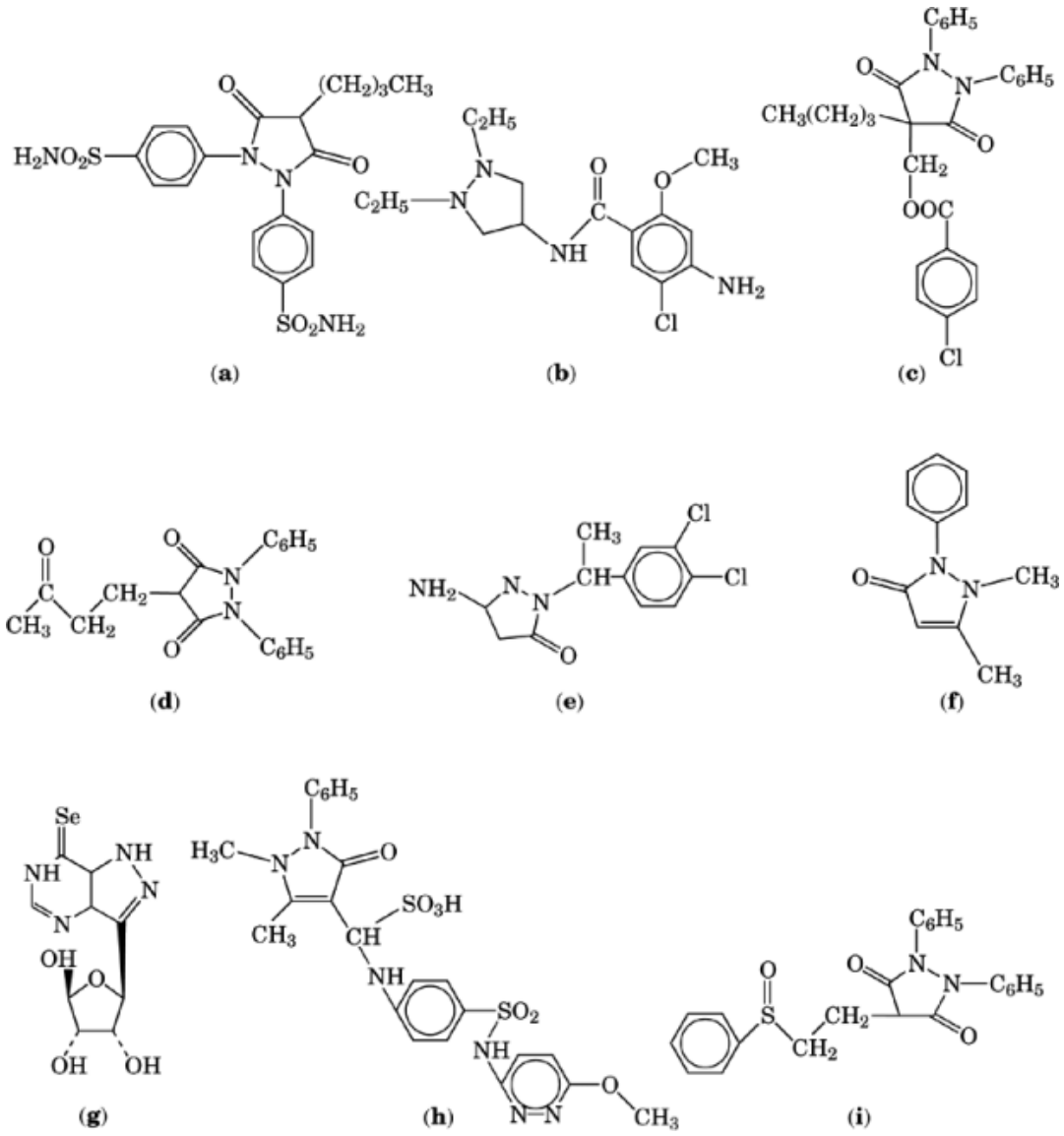
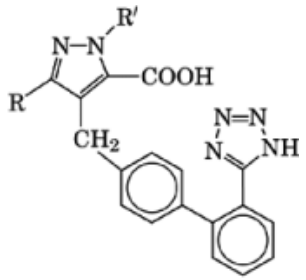
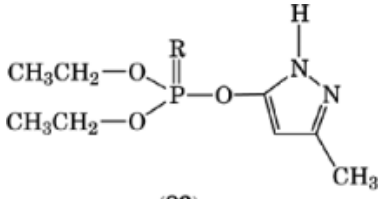


Fig. 2. Pyrazole-derived pharmaceuticals: (**a**) butaglyon [2603-23-8], an antidiabetic; (**b**) dazopride [70181-03-2], an antiemetic; (**c**) feclobuzo [23111-34-4], an antiinflammatory; (**d**) kebuzone [853-34-9], an antirheumatic; (**e**) muzolimin [55294-15-0], a diuretic; (**f**) phenazobz [20610-63-3], an antiasthmatic; (**g**) selenofob [39102-63-1], an antibiotic; (**h**) sulfamazo [65761-24-2], an antiseptic; and (**i**) sulfinpyrazone [57-96-5], an antigout preparation (50).

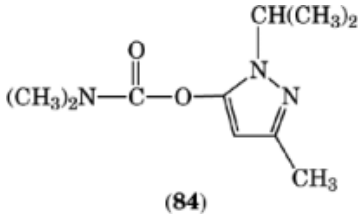


(**82**)

Compounds containing the pyrazole nucleus have also found utility in agriculture. The organophosphate and carbamoyl functionalities, which impart insecticidal activity through linkage to many organic molecules, have been attached to the pyrazole nucleus to yield compounds of type **(83)**, where R = S or O, and type **(84)**. These compounds act by interfering with acetylcholinesterase in the cholinergic synapses (7, 53).

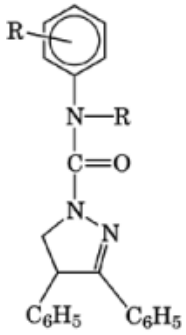


(83)

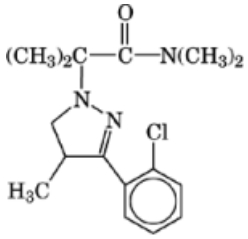


(84)

Another class of insecticides is being developed in the 1990s (54); the 3,4-diphenyl-substituted pyrazoline **(85)** is a representative member. The 5-cyanopyrazole [98477-07-7] **(64)** is being developed as a preemergent corn and post-emergent cereal herbicide (55). 3-Substituted pyrazole-5-sulfonylureas are being developed as herbicides against broad-leaf weeds and sedges in corn (10). The 3-phenylpyrazole **(86)** is a representative of a great many amidic pyrazoles having excellent preemergent herbicidal activity.



(85)



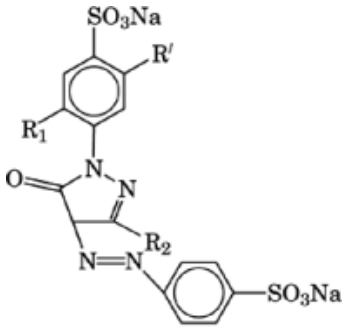
(86)

Table 4. U.S. Production and Sales of Selected Pyrazolone Derivatives[a]

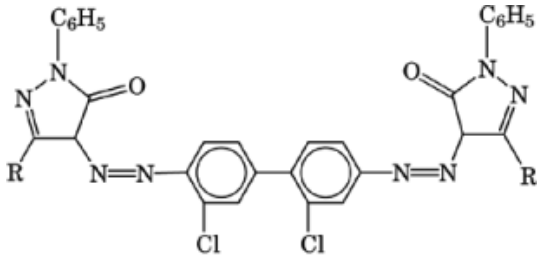
Product	CAS Registry Number	Year	Production, t	Sales	
				Quantity, t	Unit value, $/kg
acid yellow 17[b]	[6359-98-4]	1983	100	84	5.08
		1985	97	105	5.81
		1986	37	83	6.61
		1987	90	75	7.09
acid yellow 23[c]	[1934-21-0]	1983	70	74	4.62
		1985	46	79	4.26
		1986	113	94	4.25
		1987	139	118	4.33
pigment orange 13[d]	[3520-72-7]	1983	112	139	8.21
		1985	128	118	9.42
		1986	120	112	8.52
		1987	171	160	9.93
		1991	58	51	23.74
pigment red 38[e]	[6358-87-8]	1983	128	143	10.94
		1985	150	134	11.19
		1986	87	129	5.40
		1987	177	151	11.25
		1991	72	72	25.51

[a] Ref. 56.
[b] Structure **(87)**, where $R_1 = Cl$ and $R_2 = CH_3$.
[c] Structure **(87)**, where $R_1 = H$ and $R_2 = COONa$.
[d] Structure **(88)**, where $R = CH_3$.
[e] Structure **(88)**, where $R = COOCH_2CH_3$.

Dyes based on the pyrazolone nucleus were discovered in 1884 and are still in use in the 1990s. The majority of these dyes have an azo linkage attached at C_4, eg, **(87)** and **(88)**. Table 4 summarizes the production and sales figures for four important dyes.



(87)



(88)

BIBLIOGRAPHY

"Pyrazoles, Pyrazolines, Pyrazolones" in *ECT* 2nd ed., Vol. 16, pp. 763–779, by P. F. Wiley, The Upjohn Co.; in *ECT* 3rd ed., Vol. 19, pp. 436–453, by G. Kornis, The Upjohn Co.

Cited Publications

1. T. L. Jacobs, in R. C. Elderfield, ed., *Heterocyclic Compounds*, Vol. **5**, John Wiley & Sons, Inc., New York, 1957, p. 45.
2. A. N. Kost and I. I. Grandberg, in A. R. Katritzky and A. J. Boulton, eds., *Advances in Heterocyclic Chemistry*, Vol. **6**, Academic Press, Inc., New York, 1966, 347–429.
3. L. C. Behr, R. Fusco, and C. H. Jarboe, in R. H. Wiley, ed., *The Chemistry of Heterocyclic Compounds*, Wiley-Interscience, New York, 1967.
4. J. Elguero, in A. R. Katritzky and C. W. Rees, eds., *Comprehensive Heterocyclic Chemistry*, Vol. **4**, Pergamon Press, Oxford, U.K., 1984, 167–303.
5. A. R. Katritzky, *Handbook of Heterocyclic Chemistry*, Pergamon Press, Oxford, U.K., 1985.
6. A. Kotali and P. G. Tsoungas, *Heterocycles* **29**, 1615–1648 (1989).
7. R. M. Jacobson, *Spec. Publ. R. Soc. Chem.* **79**, 206–211 (1990).
8. I. R. Judson, *Anti-Cancer Drugs* **2**, 223–231 (1991).
9. K. Reszka, J. A. Hartley, and J. W. Lown, *Biophys Chem.* **35**, 313–323 (1990).
10. S. Yamamoto and co-workers, *ACS Symp. Ser.* **504**, 34–42 (1992).
11. Ref. 4, p. 173.
12. I. L. Finar, *J. Chem. Soc.* (B), 725–732 (1968).
13. R. E. Burton and I. L. Finar, *J. Chem. Soc.* (B), 1692–1695 (1970).
14. Ref. 4, 182–197.
15. Ref. 4, p. 184.
16. Ref. 4, p. 187.
17. Ref. 4, p. 191.
18. J. Elguero, M. L. Jimeno, and G. I. Yranzo, *Magn. Reson. Chem.* **28**, 807–811 (1990).
19. A. Echevarria, J. Elguero, and W. Meutermans, *J. Heterocycl. Chem.* **30**, 957–960 (1993).
20. W. Holzer, *Tetrahedron* **47**, 1393–1398 (1991).
21. G. Heinisch and W. Holzer, *Heterocycles*, **27**, 2443–2457 (1988).
22. W. T. Ashton and G. A. Doss, *J. Heterocycl. Chem.* **30**, 307–311 (1993).
23. Ref. 4, p. 203.
24. W. Nagai and co-workers, *J. Heterocycl. Chem.* **31**, 225–231 (1994).
25. D. E. Rivett, J. Rosevear, and J. F. K. Wilshire, *Aust. J. Chem.* **36**, 1649–1658 (1983).
26. Ref. 4, 197–202.
27. Ref. 4, p. 220.
28. J. P. H. Juffermans and C. L. Habraken, *J. Org. Chem.* **51**, 4656–4660 (1986).
29. H. Lammers, P. Cohen-Fernandes, and C. L. Habraken, *Tetrahedron* **50**, 865–870 (1994).

30. M. Begtrup, P. Larsen, and P. Vedso, *Acta. Chem. Scand.* **46**, 972–980 (1992); M. Sprecher, rev., *Chem. Tracts, Org. Chem.* **6**, 145–146 (1993).
31. A. R. Katritzky, P. Lue, and K. Akutagawa, *Tetrahedron* **45**, 4253–4262 (1989).
32. S. Yamamoto and co-workers, *J. Heterocycl. Chem.* **28**, 1849–1852 (1991).
33. S. Mitkidou and co-workers, *J. Org. Chem.* **55**, 4732–4735 (1990).
34. R. D. Miller and O. Reiser, *J. Heterocycl. Chem.* **30**, 755–763 (1993).
35. A. C. Kovelesky and H. J. Shine, *J. Org. Chem.* **53**, 1973–1979 (1988).
36. B. J. Gaede and L. L. McDermott, *J. Heterocycl. Chem.* **30**, 49–54 (1993).
37. R. T. Chakrasali, C. S. Rao, H. Ila, and H. Junjappa, *J. Heterocycl. Chem.* **30**, 129–134 (1993).
38. Y. Kamitori and co-workers, *J. Heterocycl. Chem.* **30**, 389–391 (1993).
39. J. Barluenga and co-workers, *J. Chem. Res. (S)*, 124–125 (1985).
40. A. Padwa and J. G. MacDonald, *J. Heterocycl. Chem.* **24**, 1225–1227 (1987).
41. O. A. Attanasi and co-workers, *J. Chem. Res. (S)*, 192–193 (1994).
42. M. P. Doyle, M. R. Colsman, and R. L. Dorow, *J. Heterocycl. Chem.* **20**, 943–946 (1983).
43. E. V. P. Tao, J. R. Rizzo, and J. Aikins, *J. Heterocycl. Chem.* **27**, 1655–1656 (1990).
44. Ref. 4, p. 285.
45. M. Komatsu and co-workers, *J. Org. Chem.* **57**, 7359–7361 (1992).
46. F. Clerici and co-workers, *Heterocycles* **27**, 1411–1419 (1988).
47. G. Menichi and co-workers, *J. Heterocycl. Chem.* **23**, 275–279 (1986).
48. J. F. Klein and co-workers, *Can. J. Chem.* **71**, 410–412 (1993).
49. H. G. Berscheid and co-workers, in F. T. Coulston and J. F. Dunne, eds., *The Potential Carcinogenicity of Nitrosatable Drugs WHO Symposium*, *Geneva, Switzerland, June 1978*, Ablex Publishing Corp., Norwood, N.J., 1980, p. 121.
50. *The DERWENT Standard Drug File of Known Drugs*, Derwent, London, 1994.
51. N. A. Meanwell and co-workers, *J. Med. Chem.* **35**, 389–397 (1992).
52. W. T. Ashton and co-workers, *J. Med. Chem.* **36**, 3595–3605 (1993).
53. Ref. 4, p. 297.
54. A. Bosum-Dybus and H. Neh, *Liebigs Ann. Chem.*, 823–825 (1991).
55. M. P. Lynch and co-workers, *ACS Symp. Ser.* **443**, 144–157 (1991).
56. *Synthetic Organic Chemicals, United States Production and Sales: 1983, USITC Public. 1588; 1985 USITC Public. 1892; 1986, USITC Public. 2009; 1987 USITC Public. 2118; 1991 USITC Public. 2607*, U.S. International Trade Commission, Washington, D.C., Feb. 1993.

GABE I. KORNIS
Pharmacia & Upjohn Inc.

Related Articles

Dyes; Pharmaceuticals