Ring Transformation of 5-Acylpyrimidines and 5-Acyluracils into Pyrazoles with Hydrazines in Acidic Medium

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Contents.

I. Introduction.

The ring transformation of pyrimidines into pyrazoles under the action of hydrazines has been well documented in a monograph of van der Plas [2]. This ring contraction reaction requires vigorous conditions for simple pyrimidines, such as pyrimidine, 4-methylpyrimidine and 4,6-dimethylpyrimidine, which can be converted to pyrazoles by heating with hydrazines at high temperature (180-200°) [3,4].

However, several pyrimidine derivatives are prone to ring fission with hydrazines and easily lead to corresponding pyrazoles. The first group of such pyrimidines is those which have decreased aromatic stability because of a fixed double bond system, as in 2-imino-1-methylpyrimidines [5] and 1,3-dimethyl-2,4-dioxopyrimidines [6]. In the case of uracils, the decrease in stability may be partly offset by resonances associated with the amidic ring system; nevertheless, some uracil derivatives are converted to pyrazoles with hydrazines [4,7-9]. The second group comprises pyrimidines in which the π-electron deficiency on the pyrimidine nucleus is brought about by the ring-nitrogen atoms, and especially by the additional substitution of an electron-withdrawing group, such as 1-methylpyrimidinium quaternary salts [10] and 5-nitropyrimidines [11,12].

Our interest in the ring transformation of 5-acylpyrimidines into pyrazoles dates back to 1984. In that year, studying the reaction of some 5-acetylpyrimidines with amidinohydrazine (aminoguanidine) in order to prepare amidinohydrazones of these pyrimidines, heterocyclic analogues of the anticancer agent methylglyoxal bis-(guanylhydrazone) (Mitoguazone) [13], we found that an unexpected ring contraction of 5-acetylpyrimidines into 4-acetylpyrazoles occurred under reflux in methanol in the presence of hydrochloric acid [14].

Indeed, 5-acylpyrimidines belong to the second group of the above-mentioned pyrimidines which are sensitive to the nucleophilic attack of hydrazines, as the electron-withdrawing acyl group must deplete the N1-C6 (N3-C4) bond of the pyrimidine ring from electrons, facilitating therefore the addition of nucleophile on C6 (or C4). In the presence of hydrochloric acid, this nucleophilic addition appears to be much easier.

The above findings prompted us to study in detail the reactivity of different 5-acylpyrimidines towards hydrazines. From these studies, it has been proved that various 5-acylpyrimidines easily underwent ring contraction, through regiospecific reaction process, with hydrazine and monosubstituted hydrazines in acidic medium under mild conditions to give 4-acylpyrazole derivatives which are otherwise difficult to synthesize or even inaccessible. We also examined the ring transformation of 5-acyluracils with hydrazines under acidic conditions, which involved the formation of pyrazole-4-carboxylic acid derivatives.

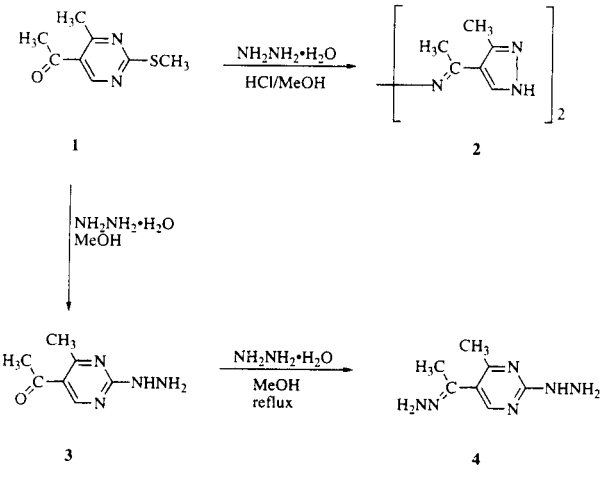
The purpose of this review is to present a survey of the ring contraction reactions of 5-acylpyrimidines and 5-acyluracils with hydrazines, and the exploitation of these reactions for the synthesis of new pyrazole derivatives.

II. Reactions of 5-Acetyl-4-methyl-2-methylthiopyrimidine with Hydrazines.

An interesting series of ring contraction reactions was observed when 5-acetyl-4-methyl-2-methylthiopyrimidine (**1**), easily prepared by condensation of *S*-methylisothiourea with ethoxymethyleneacetylacetone [15], was treated with hydrazine or monosubstituted hydrazines in hot acidic medium [14,16].

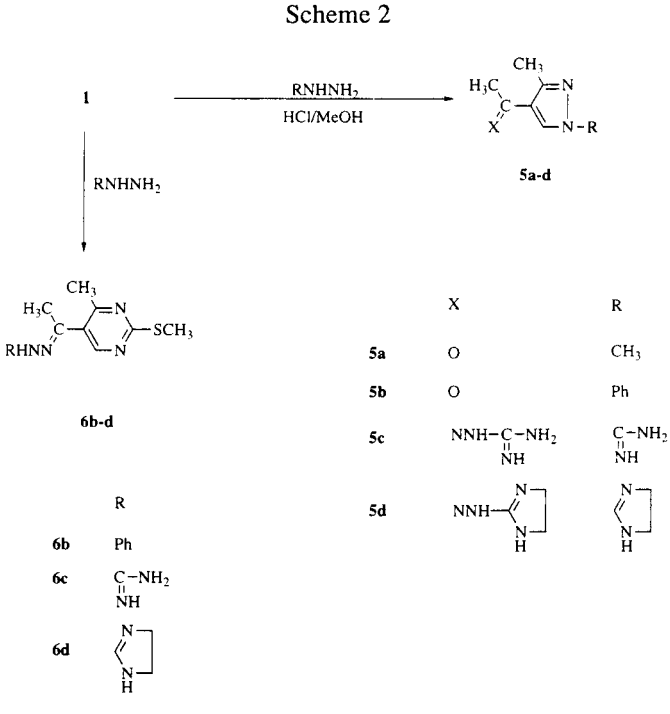
Reaction of **1** with an excess of hydrazine hydrate in boiling aqueous methanol containing hydrochloric acid gave 4-acetyl-3-methylpyrazole azine (**2**), whereas the same reagents when treated in a methanolic solution without acid gave, at room temperature, 5-acetyl-2-hydrazino-4-methylpyrimidine (**3**) and, upon boiling, the corresponding hydrazone **4** (Scheme 1).

Scheme 1



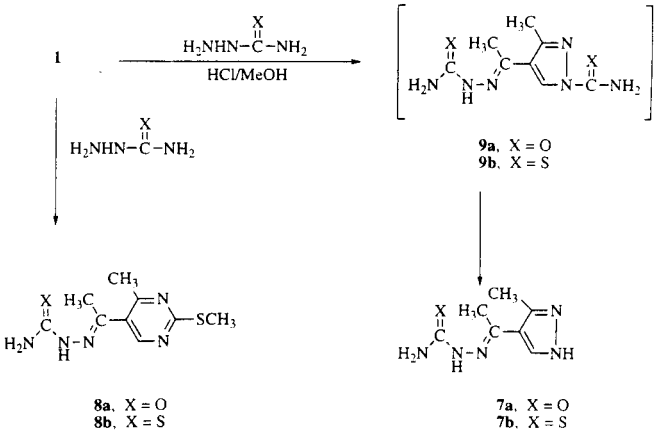
Similar reactions of **1** with an excess of monosubstituted hydrazines, such as methylhydrazine, phenylhydrazine, amidinohydrazine and 2-hydrazino-2-imidazoline, in boiling acidic methanol afforded 1-substituted 4-acetyl-3-methylpyrazoles **5a-d** (in the reactions with amidinohydrazine and its analogue, the reaction products were obtained in the form of amidinohydrazones) and, in a neutral or slightly acidic medium, the corresponding hydrazones **6b-d** of **1** (Scheme 2) (in the reaction of **1** with methylhydrazine, **1** remained unchanged).

Scheme 2



The ring contraction of **1** could also be performed with semicarbazide and thiosemicarbazide on heating under acidic conditions, resulting in the formation of the semicarbazone or thiosemicarbazone of 4-acetyl-3-methylpyrazole **7a,b**. When the same reactions were carried out in slightly acidic medium at room temperature, the semicarbazone or thiosemicarbazone **8a,b** of **1** were obtained, expectedly (Scheme 3). The formation of **7a,b** probably occurred through the hydrolysis of intermediary **9a,b** whose *N*-carbamoyl and *N*-thiocarbamoyl groups at the 1-position seem to be more unstable than the amidino one (compound **5c**) [17] under acidic conditions.

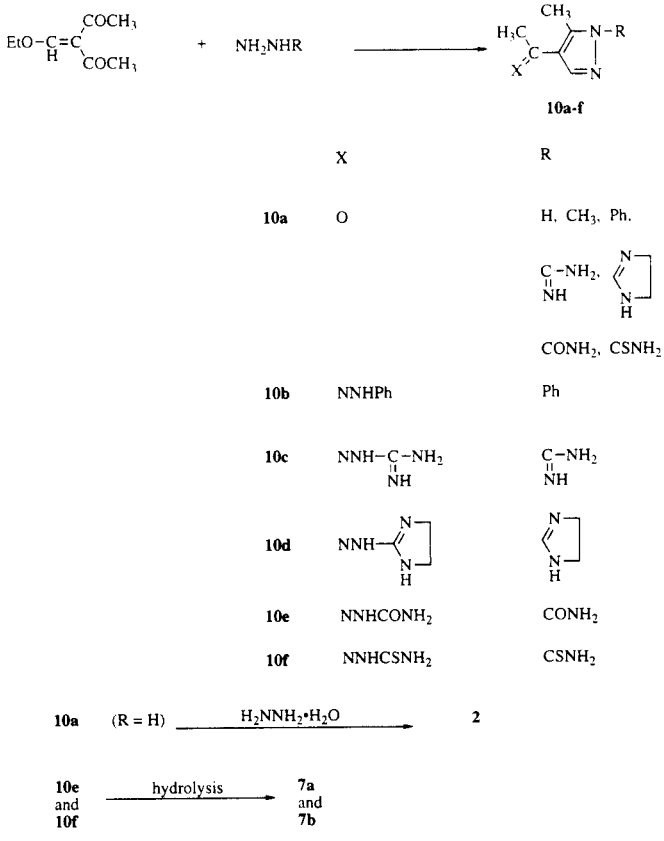
Scheme 3



In order to confirm the specific structures of the pyrazoles formed by ring contraction of **1**, we synthesized 4-acetylpyrazoles by the reactions of ethoxymethyleneacetylacetone with hydrazines according to the known method [18]. These cyclocondensation reactions carried in methanolic acidic medium at -15° gave, as expected [18], 1-substituted 4-acetyl-5-methylpyrazoles **10a** [19] or their hydrazones **10b-f** depending on the quantities of hydrazines used (Scheme 4). The stuctures of the pyrazoles **10a** (R = CH_3 and Ph) and **10c,d** thus obtained are isomeric with those of **5a-d** previously formed by the ring transformation of **1**.

The structural distinction between the pyrazoles **5** and **10** is based on the ^{1}H-nmr spectral data. The chemical shifts of the ring protons (C5-H in **5** and C3-H in **10**) of these pyrazoles in dimethyl sulfoxide-d_6 appeared downfield in **5** with respect to those in **10** (Table I). The above findings are consistent with those previously reported in the ^{1}H-nmr study of 1,3- and 1,5-disubstituted pyrazoles [20], particularly 1-arylpyrazole derivatives [21,22].

Scheme 4



The final proof of the structures of **5c** and **10c** was presented [23,24] by establishing their crystal structure using X-ray diffraction. The visualization of the differences thus observed offers a definite proof of the respective structures of these two isomers and sustains the value of the chemical and ^{1}H-nmr data hitherto put forward to characterize them.

The pyrazole **10a** (R = H), when treated with hydrazine hydrate, could be converted to the azine **2** which was identical with that obtained from **1** and hydrazine in acidic medium. Compounds **10e,f** were readily hydrolyzed to the pyrazoles **7a,b**, respectively, in an aqueous alkaline solution or in boiling methanol.

It is characteristic that the ring contraction of **1** into pyrazoles with hydrazines takes place in acidic medium (*p*H 1), but not under alkaline to slightly acidic conditions, where **1** only affords the corresponding hydrazones **4**, **6b-d**. Protonation on the ring nitrogen of **1** may facilitate the reaction of hydrazines at the electron-deficient site (C6 and C4) of the pyrimidine ring of **1**, which provokes the pyrimidine-to-pyrazole ring transformation. To our knowledge, such acid-catalyzed transformation of 5-acylpyrimidines into pyrazoles has not been described until our first report in 1984 [14].

All our observation results in the fact that, for every monosubstituted hydrazine used, we are able to prepare specifically one type of pyrazolic position isomer starting from ethoxymethyleneacetylacetone or the other type, whose synthetic method has not been established, using **1** instead of ethoxymethyleneacetylacetone. In the case of ethoxymethyleneacetylacetone which gives 1,5-disubstituted 4-acetylpyrazoles of type **10**, the carbon atom bearing the ethoxy group of ethoxymethyleneacetylacetone is first attacked by the primary amino group of monosubstituted hydrazines [18,20]. In the case of **1** which provides 1,3-disubstituted 4-acetylpyrazoles of type **5** [25], either carbonyl-C or C4 (bearing the methyl group) of **1** could be initially attacked by the primary amino group of monosubstituted hydrazines (path A or B in Scheme 5). The structural characteristics of **1** does not allow to distinguish between these two possibilities of ring modifying process. However, using an appropriate isomeric pair of 5-acylpyrimidines as starting materials, we confirmed that the transformation of 5-acylpyrimidines into pyrazoles pro-

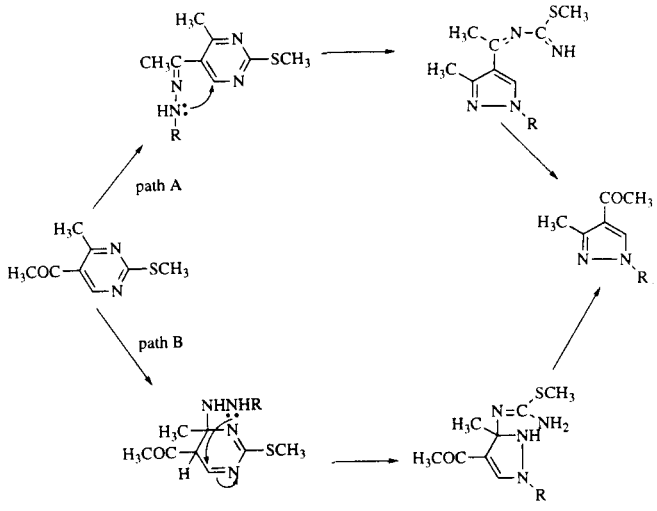
Table I

Chemical Shifts of C5-H and C3-H of **5** and **10**

Pyrazoles **5**	C5-H (ppm)	Pyrazoles **10**	C3-H (ppm)
5a, X = O, R = CH_3	8.35	**10a**, X = O, R = CH_3	7.90
5b, X = O, R = Ph	9.19	X = O, R = Ph	8.24
		X = O, R = C(=NH)-NH_2	8.50
5c, X = NNHC(=NH)-NH_2, R = C(=NH)-NH_2	9.60	**10b**, X = NNHPh, R = Ph	7.87
		10c, X = NNHC(=NH)-NH_2, R = C(=NH)-NH_2	8.41
5d, X = NNH-(imidazole), R = (imidazole)	9.30	**10d**, X = NNH-(imidazole), R = (imidazole)	8.41
13, 4-actyl-1,3-diphenylpyrazole	9.30	**16**, 4-actyl-1,5-diphenylpyrazole	8.35
14, 4-benzoyl-3-methyl-1-phenylpyrazole	8.75	**15**, 4-benzoyl-5-methyl-1-phenylpyrazole	7.80

ceeded through initial formation of hydrazones of the starting pyrimidines (path A in Scheme 5) as discussed in the following section.

Scheme 5



III. Ring Contraction Mechanism of 5-Acylpyrimidines into 4-Acylpyrazoles.

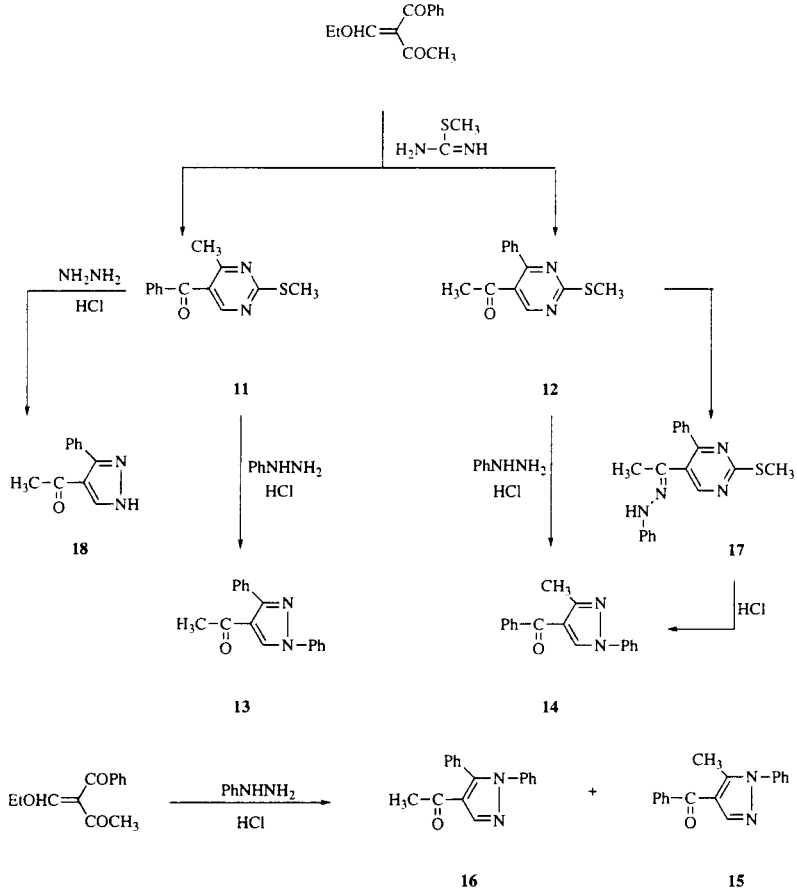
In order to elucidate the mechanism of formation of 4-acylpyrazoles from 5-acylpyrimidines and hydrazines, we selected at first two isomeric pyrimidines: 5-benzoyl-4-methyl-2-methylthiopyrimidine (**11**) and 5-acetyl-2-methylthio-4-phenylpyrimidine (**12**) as substrates for reactions with phenylhydrazine [26,27].

The starting pyrimidines **11** and **12** [27] were synthesized by reacting 2-ethoxymethylene-1-phenyl-1,3-butanedione with *S*-methylisothiourea.

When heated with phenylhydrazine in methanol in the presence of hydrochloric acid, **11** exclusively provided 4-acetyl-1,3-diphenylpyrazole (**13**), while **12** led under the same conditions to 4-benzoyl-3-methyl-1-phenylpyrazole (**14**) without formation of any other possible isomers (Scheme 6). On the other hand, the reaction of 2-ethoxymethylene-1-phenyl-1,3-butanedione with phenylhydrazine in methanol at room temperature gave a mixture of 4-benzoyl-5-methyl-1-phenylpyrazole (**15**) and 4-acetyl-1,5-diphenylpyrazole (**16**), which are isomers of **14** and **13**, respectively (Scheme 6).

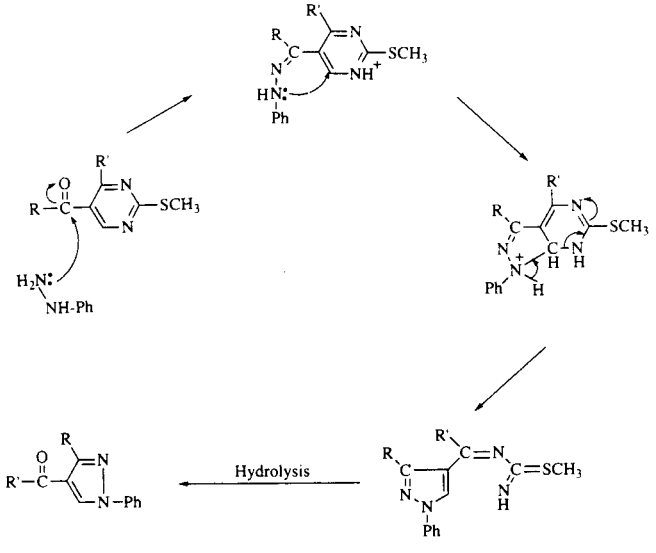
The formation of **13** and **14** implies the initial formation of phenylhydrazones of **11** and **12**, followed by intramolecular attack on C6 of the pyrimidine ring by the NH group of hydrazono function with C6-N1 bond fission to

Scheme 6



give pyrazole ring compounds which are hydrolyzed to corresponding 4-acylpyrazoles (Scheme 7). Therefore, the mechanism of formation of **13** and **14** corresponds to path A in Scheme 5 (R = Ph) without any interference of path B.

Scheme 7



In fact, we confirmed that the phenylhydrazone **17**, prepared from **12** and phenylhydrazine under mild conditions, was transformed in quantitative yield into **14** on heating in methanol containing hydrochloric acid (Scheme 6). Hydrazine hydrate also reacted with **11** in boiling acidic methanol in a similar mode to that of phenylhydrazine to give 4-acetyl-3-phenylpyrazole (**18**) (Scheme 6).

In contrast to the above results, reaction of phenylhydrazine with the same type of appropriate isomers of 5-acyl-2-phenylpyrimidines led to a mixture of two isomeric pyrazoles for each starting pyrimidines [27]. Thus, upon heating with phenylhydrazine in acidic hydroalcoholic medium, 5-acetyl-2,4-diphenylpyrimidine (**19**) [28] afforded 4-benzoylpyrazoles **14** and **15** in 46% and 31% yields, respectively (Scheme 8). Under the same conditions, 5-benzoyl-4-methyl-2-phenylpyrimidine (**20**) [28] provided with phenylhydrazine 4-acetylpyrazole **13** (40% yield) together with a small amount of its isomer **16** (Scheme 8).

These findings suggest that the primary amino group of phenylhydrazine attacks simultaneously carbonyl-C and C6 of 5-acyl-2-phenylpyrimidines, without any subsequent involvement of C4, to produce two isomeric pyrazoles.

It is noteworthy that the 2-phenyl substituent of the pyrimidine ring may favor in these cases the nucleophilic attack of the primary amino group of phenylhydrazine on C6, in contrast with the 2-methylthio group which prevents the same nucleophilic attack on C6. We can therefore conclude that the ring contraction of 5-acylpyrimidines into 4-acylpyrazoles with hydrazines alway involves attack of hydrazines on carbonyl-C and C6 (but not on C4) of 5-acylpyrimidines. The (CO)-C5-C6 fragment of the pyrimidine ring serves as a three atom synthon in the construction of the pyrazole ring. This excludes the usual and classical transformation of pyrimidines into pyrazoles which would consist of the B type reaction in Scheme 5. Particularly, the ring transformation of 5-acyl-2-methylthiopyrimidines with monosubstituted hydrazines is "regiospecific" *via* initial and exclusive for-

Scheme 8

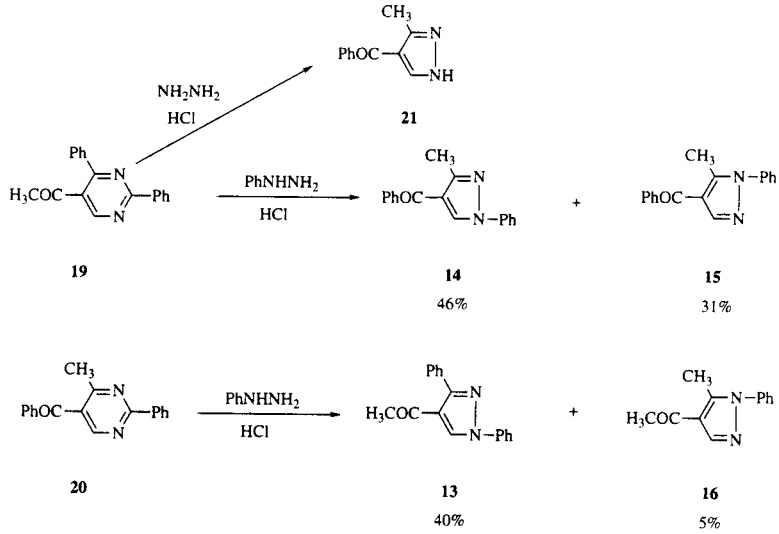
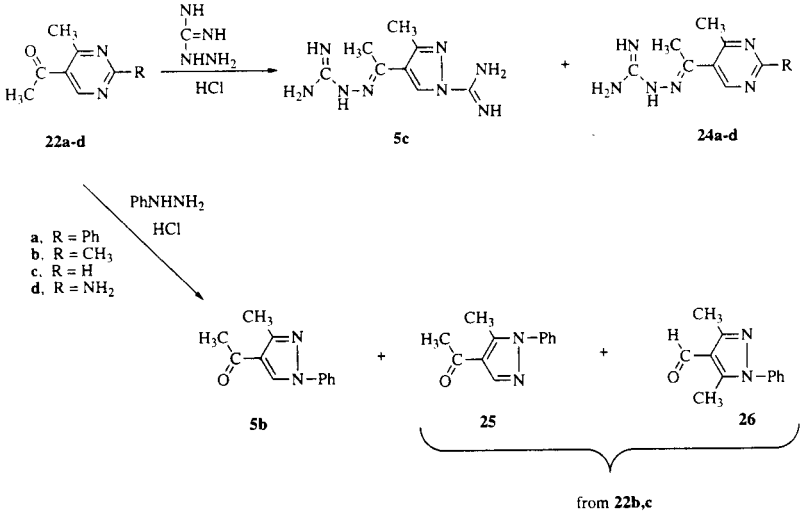


Table II.

Pyrimidines + $H_2NHNC(=NH)NH_2$		Yields % 5c	Yields % 24a-d	Pyrimidines + $PhNHNH_2$		Yields % 5b	Yields % 25	Yields % 26
22a,	R = Ph	12	88	**22a,**	R = Ph	50	0	0
22b,	CH_3	30	39	**22b,**	CH_3	60	10	20
22c,	H	65	5	**22c,**	H	50	14	21
22d,	NH_2	0	100	**22d,**	NH_2	100	0	0
1,	SCH_3	82	0	**1,**	SCH_3	86	0	0

Scheme 9



mation of the corresponding hydrazones. However, in the case of 5-acyl-2-phenylpyrimidines, first reaction of the primary amino group of phenylhydrazine is competitive between carbonyl-C and C6.

IV. Ring Transformation of Divers 5-Acylpyrimidines into Pyrazoles.

1) Reactions of 2-Substituted 5-Acetyl-4-methylpyrimidines with Hydrazines.

As an extension of the ring transformation of 5-acylpyrimidines into pyrazoles discussed in the preceding sections, we now carried out a comparative study on the reaction of 2-substituted 5-acetyl-4-methylpyrimidines **22a-d** in acidic medium, using amidinohydrazine and phenylhydrazine as nucleophiles [29].

Upon treatment of **22a-d** with amidinohydrazine (1:3 mole ratio) in boiling methanol containing an excess of hydrochloric acid for 7 hours, the pyrazole **5c** was obtained together with the amidinohydrazones **24a-c** of the starting pyrimidines except **22d** which gave only its amidinohydrazone **24d** in quantitative yield. Under the same conditions, **22a-d** all led with phenylhydrazine to the pyrazole **5b** (yield > 50%) without formation of phenylhydrazones of **22a-d** (Scheme 9). These results are summarized in Table II.

The formation of the sole pyrazole **5c** from **22a-c** demonstrates that these ring contraction reactions are also regiospecific as in the cases of 2-methylthiopyrimidines **1**, **11** and **12**. The amidinohydrazones **24** are regarded as intermediates in the ring contraction reactions. The substituent at the 2-position of **22** considerably influences the transformation of **22** into **5c**. In fact, **22c** gave **5c** in 65% yield along with a small amount of amidinohydrazone **24c**; on the contrary, **22a** mainly afforded amidinohydrazone **24a** (88% yield) with only 12% yield of **5c**. It is characteristic that the pyrimidine **22d** exclusively gave the amidinohydrazone **24d** without any formation of **5c**. From these observations, it is very likely that the conversion of **22** into **5c** depends on the reactivity of the intermediary amidinohydrazones **24** which should be initially

formed in the course of reaction.

The reaction of **22a-d** with phenylhydrazine did not afford the corresponding phenylhydrazones, but the pyrazole **5b** in satisfactory yields. Particularly, both **22a** and **22d** exclusively led to the sole product **5b**. This fact indicates that in these cases the ring contraction reactions are regiospecific. However, the reaction of **22b,c** with phenylhydrazine afforded, in contrast with **22a,d**, three isomeric pyrazoles: **5b** as main product, 4-acetyl-5-methyl-1-phenylpyrazole (**25**) and 3,5-dimethyl-1-phenylpyrazole-4-carboxaldehyde (**26**). Analogous non-regiospecific reaction has also been observed in the reaction of the pyrimidines **19** and **20** with phenylhydrazine [27].

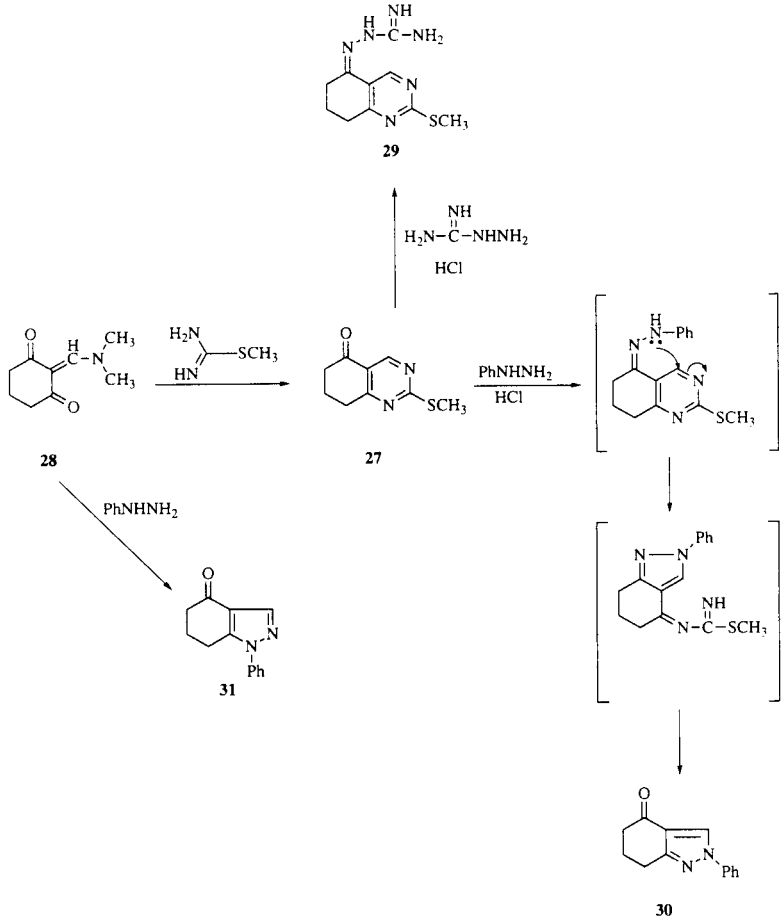
In general, phenylhydrazine appears to be more reactive than amidinohydrazine to produce the ring conversion of 5-acylpyrimidines into pyrazoles, since in the reaction of **22a-d** with phenylhydrazine, the corresponding phenylhydrazones were not detected, but a sufficient amount of pyrazole **5b** was obtained; while in the reaction with amidinohydrazine, both the amidinohydrazone **24** and the pyrazole **5c** were isolated. This difference of reactivity is quite obvious in the case of **22d** which led with phenylhydrazine to only the pyrazole **5b** in quantitative yield, and with amidnohydrazine to the amidinohydrazone **24d** with no evidence for the formation of pyrazoles. These facts suggest that the phenylhydrazone, which should be initially formed from **22a-d** and phenylhydrazine, easily change into a cyclic transition state to give the pyrazole **5b** in acidic medium, whereas the amidinohydrazones **24** are relatively stabilized by protonation under the acidic conditions.

2) Reaction of 2-Methylthio-5-oxo-5,6,7,8-tetrahydroquinazoline with Hydrazines.

The title quinazoline **27** can be looked upon as a cyclic analogue of **1** which is readily converted into pyrazoles with hydrazines as described previously. We therefore examined the reactions of **27** with amidinohydrazine and phenylhydrazine [29]. The required **27** was readily obtainable by interaction of *S*-methylisothiourea with 2-dimethylaminomethylenecyclohexan-1,3-dione (**28**) [19b] in the presence of sodium ethoxide in boiling ethanol.

Upon heating in an acidic methanolic solution with amidinohydrazine, under the same conditions as those in

Scheme 10



the reaction of **1** with amidinohydrazine, **27** gave the corresponding amidinohydrazone **29** as the sole isolable product. The crystal structure of molecules **29** and **6c** has been established [30]. The structural difference between **29** and **6c** as revealed by X-ray diffraction may suggest why **1** can undergo a ring transformation with amidinohydrazine while **27** cannot [30].

The reaction of phenylhydrazine with **27** under the same conditions afforded 4,5,6,7-tetrahydro-2-phenyl-2*H*-indazol-4-one (**30**). No formation of its isomer, 4,5,6,7-tetrahydro-1-pheny-1*H*-indazol-4-one (**31**) [19b] which has been synthesized from **28** and phenylhydrazine, was observed (Scheme 10). The transformation of **27** into **30** may be explained by the similar mechanism to that for the ring conversion of **1** into **5b**, which involves initial formation of the phenylhydrazone of **27** (Scheme 10). In this case, amidinohydrazine, contrary to phenylhydrazine, could not lead to any pyrazole ring compound, but gave only amidinohydrazone of the starting material, stressing once more the difference of reactivity between those two hydrazines.

3) Reactions of 2-Substituted Pyrimidine-5-carboxaldehydes with Hydrazines.

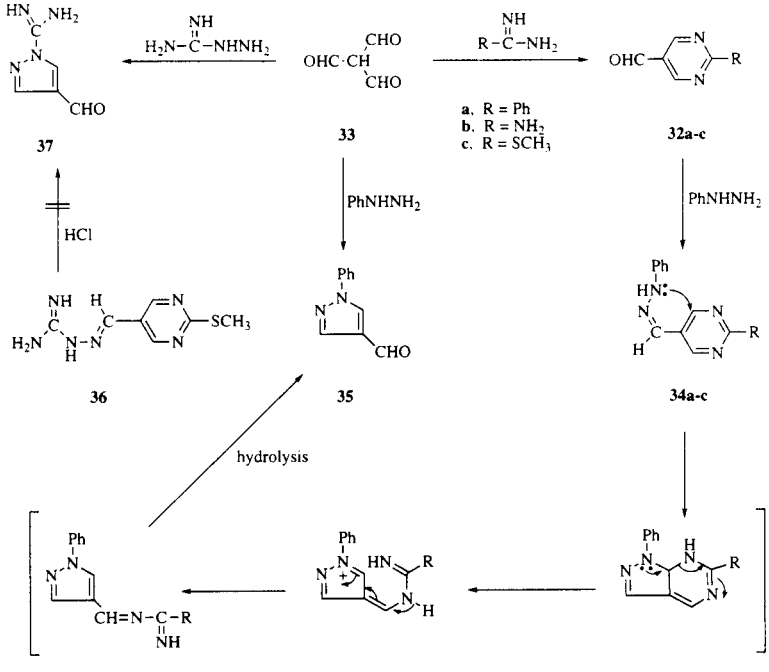
Some pyrimidine-5-carboxaldehydes were found to undergo ring transformation into pyrazoles with phenylhydrazine *via* the corresponding phenylhydrazones [31]. The starting 2-phenyl, 2-amino and 2-methylthiopyrimidine-5-carboxaldehydes **32a-c** were newly synthesized by condensation of triformylmethane (**33**) [32] with an equimolecular amount of benzamidine, guanidine and *S*-methylisothiourea, respectively, in boiling anhydrous ethanol [31].

Treatment of **32a-c** with phenylhydrazine in methanol in the presence of a catalytic amount of hydrochloric acid at room temperature gave the corresponding phenylhydrazones **34a-c**, generally in good yields. When heated with hydrochloric acid in methanol, these phenylhydrazones **34a-c** underwent ring conversion into 1-phenylpyrazole-4-carboxaldehyde (**35**) [33] which was directly obtained by condensation of **33** with phenylhydrazine in acidic methanol at room temperature (Scheme 11).

The mechanism of this ring contraction involves nucleophilic attack on C4 (or C6) of the pyrimidine ring by the phenylhydrazono group of **34** (Scheme 11). In the case of 5-acylpyrimidines, analogous ring conversion into pyrazoles proceeded by direct treatment with an excess of hydrazines in acidic medium, without (always) isolating the hydrazone intermediates. However, our attempts to obtain **35** by treatment of **32a-c** with an excess of phenylhydrazine in boiling acidic methanol were unsuccessful. This may be caused from relative instability of the aldehydes **32a-c**.

It is noteworthy that amidinohydrazone **36**, easily prepared from **32c** and amidinohydrazine according to the usual method, did not afford the expected pyrazole derivative **37** on heating in acidic methanol with the recovery of the starting **36** (**37** can be synthesized by condensation of amidinohydrazine with triformylmethane). The difference of reactivity between the phenylhydrazone **34c** and the

Scheme 11



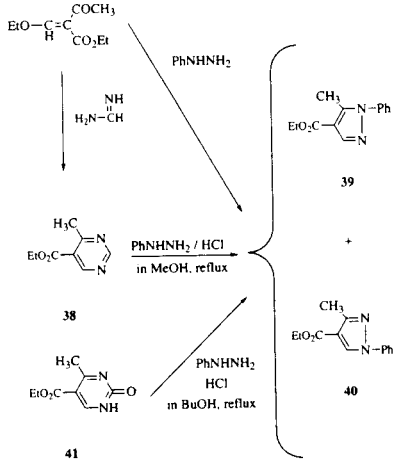
amidinohydrazone **36** is comparable with that observed in the reactions of phenylhydrazine and amidinohydrazine with certain 5-acylpyrimidines (for example: **22a,b,d** and **27**).

4) Reactions of Ethyl Pyrimidine-5-carboxylates with Hydrazines.

The ring transformation of ethyl 4-methylpyrimidine-5-carboxylate (**38**) into pyrazoles with hydrazines has been examined [29] because **38** is an analogue of the pyrimidine **22c**, possessing the ethoxycarbonyl group in replacement of the acetyl group of **22c** which easily undergoes ring contraction into pyrazoles.

The pyrimidine **38**, synthesized by condensation of ethyl ethoxymethyleneacetoacetate with formamidine in ethanol, remained unchanged on heating with amidinohydrazine in acidic methanol. The reaction of **38** with phenylhydrazine under the same conditions resulted in the formation of two isomeric pyrazoles: ethyl 5-methyl-1-phenylpyrazole-4-carboxylate (**39**) and ethyl 3-methy-1-phenylpyrazole-4-carboxylate (**40**) in 11% and 20% yields, respectively. The pyrazoles **39** and **40** were identical with those obtained by direct condensation of phenylhydrazine with ethyl ethoxymethyleneacetoacetate in methanol (this condensation provided a mixture of **39** and **40** in 7:1 ratio) [29] (Scheme 12).

Scheme 12



Ethyl 4-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate (**41**) [34] did not react with amidinohydrazine and phenylhydrazine in boiling acidic methanol. However, when heated with phenylhydrazine in butanol containing hydrochloric acid, **41** led to a mixture of **39** and **40** in 15% and 11% yields, respectively (Scheme 12).

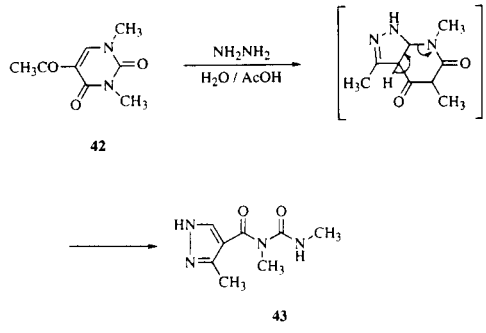
The simultaneous formation of **39** and **40** indicates that the nucleophilic attack of two nitrogen atoms of phenylhydrazine takes place non-selectively on both C4 and C6 of the pyrimidine ring of **38** and **41** without any involvement of the ethoxycarbonyl group at the 5-position. This mechanism is similar to that of the classical ring contraction of non-acylated pyrimidines into pyrazoles. In acidic alcoholic medium, the Michael-type addition of phenylhydrazine on C4 and C6 of the ethyl pyrimidine-5-carboxylates may be more favorable than the condensation on the ethoxycarbonyl group.

V. Ring Transformation of 5-Acyluracils into Pyrazoles.

1) Reactions of 5-Acetyluracils with Hydrazines.

In 1983, Hirota *et al.* [35] reported that 5-acetyl-1,3-dimethyluracil (**42**) was easily converted into a 4-allophanoylpyrazole derivative **43** on heating with hydrazine hydrate for 2 hours in water containing acetic acid (Scheme 13). This reaction can be explained by condensation of hydrazine on the enaminocarbonyl sequence (O=C-C5=C6-N) of **42** with N1-C6 bond fission of the uracil ring. The uracil **42** acts like an α,β-unsaturated ketone with hydrazine because of its characteristic structure which has a fixed double bond system.

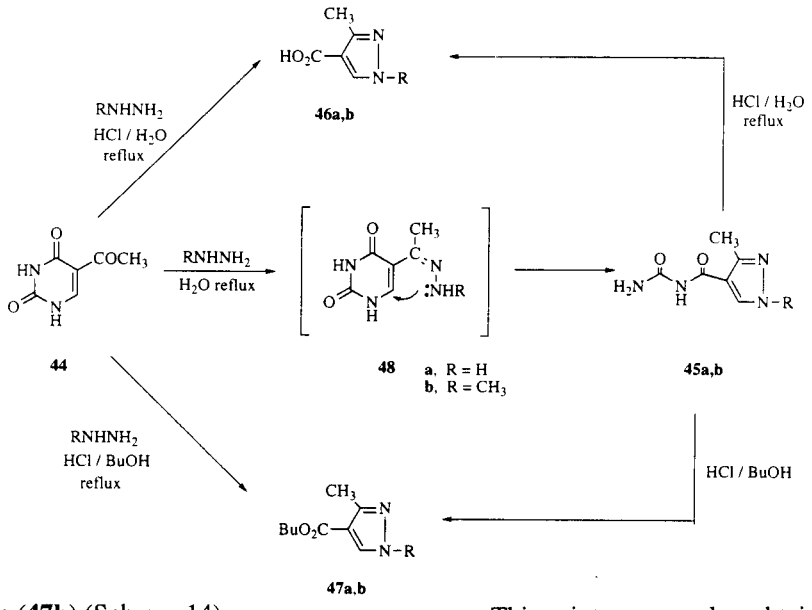
Scheme 13



Analogous results were obtained [36] in the reactions of 5-acetyluracil (**44**) [37] with hydrazines. Upon heating with hydrazine hydrate in water for 1 hour, the uracil **44** led to 4-allophanoyl-3-methylpyrazole (**45a**) in 72% yield. When the same reaction was carried out in the presence of hydrochloric acid in boiling water 3-methylpyrazole-4-carboxylic acid (**46a**) was mainly obtained together with a small amount of **45a** (Scheme 14). In fact, **45a** was readily hydrolyzed into **46a** on heating in diluted hydrochloric acid. Moreover, when treated under reflux in butanol containing hydrochloric acid, **45a** was converted, in good yield, into butyl 3-methylpyrazole-4-carboxylate (**47a**) which could be also synthesized by direct treatment of **44** with hydrazine hydrate in boiling butanol in the presence of hydrochloric acid (Scheme 14).

In the reaction of **44** with methylhydrazine, the same type of ring contraction was observed [36]. Thus, **44** led with methylhydrazine in boiling water into 4-allophanoyl-1,3-dimethylpyrazole (**45b**), in boiling diluted hydrochloric acid into 1,3-dimethylpyrazole-4-carboxylic acid (**46b**) and in boiling acidic butanol into butyl 1,3-dimethylpyra-

Scheme 14

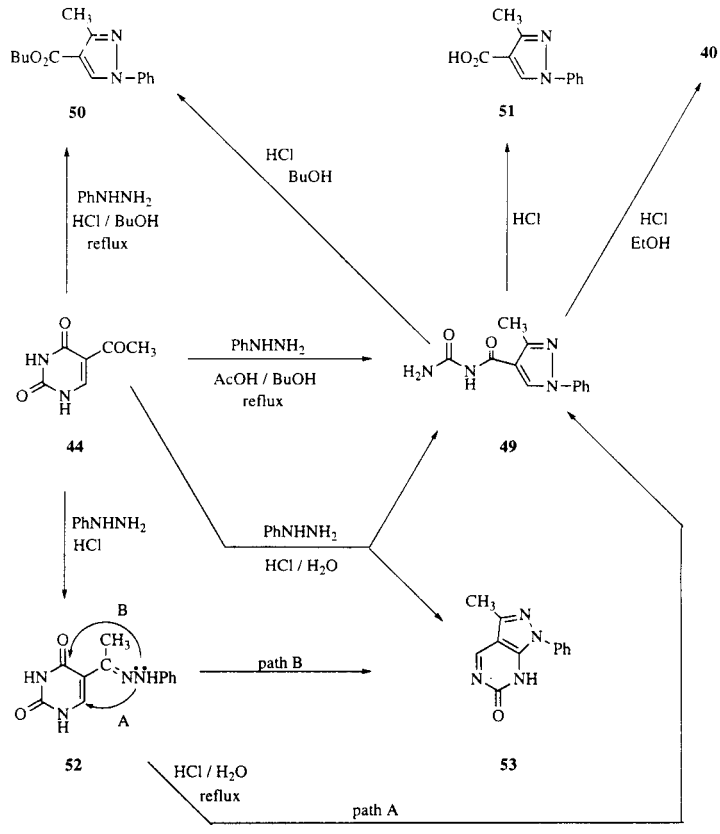


zole-4-carboxylate (**47b**) (Scheme 14).

These results clearly indicate that the two amino groups of hydrazines react with carbonyl-C and C6, respectively, of **44** to form the pyrazole ring; the reaction probably proceeds *via* initial formation of the hydrazone-type intermediates **48** because the resonance of amidic system of the uracil ring in **44** may somewhat hinder N1-C6 polarization, making first attack of hydrazines on C6 less favorable. In the case of methylhydrazine, the primary amino group selectively condenses with carbonyl-C of **44** and the secondary amino group acts on C6, resulting in the exclusive formation of 1,3-dimethylpyrazole derivatives (without formation of the corresponding 1,5-dimethyl isomers). Analogous mechanism has been discussed in the formation of 4-allophanoylpyrazoles from uracil-5-carboxaldehydes and methylhydrazine [35].

The uracil **44** also undergoes ring contraction with phenylhydrazine into several pyrazole derivatives according to the conditions used [36]. Treatment of **44** with phenylhydrazine in boiling butanol (but not in water) containing acetic acid afforded 4-allophanoyl-3-methyl-1-phenylpyrazole (**49**). The same reaction, carried out in the presence of hydrochloric acid in boiling butanol, led to the formation of butyl 3-methyl-1-phenylpyrazole-4-carboxylate (**50**) which was also prepared by heating **49** in a mixture of butanol and hydrochloric acid. Upon heating in diluted hydrochloric acid, **49** was easily hydrolyzed into 3-methyl-1-phenylpyrazole-4-carboxylic acid (**51**) in good yield. When treated with an excess of phenylhydrazine in an aqueous solution for 1 hour, **44** was exclusively converted to its phenylhydrazone **52** which provided, on treatment in boiling water containing hydrochloric acid, a mixture of **49** (20% yield) and 3-methyl-1-phenyl-6-oxo-6,7-dihydropyrazolo[3,4-*d*]pyrimidine (**53**) (32% yield). This mixture was also obtained by direct reaction of **44** with phenylhydrazine in diluted hydrochloric acid.

Scheme 15



On the basis of the above results, we can postulate a mechanism for the ring contraction of **44** with phenylhydrazine, which involves initial formation of the intermedi-

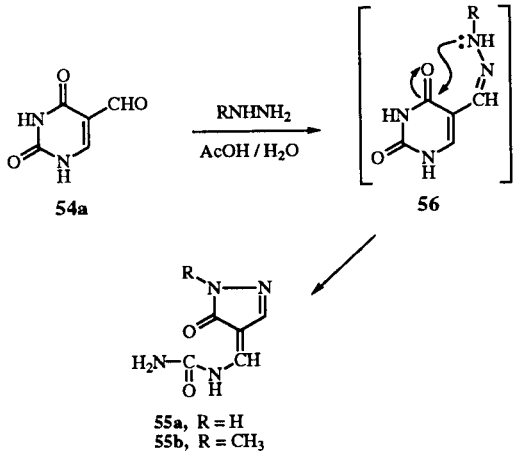
ate phenylhydrazone **52**, followed by intramolecular nucleophilic attack of the phenylamino group of **52** on C6 to give the pyrazole **49** (path A in Scheme 15) or at C4 to yield **53** (path B in Scheme 15). The former pathway seems to be predominant, and only in an aqueous medium, these two cyclization process take place simultaneously, giving a mixture of **49** and **53**. The elimination of urea from **49** by hydrolysis or alcoholysis obviously leads to the acid **51** or the ester **50**. The formation of 3-methyl-1-phenylpyrazole derivatives (no evidence for the formation of 5-methyl-1-phenyl isomers) excludes the Michael-type addition of the primary amino group of phenylhydrazine on C6 of **44**.

The alcoholysis of **49** also occurred in boiling acidic ethanol to afford ethyl 3-methyl-1-phenylpyrazole-4-carboxylate (**40**) in 90% yield, which is available only as a by-product in the formation of ethyl 5-methyl-1-phenylpyrazole-4-carboxylate (**39**) [29] by condensation between ethyl ethoxymethyleneacetoacetate and phenylhydrazine (Scheme 12).

2) Reactions of Uracil-5-carboxaldehydes with Hydrazines.

The first example of ring transformation of a pyrimidine having a carbonyl group at the 5-position into pyrazoles by the action of hydrazines was reported in 1968 by Zee-Cheng and Cheng [38]. They described that uracil-5-carboxaldehyde (**54a**) [39,40] was converted with simple hydrazine or monomethylhydrazine in the presence of acetic acid in boiling water into 4-ureidomethylene-1*H*-pyrazol-5-one (**55a**) and 1-methyl-4-ureidomethylene-1*H*-pyrazol-5-one (**55b**), respectively (Scheme 16). This ring transformation was explained by initial formation of the phenylhydrazones **56**, followed by intramolecular cyclization of the terminal amino (or methylamino) group of **56** on C4 of the uracil ring with concomitant N3-C4 bond fission (Scheme 16).

Scheme 16



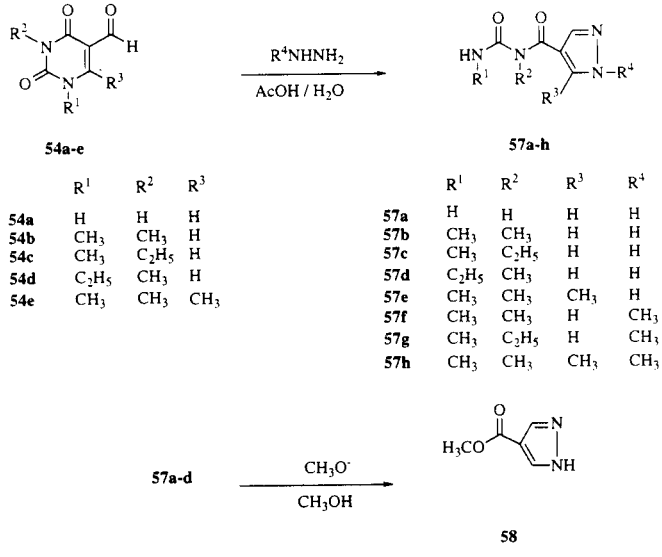
54a **56**

55a, R = H
55b, R = CH_3

However, Hirota *et al.* demonstrated [35,41] that the pyrazoles **55a,b** must have, in fact, the structures of 4-allophanoylpyrazole of type **57** (Scheme 17) because the pyrazole **57a**, earlier assumed to have the structure **55a**, readily produce, on treatment with methanolic sodium methoxide, methyl pyrazole-4-carboxylate (**58**) in quantitative yield (Scheme 17).

The same authors studied in detail [35] analogous reactions of 1,3-disubstituted uracil-5-carboxaldehydes **54b-e** with hydrazine hydrate and monomethylhydrazine. The reactions, carried out in the presence of acetic acid in water, gave in all cases the 4-allophanoylpyrazole derivatives **57b-h** (Scheme 17), among which **57b-d** were easily converted into the ester **58** on heating in methanolic sodium methoxide. For the ring conversion of **54** to **57**, two

Scheme 17



54a-e **57a-h**

	R^1	R^2	R^3
54a	H	H	H
54b	CH_3	CH_3	H
54c	CH_3	C_2H_5	H
54d	C_2H_5	CH_3	H
54e	CH_3	CH_3	CH_3

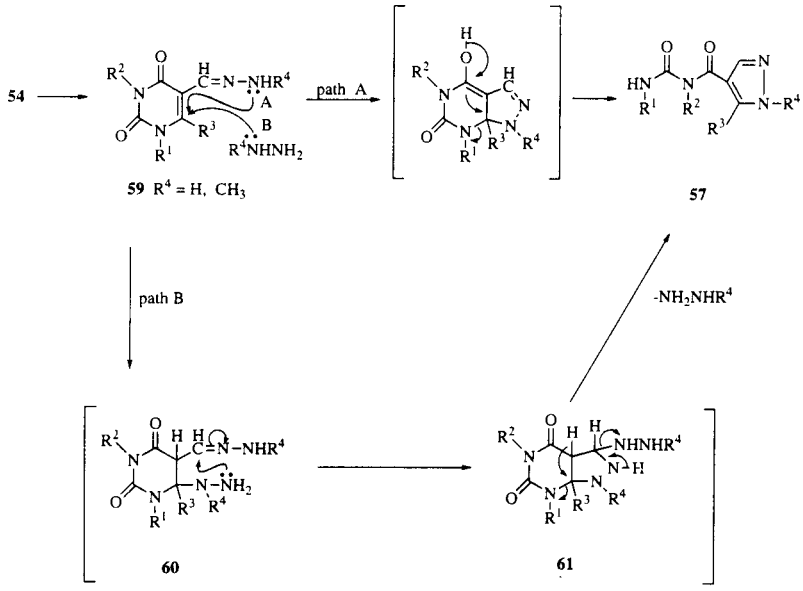
	R^1	R^2	R^3	R^4
57a	H	H	H	H
57b	CH_3	CH_3	H	H
57c	CH_3	C_2H_5	H	H
57d	C_2H_5	CH_3	H	H
57e	CH_3	CH_3	CH_3	H
57f	CH_3	CH_3	H	CH_3
57g	CH_3	C_2H_5	H	CH_3
57h	CH_3	CH_3	CH_3	CH_3

57a-d **58**

possible mechanisms have been proposed: the hydrazones **59** are initially formed and the subsequent intramolecular attack of the terminal amino group of hydrazono moiety on C6 of the uracil ring (path A in Scheme 18) provides the pyrazole compounds **57**. An alternative pathway involves the hydrazine adducts **60** which may be formed by addition of hydrazines on C6 of **59**. The adducts **60** then cyclize to the intermediates **61** which can be rearranged to the pyrazole ring compounds **57** with the elimination of hydrazines (path B in Scheme 18).

We also found that the uracil **54a** led to pyrazoles under the action of phenylhydrazine in acidic medium [42], contrary to the preceding reports [35,38,39] which described that similar reactions of some uracil-5-carboxaldehydes with phenylhydrazine only gave the corresponding phenylhydrazones, but not pyrazoles (the reason has been explained with respect to the less basicity of phenylhydrazine). Thus, when treated with phenylhydrazine in boiling

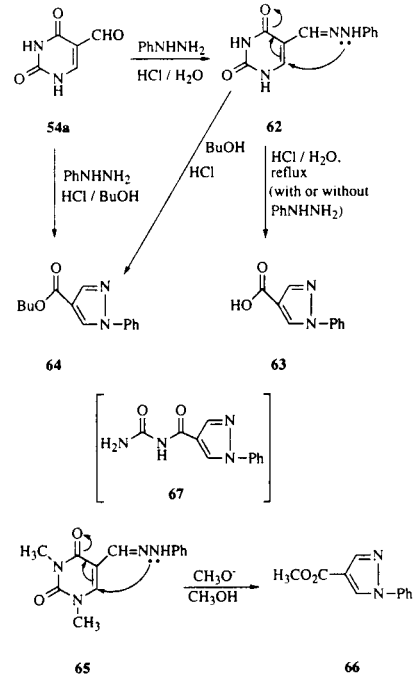
Scheme 18



water in the presence of an excess of hydrochloric acid, **54a** immediately gave the phenylhydrazone **62** as abundant precipitate. However, heating under reflux for 120 hours of this suspension with stirring resulted in the formation of 1-phenylpyrazole-4-carboxylic acid (**63**) [43] in 80% yield (Scheme 19). Since the phenylhydrazone **62** has very little solubility in boiling water, the conversion of **62** to **63** must require the prolonged heating of the reaction mixture. Moreover, it was confirmed that **62** under suspension in boiling diluted hydrochloric acid (without phenylhydrazine) could be transformed into **63**. Analogous transformation of **62** was accomplished on heating in butanol containing hydrochloric acid to yield butyl 1-phenylpyrazole-4-carboxylate (**64**) which was directly obtained from **54a** and phenylhydrazine in boiling acidic butanol (Scheme 19). Similar reaction of 1,3-dimethyluracil-5-carboxaldehyde phenylhydrazone (**65**) with sodium methoxide in methanol has been reported [35] to give methyl 1-phenylpyrazole-4-carboxylate (**66**) (Scheme 19).

From these findings, a mechanism to account for the formation of **63** from **54a** is rationalized by intramolecular attack of the phenylamino group of initialy formed **62** on C6 of the uracil ring to produce intermediate 4-allophanoyl-1-phenylpyrazole (**67**) which is hydrolyzed into **63** under reflux in aqueous acidic medium. The reaction conditions which are indispensable for the generation of the pyrazole ring from **62** (prolonged heating in acidic medium) did not allow to isolate the intermediate **67**. Similarly, the ester **64** may be formed *via* alcoholysis of the same intermediate **67** in boiling butanol. In conclusion, phenylhydrazine, as well as simple hydrazine and monomethylhydrazine, is capable to transform **54a**, *via* its

Scheme 19



phenylhydrazone, into the pyrazole-4-carboxylic acid derivatives in the presence of hydrochloric acid. The protonation on the uracil ring may favor, also in this case, the ring transformation into pyrazoles.

REFERENCES AND NOTES

[1] Present address: Division of Chemistry, College of Liberal Arts and Sciences, Kitasato University, 1-15-1, Kitasato, Sagamihara-shi, Kanagawa-ken 228, Japan.

[2] H. C. van der Plas, Ring Transformation of Heterocycles, Vol **2**, Academic Press, New York, NY, 1973, pp 119-123.

[3] H. C. van der Plas and H. Jongejan, *Tetrahedron Letters*, 4385 (1967); *ibid*, *Rec. Trav. Chim. Pays-Bas*, **87**, 1065 (1968).

[4] F. Baumbach, H.G. Henning and G. Hilgetag, *Z. Chem.*, **4**, 67 (1964).

[5] D. J. Brown, P. W. Ford and M. N. Paddon-Row, *J. Chem. Soc. (C)*, 1452 (1968).

[6] H. Wamhoff and K. Wald, *Chem. Ber.*, **110**, 1716 (1977).

[7] R. Fosse, A. Hieulle and L. W. Bass, *Compt. Rend. Acad. Sci.*, **178**, 811 (1924).

[8] F. Lingens and H. Schneider-Bernlöhr, *Liebigs Ann. Chem.*, **686**, 134 (1965).

[9] D. H. Hayes and F. Hayes-Baron, *J. Chem. Soc. (C)*, 1528 (1967).

[10] H. C. van der Plas, *Heterocycles*, **9**, 33 (1978).

[11] M. E. C. Biffin, D. J. Brown and Q. N. Porter, *Tetrahedron Letters*, 2029 (1967).

[12] H. C. van der Plas, H. Jongejan and A. Koudijs, *J. Heterocyclic Chem.*, **15**, 485 (1978).

[13a] E. Mihichi in Antineoplastic and Immunosuppressive Agents Tome **II**, A. C. Sartorelli and D. G. Johns, eds, Springer-Verlag, Berlin, 1975, pp 766-788; [b] C. W. Porter, C.V. Dave and E. Mihichi in Polyamines in Biology and Medicine, D. R. Morris and L. J. Marton, eds, Marcel Dekker Inc., 1981, pp 407-436.

[14] G. Menichi, J. Naciri, B. Kokel and M. Hubert-Habart, *Heterocycles*, **22**, 2013 (1984).

[15] V. P. Arya, J. David, A. S. Grewal, S. B. Marathe and S. D. Patil, *Indian J. Chem.*, **15B**, 1129 (1977).

[16] G. Menichi, M. Boutar, B. Kokel, K. Takagi and M. Hubert-Habart, *J. Heterocyclic Chem.*, **23**, 275 (1986).

[17] S. C. De and P. C. Rakshit, *J. Indian Chem. Soc.*, **13**, 509 (1936).

[18] It has been reported that the reaction of ethoxymethylene-acetylacetone with phenylhydrazine gave 4-acetyl-5-methyl-1-phenyl-pyrazole: L. Claisen, *Liebigs Ann. Chem.*, **295**, 321 (1897).

[19] Pyrazoles **10a** (R = H, CH_3, Ph) were already synthesized: [a] R = H, L. Pannizi and O. Benati, *Gazz. Chim. Ital.*, **76**, 66 (1946); [b] R = CH_3, P. Schenone, L. Mosti and G. Menozzi, *J. Heterocyclic Chem.*, **19**, 1355 (1982); [c] R = Ph, see Ref [18].

[20] K. Nagarajan, V. P. Arya and S. J. Shenoy, *J. Chem. Res. (S)*, 166 (1986); *(M)*, 1401 (1986).

[21] J. Elquero, R. Jacquier and H. Cung N. Tien Duc, *Bull. Soc. Chim. France*, 3727 (1966).

[22] L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).

[23] A. Cousson, F. Robert and M. Hubert-Habart, *Acta Cryst.*, **C47**, 395 (1991).

[24] A. Cousson, B. Bachet, B. Kokel and M. Hubert-Habart, *Acta Cryst.*, **C47**, 1885 (1991).

[25] Only compounds **5a,b** have been detected as by-products in the preparation of **10a** (R = CH_3 and Ph), see Ref [19b] and [20].

[26] A. Bajnati, M. Hubert-Habart, K. Takagi and H. Terada, *Heterocycles*, **29**, 1583 (1989).

[27] K. Takagi, A. Bajnati, M. Hubert-Habart and H. Terada, *J. Heterocyclic Chem.*, **27**, 1847 (1990).

[28] T. J. Schwan, N. J. Milles and J. C. Butterfield, *J. Heterocyclic Chem.*, **13**, 973 (1976).

[29] A. Bajnati, B. Kokel and M. Hubert-Habart, *Bull. Soc. Chim. France*, 318 (1987).

[30] A. Cousson, F. Nextoux, B. Bachet, B. Kokel and M. Hubert-Habart, *Acta Cryst.*, **C50**, 286 and 289 (1994).

[31] K. Takagi, A. Bajnati and M. Hubert-Habart, *Heterocycles*, **31**, 1105 (1990); *ibid*, *Bull. Soc. Chim. France*, **127**, 660 (1990).

[32a] Z. Arnold, *Collect. Czech. Chem. Commun.*, **26**, 3051 (1961); [b] Z. Arnold and J. Zemlicka, *Collect. Czech. Chem. Commun.*, **25**, 1318 (1960).

[33] Synthesis of **35** by oxydation of 4-chloromethyl-1-phenylpyrazole and the formylation of 1-phenylpyrazole has been reported, I. L. Finar and G. H. Lord, *J. Chem. Soc.*, 3314 (1957).

[34] W. Bergman and T. B. Johnson, *Ber.*, **66**, 1492 (1933).

[35] K. Hirota, Y. Kitade, K. Shimada, S. Senda and Y. Maki, *J. Chem. Soc., Perkin Trans. I*, 1293 (1983).

[36] A. Bajnati and M. Hubert-Habart, *Bull. Soc. Chim. France*, 540 (1988).

[37] W. Bergman and T. B. Johnson, *Ber.*, **66B**, 1492 (1933).

[38] K.-Y. Zee-Cheng and C. C. Cheng, *J. Org. Chem.*, **33**, 892 (1968).

[39] R. H. Wiley and Y. Yamamoto, *J. Org. Chem.*, **25**, 1906 (1960).

[40] R. Brossmer and D. Ziegler, *Tetrahedron Letters*, 5253 (1966).

[41] K. Hirota, Y. Kitade, K. Shimada and S. Senda, *Chem. Pharm. Bull.*, **29**, 3760 (1981).

[42] A. Bajnati, Thèse de Doctorat, Université de Paris, 1992, pp 64-72.

[43] I. L. Finar and K. E. Godfrey, *J. Chem. Soc.*, 2293 (1954).