Pyrimidine Derivatives and Related Compounds. Part 45.[1] Synthesis of 4-Allophanoylpyrazoles *via* a Pyrimidine-to-pyrazole Ring Transformation [2]

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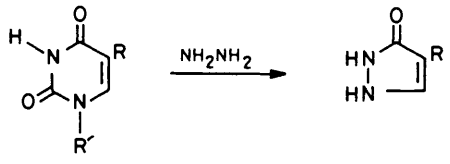
Reaction of the 5-formyluracil derivatives (1a—f) with hydrazines in the presence of acetic acid produced a ring contraction to give the corresponding 4-allophanoylpyrazoles (2a—h). Further treatment of these pyrazoles (2a—h) with sodium methoxide afforded methyl pyrazole-4-carboxylate (3a). Conceivable mechanisms for the present pyrimidine-to-pyrazole transformation were discussed.

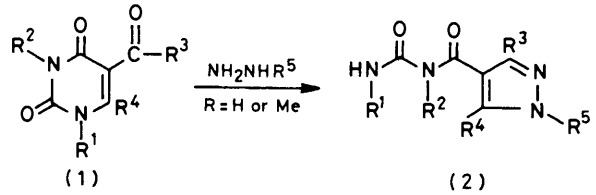
Methods for the synthesis of heterocycles by ring transformation are of constant interest, as evidenced by the vast literature on this subject.[3] Certain ring transformations have been utilized efficiently in the synthesis of heterocycles possessing a special functional group. Along these lines, we have reported that uracil derivatives react with various 1,3-ambident nucleophiles to give important six-membered heterocycles.[4,5] One such conversion was advantageously employed for the large-scale preparation of ψ-isocytidine from ψ-uridine.[4]

Hydrazinolysis of uracil derivatives to afford pyrazolones has precedent (Scheme 1).[6] The ring contraction has been employed in particular areas such as the chemical modification of nucleic acids.[7] Further studies on its application to other heterocycle syntheses, however, are few.[8]

In the course of our studies [8] on the reaction of 5-substituted uracils with hydrazines, we found a novel pyrimidine-to-pyrazole ring transformation in the hydrazinolysis of 5-formyluracils (1) and we exploited this reaction for the synthesis of 4-allophanoylpyrazoles (2) and pyrazole-4-carboxylates (3), whose syntheses are otherwise very difficult by other, conventional methods.[9]



Scheme 1.



(1) (2)

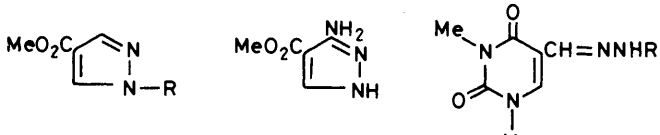
	R^1	R^2	R^3	R^4
a;	H	H	H	H
b;	Me	Me	H	H
c;	Me	Et	H	H
d;	Et	Me	H	H
e;	Me	Me	Me	H
f;	Me	Me	H	Me

Scheme 2.

Results and Discussion

Treatment of 5-formyluracil (1a) with hydrazine hydrate in the presence of acetic acid in boiling water afforded 4-allophanoylpyrazole (2a) in 69% yield.† Its available spectral data did not, however, allow us to confirm the structure. The ultimate proof of the structure of compound (2a) rests upon its conversion into methyl pyrazole-4-carboxylate (3a). Thus, heating compound (2a) in methanolic sodium methoxide gave the methyl carboxylate (3a) in 89% yield. Compound (3a) was identical with an authentic sample prepared by the deamination of methyl 3-aminopyrazole-4-carboxylate (4).[10]

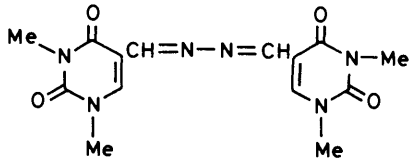
Analogous treatment of 5-formyl-1,3-dimethyluracil (1b), 3-ethyl-5-formyl-1-methyluracil (1c), and 1-ethyl-5-formyl-3-methyluracil (1d) with hydrazine hydrate gave the corresponding 4-allophanoylpyrazole derivatives (2b), (2c), and (2d), respectively (Scheme 2). The use of methylhydrazine in reactions with the uracils (1b) and (1c) resulted in the formation of the 1-methylpyrazoles (2e) and (2f), respectively.



(3) (4) (5)

a; R = H
b; R = Ph

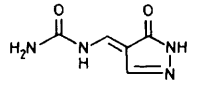
a; R = Ph
b; R = H



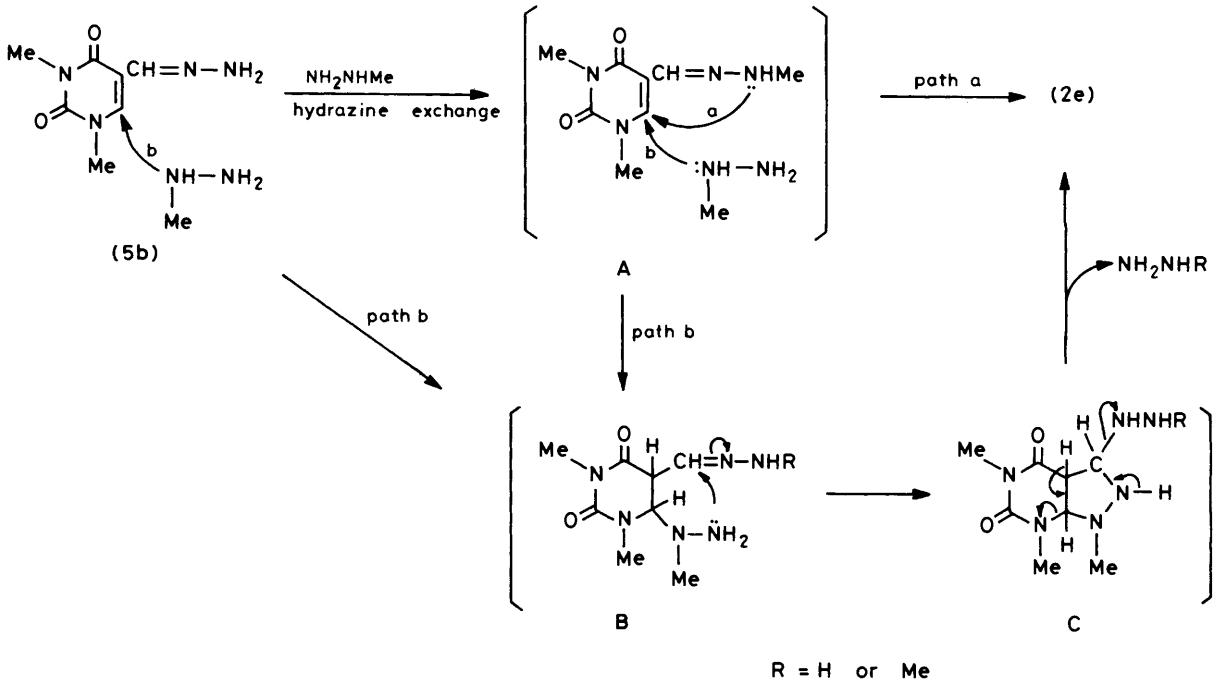
(6)

However, the reaction of the uracil (1b) with phenylhydrazine gave the phenylhydrazone (5a) in 97% yield instead of the expected 1-phenylpyrazole. Methyl 1-phenylpyrazole-4-carboxylate (3b) [11] was easily obtained by treatment of the

† Zee-Cheng and Cheng reported that the reaction of the uracil (1a) with hydrazine hydrate under the same conditions gave 4,5-dihydro-4-ureidomethylenepyrazol-5-one (I) (K.-Y. Zee-Cheng and C. C. Cheng, *J. Org. Chem.*, 1968, **33**, 892). The results of our reinvestigation, however, confirmed our preliminary report [2] that Cheng's compound has structure (2a).



(I)

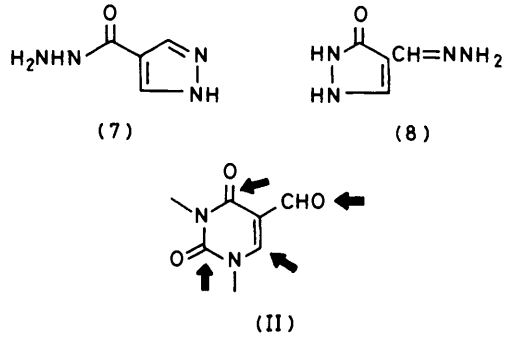


Scheme 3.

hydrazone (5a) with sodium methoxide. 5-Acetyl-1,3-dimethyluracil (1e) was allowed to react with hydrazine hydrate under the same conditions as previously described to produce the 3-methylpyrazole (2 g) which could also be prepared by the reaction of 5-formyl-1,3,6-trimethyluracil (1f) with hydrazine hydrate. Similar treatment of compound (1f) with methylhydrazine gave the 1,5-dimethylpyrazole (2 h), whose structure was presumed on the basis of mechanistic considerations described below.

In order to obtain some insight into the mechanisms of these reactions the synthesis of the hydrazone intermediate (5b) and its conversion into the pyrazoles under several conditions were investigated. The hydrazone (5b) was obtained in 83% yield upon treatment of the aldehyde (1b) with aqueous hydrazine at room temperature. Under the conditions employed for the ring transformation, the uracil (5b) was converted into the pyrazole (2b) in 68% yield, which is better than that in the formation of the same pyrazole from compound (1b). These data suggest that compound (5b) may be an intermediate of the present ring transformation reactions. When the hydrazone (5b) was treated in the absence of acetic acid, the dimer (6) was obtained in 97% yield, rather than the expected pyrazole (2b). The reaction of the uracil (5b) with hydrazine hydrate (1 equiv.) proceeded smoothly to give the expected pyrazole (2b) in high yield (86%). These reactions indicate that the addition of hydrazines to the reaction mixture accelerated the conversion of (5b) into (2b). Treatment of compound (5b) with methylhydrazine led to the formation of the 1-methylpyrazole (2e) arising from incorporation of a methylhydrazine in place of a hydrazine moiety. Furthermore, the reaction of the hydrazone (5b) with phenylhydrazine gave, *via* hydrazine exchange, the phenylhydrazone (5a) quantitatively.

On the basis of the above results, two reaction sequences for the present ring transformation are proposed. The sequences for the formation of the 1-methylpyrazole (2e) from (5b), as a representative example, are outlined in Scheme 3. A methylhydrazone intermediate A may be formed as a result of hydrazine exchange of the initially formed hydrazone (5b).



(7) (8)

(II)

This step accommodates the transformation of (5b) into (5a) mentioned above. Formation of the pyrazole (2e) from A would involve intramolecular nucleophilic attack of the terminal methylamino group at the 6-position of the uracil ring (path a). An alternative pathway to (2e) involves the possible intermediate B; further nucleophilic attack of methylhydrazine at the 6-position of either (5b) or A would give an adduct B, which may cyclize to an intermediate C; this could subsequently produce the pyrazole (2e) with the release of hydrazine or methylhydrazine (path b). The latter sequence (path b) is closely related to that of pyrazol[3,4-*d*]pyrimidine synthesis by the reaction of 6-chloro-1,3-dimethyluracil-5-carbaldehyde phenylhydrazone with methylhydrazine.[12]

The present reaction takes place in a different fashion from the well known uracil-to-pyrazole transformation [6,7] (see Scheme 1) in respect of the reaction sequence. When the uracil (1b) was heated in hydrazine hydrate under conventional transformation conditions,[13] the pyrazole-4-carbohydrazine (7) was obtained, instead of the conventional type of pyrazolone (8), presumably *via* compound (2b) as an intermediate. The structure of compound (7) was confirmed by direct comparison of an authentic sample prepared by the reaction of the pyrazole (2b) with hydrazine hydrate. 5-Formyluracils (1) have four sites for nucleophilic attack as shown in

Table 1. Formation of 4-allophanoylpyrazoles (2)

Starting material	Hydrazine	Product	R^1	R^2	R^3	R^4	R^5	Reaction time (h)	Recrystallization solvent	Yield (%)
(1a)	$NH_2NH_2{\cdot}H_2O$	(2a)	H	H	H	H	H	8	H_2O	69
(1b)	$NH_2NH_2{\cdot}H_2O$	(2b)	Me	Me	H	H	H	7	H_2O	48
(1c)	$NH_2NH_2{\cdot}H_2O$	(2c)	Me	Et	H	H	H	10	EtOH	57
(1d)	$NH_2NH_2{\cdot}H_2O$	(2d)	Et	Me	H	H	H	12	EtOH	25
(1b)	NH_2NHMe	(2e)	Me	Me	H	H	Me	5	EtOH	73
(1c)	NH_2NHMe	(2f)	Me	Et	H	H	Me	4	Light petroleum [a]	68
(1e)	$NH_2NH_2{\cdot}H_2O$	(2g)	Me	Me	Me	H	H	2	EtOH	72
(1f)	$NH_2NH_2{\cdot}H_2O$	(2g)	Me	Me	H	Me	H	8	EtOH	57
(1f)	NH_2NHMe	(2h)	Me	Me	H	Me	Me	8	EtOH	81

[a] Boiling range 75—120 °C.

Table 2. Physical data for 4-allophanoylpyrazoles (2)

Compound	M.p. (°C)	^{1}H N.m.r. (δ downfield from $SiMe_4$)	Solvent	U.v. (H_2O) $\lambda_{max.}$ (nm)	U.v. (H_2O) ε
(2a)	274—277	7.27 (1 H, br), 8.09 (1 H, br), 8.34 (2 H, s), 10.18 (1 H, br), 13.31 (1 H, br)	$(CD_3)_2SO$	230	12 500
(2b)	224	2.74 (3 H, d, *J* 5 Hz), 3.30 (3 H, s), 8.03 (2 H, s), 8.74 (1 H, br)	$(CD_3)_2SO$	227	9 990
(2c)	192—194	1.14 (3 H, d, *J* 7 Hz), 2.68 (3 H, *d*, *J* 5 Hz), 3.74 (2 H, q, *J* 7 Hz), 7.89 (2 H, s), 8.39 (1 H, br)	$(CD_3)_2SO$	219	9 680
(2d)	97—98	1.19 (3 H, t, *J* 7 Hz), 3.33 (2 H, dq, *J* 7 and 2 Hz), 3.48 (3 H, s), 8.00 (2 H, s), 9.25 (1 H, br)	$CDCl_3$	225	9 500
(2e)	97—98	2.88 (3 H, d, *J* 5 Hz), 3.46 (3 H, s), 3.92 (3 H, s), 7.78 (1 H, s), 7.83 (1 H, s), 9.10 (1 H, br)	$CDCl_3$	225	8 900
(2f)	88—92	1.32 (3 H, t, *J* 7 Hz), 2.89 (3 H, d, *J* 5 Hz), 3.94 (3 H, s), 3.99 (2 H, q, *J* 7 Hz), 7.78 (1 H, s), 7.82 (1 H, s), 9.10 (1 H, br)	$CDCl_3$	224	10 000
(2g)	178—179	2.30 (3 H, s), 2.68 (3 H, d, *J* 5 Hz), 3.17 (3 H, s), 7.65 (1 H, br), 8.55 (1 H, br)	$(CD_3)_2SO$	223	8 860
(2h)	127—129	2.41 (3 H, s), 2.89 (3 H, d, *J* 5 Hz), 3.37 (3 H, s), 3.79 (3 H, s), 7.55 (1 H, s) 9.02 (1 H, br)	$CDCl_3$	225	9 500

structure (II). On the basis of the above experimental results, the order of reactivity of the compound (1) towards hydrazines appears to be C(5)-*C*HO > C(6) > C(4) > C(2).

Reaction of the pyrazole (2b) with methanolic sodium methoxide afforded the ester (3a) (79%) and 1,3-dimethylurea (83%). Under the same conditions the pyrazoles (2c) and (2d) were converted into the ester (3a) and 1-ethyl-3-methylurea. Therefore this procedure is useful for the preparation of the pyrazole-4-carboxylates (3).

Experimental

M.p.s were determined on a Yanagimoto melting-point apparatus and are uncorrected. I.r. spectra were recorded with an Hitachi Model 215 spectrometer, using KBr pellets; ^{1}H n.m.r. spectra were determined with an Hitachi–Perkin-Elmer R-20B 60-MHz instrument, using tetramethylsilane as internal standard; mass spectra were taken on a JEOL JMS-D300 machine operating at 70 eV. U.v. spectra were recorded for solutions in water on an Hitachi 525 spectrophotometer. Elemental analyses were carried out at the Microanalytical Laboratory of our college.

4-Allophanoylpyrazoles (2a—h).—*General procedure.* A solution of the appropriate hydrazine (0.0065 mol) in water (30 ml) was added dropwise to a warm, stirred solution (50—60 °C) of a 5-formyluracil derivative (1a—f) (0.005 mol) in water (40 ml) containing acetic acid (0.05 g). The resulting solution was then heated at 100 °C and stirred for the time given in Table 1. The mixture was cooled and the precipitate was filtered off. In cases where there was no precipitate, the aqueous solution was extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to dryness. Recrystallization of the residue from an appropriate solvent (Table 1) gave the corresponding *4-allophanoylpyrazoles* (2a—h) (physical data are given in Tables 2 and 3).

Alternative route from the uracil (5b). (a) A mixture of (5b) (0.547 g, 0.003 mol) and acetic acid (0.03 g) in water (24 ml) was heated at 100 °C for 12 h and was then treated as described above to give the pyrazole (2b) (0.37 g, 68%).

Table 3. Analytical data (%)

Compound	Formula	Found (Required) C	H	N
(2a)	$C_5H_6N_4O_2$	38.7 (38.95	3.75 3.9	36.2 36.35)
(2b)	$C_7H_{10}N_4O_2$	46.1 (46.15	5.5 5.5	30.85 30.75)
(2c)	$C_8H_{12}N_4O_2$	49.0 (48.95	6.05 6.15	28.6 28.55)
(2d)	$C_8H_{12}N_4O_2$	49.25 (48.95	6.0 6.15	28.3 28.55)
(2e)	$C_8H_{12}N_4O_2$	49.0 (48.95	6.25 6.15	28.7 28.55)
(2f)	$C_9H_{14}N_4O_2$	51.15 (51.4	6.6 6.2	26.4 26.65)
(2g)	$C_8H_{12}N_4O_2$	49.05 (48.95	6.25 6.15	28.6 28.55)
(2h)	$C_9H_{14}N_4O_2$	51.15 (51.4	6.8 6.7	26.55 26.65)
(3a)	$C_5H_6N_2O_2$	47.35 (47.6	4.8 4.8	22.2 22.2) [a]
(3b)	$C_{11}H_{10}N_2O_2$	65.35 (65.35	4.95 5.0	13.95 13.85) [a]
(5a)	$C_{13}H_{14}N_4O_2$	60.65 (60.45	5.4 5.45	21.85 21.7)
(5b)	$C_7H_{10}N_4O_2$	46.35 (46.15	5.4 5.5	30.5 30.75)
(6)	$C_{14}H_{16}N_4O_4$	50.6 (50.6	4.7 4.85	25.25 25.3)
(7)	$C_4H_6N_4O$	37.85 (38.1	4.75 4.8	44.6 44.45)

[a] Calculated values (known compound).

(b) A mixture of (5b) (0.547 g, 0.003 mol), hydrazine hydrate (0.15 g, 0.003 mol), and acetic acid (0.03 g) in water (24 ml) was heated at 100 °C for 7 h and then treated as described above to give the pyrazole (2b) (0.47 g, 86%).

(c) A mixture of (5b) (0.547 g, 0.003 mol), methylhydrazine (0.138 g, 0.003 mol), and acetic acid (0.03 g) in water (24 ml) was heated at 100 °C for 8 h and then treated as described above to give the pyrazole (2e) (0.317 g, 58%).

Reaction of the 4-Allophanoylpyrazoles (2a—d) *with Sodium Methoxide.*—A solution of a 4-allophanoylpyrazole (2a—d) (0.005 mol) and sodium methoxide from [Na (0.23 g) dissolved in dry methanol (65 ml)] was refluxed and stirred for 2 h. The solvent was removed under reduced pressure and the residue was treated with water (20 ml). The solution was neutralized with 10% HCl solution and the aqueous solution was extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to dryness. Recrystallisation of the residue from benzene gave analytical pure methyl pyrazole-4-carboxylate (3a), m.p. 145—146 °C (lit.,[10] 135—136 °C); *m/z* 126 (M^+); δ ($CDCl_3$) 3.89 (3 H, s) and 8.13 (2 H, s).

The remaining aqueous solution was evaporated to dryness and the residue was washed with dry ethanol. The mixture was evaporated to dryness to give a 1,3-disubstituted urea (see Table 4).

Alternative Preparation of Methyl Pyrazole-4-carboxylate (3a).[10]—Methyl 3-aminopyrazole-4-carboxylate (4) (0.706 g, 0.005 mol) and sodium nitrite (0.345 g, 0.005 mol) were dissolved in 15% NaOH solution (10 ml). The solution was added dropwise to a stirred mixture of concentrated HCl (2.5 ml) and ice (2.5 g) at <10 °C. The precipitate, a diazonium compound, was separated by decantation. The diazonium slurry was added portionwise to an ethanolic suspension of ground $CuSO_4$ (0.015 g) at 60—70 °C. The mixture was then cooled, the solvent was removed under reduced pressure, and the residue was dissolved in ice-cold water (20 ml). The solution was extracted with dichloromethane and the extract was dried ($MgSO_4$) and evaporated to dryness. The resulting crude product was recrystallized from benzene to give crystals of the ester (3a) (0.3 g, 48%), identical with the sample prepared by the reaction of the compounds (2a—d) with sodium methoxide.

Table 4. Preparation of methyl pyrazole-4-carboxylate (3a) and 1,3-disubstituted ureas

Starting material	Product and yield (%) (3a)	urea
(2a)	89	
(2b)	79	MeHNCONHMe (83)
(2c)	83	MeHNCONHEt (84)
(2d)	74	MeHNCONHEt (70)

Methyl 1-Phenylpyrazole-4-carboxylate (3b).[11]—Compound (5a) (0.774 g, 0.003 mol) was dissolved in methanolic sodium methoxide [prepared from Na (0.138 g) in dry methanol (40 ml)] and the solution was stirred and refluxed for 6 h. The solvent was removed under reduced pressure and the residue was treated with water (20 ml). The solution was neutralized with concentrated HCl and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to dryness. Recrystallization of the residue from benzene gave analytical pure methyl 1-phenylpyrazole-4-carboxylate (3b) (0.49 g, 81%), m.p. 130—131 °C; *m/z* 202 (M^+); δ [$(CD_3)_2SO$] 3.82 (3 H, s), 7.35—8.05 (5 H, m), 8.17 (1 H, s), and 9.10 (1 H, s).

1,3-*Dimethyluracil-5-carbaldehyde Phenylhydrazone* (5a).—(*a*) A solution of phenylhydrazine (0.7 g, 0.006 5 mol) in water (3 ml) was added dropwise to a stirred solution of the aldehyde (1b) (0.84 g, 0.005 mol) in water (40 ml) containing acetic acid (0.05 g). The solution was stirred and heated at 100 °C for 5 h. After the mixture had cooled the precipitate was filtered off. Recrystallization from ethanol gave analytical pure 1,3-*dimethyluracil-5-carbaldehyde phenylhydrazone* (5a) (1.25 g, 97%), m.p. 215—216 °C; *m/z* 258 (M^+); $\nu_{max.}$ 3 290, 1 705, 1 642, and 1 607 cm^{-1}; δ [$(CD_3)_2SO$] 3.19 (3 H, s), 3.40 (3 H, s), 6.5—7.4 (5 H, m), 7.78 (1 H, s), 8.12 (1 H, s), and 10.15 (1 H, br).

(*b*) A mixture of the hydrazone (5b) (0.547 g, 0.003 mol), phenylhydrazine (0.432 g, 0.004 mol), and acetic acid (0.03 g) in water (24 ml) was stirred for 10 min at room temperature; the yellow needles were filtered off to afford compound (5a) (0.75 g, 97%).

1,3-*Dimethyluracil-5-carbaldehyde Hydrazone* (5b).—Hydrazine hydrate (0.55 g, 0.11 mol) was added dropwise to a stirred solution of the aldehyde (1b) (1.66 g, 0.01 mol) in water (80 ml). The mixture was stirred for 10 min and a small quantity of a yellow precipitate was filtered off. The filtrate was extracted with chloroform and the extract was dried ($MgSO_4$) and evaporated to dryness. Recrystallization of the residue from benzene gave analytical pure 1,3-*dimethyluracil-5-carbaldehyde hydrazone* (5b) (1.394 g, 83%), m.p. 178—180 °C [at this temperature, the product oxidatively dimerizes to 1,3-dimethyluracil-5-carbaldehyde azine * (6)]; *m/z* 182

* Non-systematic name used for simplicity.

(M^+); $\nu_{max.}$ 3 430, 1 705, and 1 638 cm^{-1}; δ ($CDCl_3$) 3.35 (3 H, s), 3.43 (3 H, s), 5.51 (2 H, br), 7.71 (1 H, s), and 7.76 (1 H, s).

1,3-*Dimethyluracil-5-carbaldehyde Azine* (6).—A solution of the hydrazone (5b) (0.547 g, 0.003 mol) in water (24 ml) was refluxed for 12 h. After the mixture had cooled the precipitate was filtered off and washed with diethyl ether to give the *title azine* (6) (0.485 g, 97%), m.p. >300 °C; *m/z* 333 (M^+); $\nu_{max.}$ 3 060, 1 700, 1 650, and 1 610 cm^{-1}; δ (CF_3CO_2H) 3.58 (3 H, s), 3.78 (3 H, s), 8.68 (1 H, s), and 8.94 (1 H, s).

Pyrazole-4-carbohydrazide (7).—(*a*) A mixture of the uracil (1b) (1.68 g, 0.01 mol) and hydrazine hydrate (2.5 ml) was heated at 100 °C for 3 h. The reaction mixture was evaporated to dryness under reduced pressure and the residue was treated with ethanol. The precipitate was filtered off. Recrystallization from water gave an analytically pure sample of the *hydrazide* (7) (0.5 g, 40%), m.p. 245—250 °C; *m/z* 126 (M^+); δ [$(CD_3)_2SO$] 8.07 (s); the signals due to the amino groups could not be observed.

After evaporation of the ethanolic filtrate, the residue was subjected to column chromatography (silica gel; chloroform) to afford 1,3-dimethyluracil (0.16 g, 11%), identical with an authentic sample.

(*b*) A mixture of compound (2b) (0.3 g, 0.001 5 mol) and hydrazine hydrate (1.5 ml) was heated at 100 °C for 3 h. After the mixture had cooled the precipitate was filtered off (0.16 g, 85%) and was shown to be identical with a sample of the hydrazide (7) prepared by reaction (*a*) above.

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