Reactions of Glyoxals with Hydrazones: A New Route to 4-Hydroxypyrazoles

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N-Substituted hydrazones of aldehydes react with glyoxals under non-aqueous conditions to give *N*-substituted 4-hydroxypyrazoles; fourteen such products are described. In the presence of water, *N*-substituted 3-acyl-4-hydroxypyrazoles are produced from 2-oxoaldehyde hydrazones and glyoxals. It is shown that glyoxals combine in a 1:1 ratio with *N*-monosubstituted hydrazines to give 2-hydrazonoaldehydes as the kinetically controlled products. At room temperature or lower, these hydrazonoaldehydes rearrange to the more stable 2-oxoaldehyde hydrazones and react with glyoxals to give *N*-substituted 3-acyl-4-hydroxypyrazoles; sixteen such products are described. This synthesis, involving easily accessible starting materials, opens up a new, and for certain derivatives exclusive, route to 4-hydroxypyrazoles.

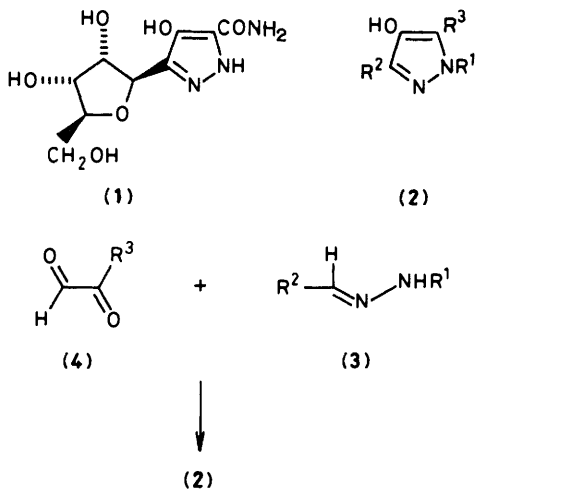
The discovery of pyrazomycin (**1**), an antiviral, microbial compound,[1] has stimulated interest in 4-hydroxypyrazoles (**2**), a class of compound less well explored than their 3- and 5-hydroxy-substituted counterparts. Reported syntheses of 4-hydroxypyrazoles (**2**) fall into two categories, one characterised by the formation of C–N bonds only,[2–7] and the other involving C–C bond formation(s). The combinations of α-diazoesters with alkyl malonates,[8–10] or of alkyl hydrazinoacetates with α-oxoesters,[11] to give 4-hydroxypyrazoles, seem to be the only known examples of the C–C bond-forming type of synthesis.

The inherent limitations in the substitution patterns attainable through the known methodology motivated our search for alternative routes to the 4-hydroxypyrazoles (**2**), all involving C–C bond-forming reactions. We describe our results here.

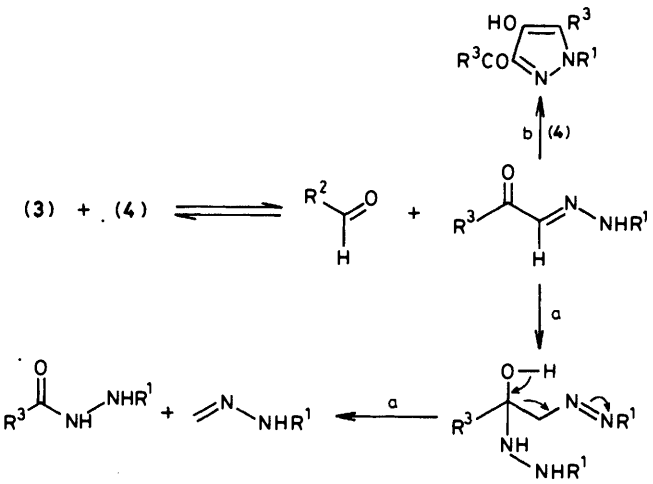
Results and Discussion

A retrosynthetic inspection of structure (**2**) suggests the reaction of aldehyde hydrazones (**3**) and glyoxals (**4**) to be an obvious, though apparently neglected, synthetic possibility (Scheme 1). In fact, we found that the aldehyde hydrazones (**3**; R^1 = Me or Ph, R^2 = H, Me, Et, Pr, or Ph) and the glyoxals (**4**; R^3 = H, Me, or Ph), when heated together under anhydrous conditions in butyl acetate containing acetic acid, afforded moderate to excellent yields of the 4-hydroxypyrazoles (**2**); fourteen representatives of these are listed in Table 1 (entries 1—14). The structural assignment of these rests on (i) agreement in m.p.s [mixed m.p. in the case of (**2**; R^1 = Ph, R^2 = H, R^3 = Me)] with eight previously described compounds of this series, and (ii) comparison of the ^1H and ^{13}C n.m.r. spectra with those recorded for the authentic specimens (entries 3,4,6—9, 13, and 14 in Table 1) [The ^{13}C n.m.r. spectral results are given in Table 2. The ^1H n.m.r. results are available as a supplementary Publication (SUP No. 56091, 2 pp.).*]

The hydrazones of lower aldehydes, (**3**; R^1 = Me or Ph; R^2 = H, Me, Et, or Pr), are of limited stability.[12,13] In the experiments where they were generated *in situ* from the reaction of the aldehyde and *N*-substituted hydrazine followed by the addition of the glyoxal, the expected 4-hydroxypyrazoles (**2**; R^2 = Me, Et, or Pr) were invariably accompanied by the corresponding 3-unsubstituted analogues (**2**; R^2 = H), suggesting the competitive involvement of the formaldehyde hydrazones (**3**; R^2 = H). Conceivably, these could arise by 'transhydrazonation', followed by C–C bond fission, as indicated in Scheme 2 (path a).



Scheme 1.



Scheme 2.

When conducted in the presence of water, the reaction between compounds (**3**) and (**4**) afforded 3-acyl-4-hydroxypyrazoles, obviously deriving from the reaction between the glyoxal hydrazones and the glyoxals (**4**), the former compounds arising from (**3**) and (**4**) by 'transhydrazonation' (Scheme 2,

* For details of the Supplementary Publications Scheme see Instructions for Authors (1985) in *J. Chem. Soc., Perkin Trans. 1*, 1985, Issue 1.

Table 1. Preparation of the 4-hydroxypyrazoles (**2**) and (**8**) from the hydrazones (**3**) and (7), respectively

Entry no.	R^1	R^2	R^3	Reaction[a] conditions	Work-up conditions	Yield of crude product (%)	M.p. (°C)	Recrystallization medium[b]	M.p. of pure compound[c] (°C)	Reported m.p. (°C)	Analysis (%) Found (Required) C	H	N
Product (**2**), from starting materials (**3**) and (**4**)													
1	Me	H	Me	(*b*)	(*g*)	31	112—118	E	120—122		53.35 (53.55)	7.4 (7.2)	24.75 (25.0)
2	Me	H	Ph	(*b*)	(*p*)	35	140—142	C	149—150		68.65 (68.95)	5.75 (5.8)	15.95 (16.1)
3	Me	Me	Me	(*b*)	(*i*)	23[d]	174—177	F	181—183	187—189[i]			
4	Me	Me	Ph	(*b*)	(*a*)	15[e]	149—154	C	153—155	160[j]	70.0 (70.2)	6.5 (6.45)	14.75 (14.9)
5	Me	Ph	Me	(*a*)	(*d*)	46	177—179	C	178—180		69.8 (70.2)	6.45 (6.45)	14.8 (14.9)
				(*b*)	(*d*)	14	175—177						
6	Me	Ph	Ph	(*a*)	(*b*)	86	142—149	C	170—172	175—177[i]			
7	Ph	H	Me	(*b*)	(*a*)	35	124—126	D	136	137—138[k]			
				(*a*)	(*a*)	31	124—126						
8	Ph	H	Ph	(*b*)	(*e*)	66	157—161	C	180—182	179[j]	76.55 (76.25)	5.2 (5.1)	12.0 (11.85)
9	Ph	Me	Me	(*b*)	(*t*)	23[f]	Oil		*h*	138—140[i]			
10	Ph	Et	Me	(*a*)	(*q*)	27[f]	122—125	I	134—135		71.0 (71.25)	7.1 (7.0)	13.7 (13.85)
				(*b*)	(*r*)	19[f]	122—125						
11	Ph	Pr^n	Me	(*a*)	(*s*)	14[f]	63—71	I	88—90		72.2 (72.2)	7.55 (7.45)	12.65 (12.95)
12	Ph	Ph	Me	(*a*)	(*a*)	35	119—133	C	144		76.75 (76.8)	5.65 (5.65)	11.0 (11.2)
13	Ph	Me	Ph	(*b*)	(*h*)	45[g]	153—158	C	170	175[j]	76.65 (76.8)	5.65 (5.65)	11.0 (11.2)
14	Ph	Ph	Ph	(*c*)	(*u*)	70	148—149	*G,J*	148—149	252[i]	80.6 (80.8)	5.2 (5.15)	8.7 (8.95)
Product (**8**), from starting materials (**4**) and (**7**)													
15	Me	Me	H	(*d*)	(*j*)	90	85—90	A	92		51.1 (51.4)	5.75 (5.75)	19.85 (20.0)
16	Me	Me	Me	(*e*)	(*k*)	53	48—61	B	66—67		54.15 (54.55)	6.5 (6.55)	17.9 (18.15)
17	Me	Me	Ph	(*c*)	(*m*)	74	110—115	A	119—121		66.95 (66.65)	5.65 (5.6)	12.85 (12.95)
18	Me	Ph	H	(*c*)	(*n*)	66	64—66	A	68—69		65.2 (65.35)	5.0 (5.0)	13.75 (13.85)
19	Me	Ph	Me	(*c*)	(*e*)	82	61—67	B,H	87—88		67.1 (66.65)	5.55 (5.6)	12.6 (12.95)
				(*a*)	(*a*)	57	67—68						
20	Me	Ph	Ph	(*c*)	(*e*)	52	92—98	B	107—108		73.55 (73.35)	5.05 (5.05)	10.15 (10.05)
				(*a*)	(*a*)	0							
21	Ph	H	H	(*c*)	(*a*)	42	132—136	C,H	143—145		63.5 (63.8)	4.2 (4.3)	14.8 (14.9)
22	Ph	H	Me	(*a*)	(*a*)	46	76—80	A	81—82		65.55 (65.35)	5.05 (5.0)	13.95 (13.85)
				(*c*)	(*n*)	35	76—80						
23	Ph	H	Ph	(*a*)	(*e*)	100	122—125	C,H	130		72.7 (72.7)	4.55 (4.6)	10.65 (10.6)
				(*c*)	(*e*)	22	122—125						
24	Ph	Me	H	(*c*)	(*n*)	40	92—98	A	98—100		65.4 (65.35)	5.0 (5.0)	13.85 (13.85)
25	Ph	Me	Me	(*a*)	(*c*)	61	79—80	A	79—81		66.8 (66.65)	5.65 (5.6)	12.9 (12.95)
				(*f*)	(*o*)	38	76—80						
26	Ph	Me	Ph	(*a*)	(*b*)	91	121—122	H	121		73.25 (73.35)	5.05 (5.05)	10.0 (10.05)
27	Ph	Ph	H	(*c*)	(*e*)	84	101—105	B	106—107		72.85 (72.7)	4.55 (4.6)	10.6 (10.6)
28	Ph	Ph	Me	(*c*)	(*f*)	46	98—99	B	101—103		73.75 (73.35)	5.15 (5.05)	9.95 (10.05)
				(*a*)	(*b*)	26	101—103						

[a] See Experimental section for details. The hydrazones (**3**) and (7) were prepared *in situ* when reaction conditions (*b*), (*e*), or (*f*) were used. [b] A, hexane; B, ligroin (b.p. 80—110 °C); C, ethyl acetate; D, ethyl acetate–hexane; E, propan-2-ol; F, ethanol; G, chloroform; H, methanol; I, toluene; and J, toluene–hexane. [c] Most of the 4-hydroxypyrazoles were colourless with a few exceptions which were slightly yellow. [d] In addition, compound (**2**; R^1 = R^3 = Me, R^2 = H) (27%) was present in the combined ether and ethyl acetate extracts (n.m.r.). [e] In addition, compound (**8**; R^1 = Me, R^2 = R^3 = Ph) (46%) was isolated from the dichloromethane extract of the basic solution. The dichloromethane was removed and the residue worked up as in (*e*). [f] In addition, compound (**2**; R^1 = Ph, R^2 = H, R^3 = Me) was formed. Yields are specified under the work-up conditions. [g] In addition, compound (**8**; R^1 = R^2 = R^3 = Ph) (26%) was isolated as described in work-up conditions (*h*). [h] The product was converted into its crystalline *O*-acetyl derivative as described under work-up conditions (*t*). [i] Ref. 8. [j] Ref. 26. [k] Ref. 6.

Table 1 (*continued*)

Product (**2**), from starting materials (**3**) and (**4**)

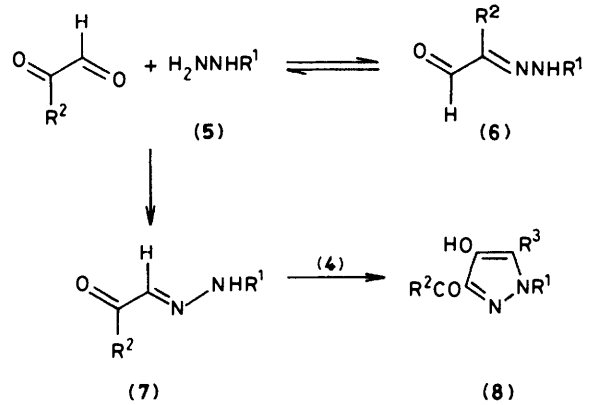
Entry no.	R^1	R^2	R^3	Reaction[a] conditions	Work-up conditions	Yield of crude product (%)	M.p. (°C)	Recrystallization medium[b]	M.p. of pure compound[c] (°C)	Reported m.p. (°C)	Analysis (%) Found (Required) C	H	N
29	Ph	Ph	Ph	(*c*)	(*e*)	87	154—159	C	159—160		77.55 (77.65)	4.7 (4.75)	8.05 (8.25)
30	Bn	Me	Me	(*f*)	(*l*)	39	46—51	B	45		67.6 (67.8)	6.05 (6.15)	12.15 (12.15)

Table 2. ^{13}C N.m.r. shifts (in p.p.m. relative to the $CDCl_3$ centre peak at δ 76.90 p.p.m.) of the 4-hydroxypyrazoles (**2**) and (**8**) dissolved in 0.58M-$CDCl_3$

R^1	R^2	R^3	δ/p.p.m. C=O	C-3	C-4	C-5	C-1′	C-2′	C-3′	C-4′	NMe	3-Me or 5-Me		COMe
Compound (**2**)														
Me	H	Me		126.8	138.3	125.4					36.2		7.8	
Me	Me	Me[a]		136.0	135.6	125.6					35.8	10.0	8.0	
Me	H	Ph[b]		127.2	138.8	129.8		128.6	129.1	128.1	37.5			
Me	Me	Ph[b]		135.6	136.8	130.9		128.5	129.0	128.0	36.9	9.9		
Me	Ph	Me		133.9	136.7	126.4	135.9	125.3	128.1	126.2	36.6		8.2	
Ph	H	Me		129.7	139.5	125.8	139.4	124.3	129.0	127.4			9.1	
Ph	Me	Me		136.9	139.4	125.3	139.4	123.9	128.6	126.7		9.7	9.1	
Ph	Ph	Ph[a]		132.8	137.6	131.5								
Compound (**8**)														
Me	Me	H	197.9	136.3	146.6	115.7					40.1			25.3
Me	Me	Me	197.8	135.2	142.9	123.3					37.3		7.6	25.2
Me	Me	Ph	198.0	135.5	143.2	127.5	128.0	128.6	128.6	128.3				
Me	Ph	H	190.1	135.1	149.4	115.4	136.2	128.1	130.2	132.9	40.4			
Me	Ph	Me	190.1	134.5	145.6	122.8	136.4	128.0	130.2	132.8	37.5		7.6	
Me	Ph	Ph	190.0	135.0	146.4	127.7					39.1			
Ph	H	H[a]	185.6	139.0	144.7	113.4	138.7	118.2	128.6	126.6				
Ph	H	Me	189.4	137.7	142.9	124.5	139.1	124.4	129.1	128.6			8.9	
Ph	H	Ph	189.6	138.1	143.2	127.2								
Ph	Me	H	198.5	137.8	147.0	112.4	139.6	119.2	129.3	127.3				25.5
Ph	Me	Me	198.5	136.9	143.5	123.8	139.4	124.6	129.1	128.4			9.0	25.5
Ph	Me	Ph	198.7	137.2	143.8	127.3								25.6

[a] Solvent: $CDCl_3$–$(CD_3)_2SO$ (12:1). [b] Saturated solution.

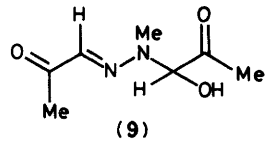
path b). This casual observation prompted a more detailed study of the synthesis of α-oxoaldehyde hydrazones (**7**) as the starting materials for the production of the potentially useful 3-acyl-4-hydroxypyrazoles (**8**). At 0 °C or below, methylglyoxal combines with methyl- or phenyl-hydrazine (**5**; R^1 = Me or Ph) (Scheme 3) to give the hydrazonoaldehydes (**6**; R^1 = Me or Ph, R^2 = Me) in a kinetically controlled reaction. In acidic solution, isomerisation to the more stable oxohydrazones (**7**; R^1 = Me or Ph, R^2 = Me) occurs at room temperature, making the last-named compounds easily accessible starting materials for the synthesis of the 3-acyl-4-hydroxypyrazoles (**8**). Six oxohydrazones (**7**; R^1 = Me, Ph, or $PhCH_2$, R^2 = H, Me, or Ph) were thus prepared and converted into the sixteen new 3-acyl-4-hydroxypyrazoles (**8**) listed in Table 1 (entries 15—30); they were characterised by comparisons of their ^1H and ^{13}C n.m.r. spectra with those of compound (**8**; R^1 = Ph, R^2 = H, R^3 = Me) (entry 22), the structure of which was established by oxidation to the carboxylic acid, followed by decarboxylation to give a product identical with an authentic specimen of 4-hydroxy-5-methyl-1-phenylpyrazole.[6] In no case did the hydrazonoaldehyde (**6**; R^1 = Me or Ph, R^2 = Me) give rise to the formation of *N*-substituted 5-acetyl-4-hydroxypyrazoles;



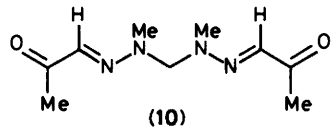
Scheme 3.

obviously rearrangement to the oxohydrazones (**7**) took place before the condensation reaction.

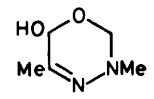
Careful n.m.r. monitoring of a mixture of methylglyoxal and



(9)



(10)



(11)

compound (**5**; R^1 = Me) (Scheme 3) as a function of time revealed the sequential appearance of (**6**; $R^1 = R^2$ = Me), (**7**; $R^1 = R^2$ = Me), a diketone, isolated and identified as (**9**), and, finally, the 3-acyl-4-hydroxypyrazole (**8**; $R^1 = R^2 = R^3$ = Me), accompanied by the formaldehyde aminal (**10**) which was identified by comparison with a specimen synthesized from compound (**7**; $R^1 = R^2$ = Me) and formaldehyde by a known method.[14]

The diketone (**9**) is apparently not an intermediate in the pathway to compound (**8**; $R^1 = R^2 = R^3$ = Me), as neither the expected 3-acetyl-5-hydroxy-1,4-dimethylpyrazole, nor the possible 5-acetyl-4-hydroxy-1-methylpyrazole, were observed in the reaction mixture. The formation of compound (**10**) requires the intermediacy of formaldehyde, or its equivalent, conceivably arising from the reaction of compounds (**7**; $R^1 = R^2$ = Me) and (**4**; R^3 = Me) as outlined in Scheme 2.

Interestingly, the hydrazonoaldehyde (**6**; $R^1 = R^2$ = Me) reacted with formaldehyde in the ratio 1:1 to give a product possessing the characteristics expected for the dihydro-1,3,4-oxadiazine derivative (**11**).

In summary, aldehyde hydrazones and glyoxals, both easily accessible starting materials, serve well for the synthesis of 4-hydroxypyrazoles, including the 3-acyl derivatives. The choice between non-aqueous or aqueous conditions depends on the structure of the target molecules and can easily be made on the basis of the above discussion.

Experimental

Solvents were removed under reduced pressure. Flash chromatography was performed as described in ref. 15. The purity and identity of all compounds were confirmed using t.l.c., m.p.s, and i.r., ^{1}H n.m.r., and mass spectra. ^{1}H N.m.r. spectra were recorded on a Bruker HX-90 instrument. ^{13}C N.m.r. spectra were obtained on a Bruker WH-90 instrument and assigned as described previously.[16] Mass spectra were obtained on a V.G. Micromass 7070 F instrument.

Benzylhydrazine,[17] formaldehyde phenylhydrazone,[18] glyoxal phenylhydrazone,[19] 1-phenylhydrazono-2-phenylethanone,[20] benzaldehyde methylhydrazone,[21] and benzaldehyde phenylhydrazone,[22] were prepared by literature methods. Anhydrous methylglyoxal was prepared by stirring a commercial 50% aqueous solution (2.60 ml), n-butyl acetate (10 ml), and anhydrous sodium sulphate (2 g) for 15 min. The organic solution was decanted off, stirred for 15 min with anhydrous magnesium sulphate (2 g), and filtered. Anhydrous phenylglyoxal was obtained by distilling its hydrate.[23] Ether refers to diethyl ether.

Preparation of 4-Hydroxypyrazoles.—Reaction conditions. (*a*) The hydrazone (**3**) or (**7**) (7.75 mmol) was mixed at 0 °C with the glyoxal (**4**) (15.7 mmol), dissolved in dry n-butyl acetate, magnesium sulphate (1.0 g), and acetic acid (1.0 ml). Stirring was continued at 20 °C for 10 min and then at 110 °C for 1 h.

(*b*) The hydrazone (**3**) was prepared *in situ* by adding the aldehyde (7.75 mmol) with stirring at 0 °C to the hydrazine (7.75 mmol) in butyl acetate (3.0 ml). Stirring was continued at 0 °C for 10 min and then at 20 °C for 1 h. In the case of formaldehyde a 40% aqueous solution (0.58 ml) was used and anhydrous sodium sulphate (1.0 g) was added. This was decanted off and extracted with butyl acetate (2 × 1 ml).

(*c*) The hydrazone (**3**) or (**7**) (7.75 mmol), the glyoxal (7.75 mmol) (glyoxal in 40%, methyl glyoxal in 50% aqueous solution), and acetic acid (21 ml) were stirred at 110 °C for 1 h.

(*d*) As in (*c*) but replacing acetic acid with water (40 ml).

(*e*) The hydrazine (**5**) (7.75 mmol), the glyoxal (**4**) (23.3 mmol) in aqueous solution, and water (40 ml) were heated to reflux for 3 h.

(*f*) As in (*e*) but replacing water with acetic acid (40 ml) and 1M-hydrochloric acid (40 ml).

Work-up conditions. (*a*) The reaction mixture was filtered while still hot. Extraction with boiling butyl acetate (2 × 5 ml) and removal of the solvent gave a residue which was dissolved in 1M-aqueous sodium hydroxide (20 ml). Washing with dichloromethane (2 × 20 ml), acidification to pH *ca.* 2 with conc. hydrochloric acid, extraction with dichloromethane (2 × 10 ml), washing with saturated aqueous hydrogen carbonate (2 × 5 ml) (this washing was necessary only when phenylglyoxal was used as the 2-oxo-aldehyde), drying ($MgSO_4$), and removal of the dichloromethane gave a residue which was extracted with boiling ethyl acetate (20 + 4 × 5 ml). The hot extracts were filtered through silica gel (2.5 g) and activated carbon (1 g). Removal of the ethyl acetate afforded the crude product.

(*b*) In cases where the sodium salt of the hydroxypyrazole does separate it was isolated and washed with ethyl acetate (2 × 20 ml). The aqueous filtrate was washed with dichloromethane (2 × 20 ml) and combined with the washed salt. The mixture was acidified and work-up continued as in (*a*).

(*c*) Alternatively, the sodium salt was dissolved by addition of water (20 ml). Washing with dichloromethane (2 × 20 ml), acidification to pH *ca.* 2 with conc. hydrochloric acid, extraction with dichloromethane (3 × 20 ml), drying ($MgSO_4$), filtration through silica gel (1 g) and activated carbon (0.5 g), and removal of the dichloromethane gave a residue which was extracted with boiling ligroin (b.p. 80—110 °C) (3 × 5 ml). The volume was reduced to *ca.* 2 ml and the mixture cooled to 0 °C. Filtration gave the crude product.

(*d*) When the hydroxypyrazole is slightly soluble in dichloromethane and separates in the crystalline state, work-up was performed as in (*a*). However, after the acidification the mixture was left overnight. Filtration, washing with water (2 × 2 ml), drying, extraction with boiling ethyl acetate (20 + 4 × 5 ml), filtration of the hot extract through silica gel (2.5 g) and activated carbon (1 g), and removal of the ethyl acetate gave a residue which was triturated with boiling hexane (3 × 5 ml) and with 20 °C chloroform (2 + 3 × 1 ml), and the residue collected on a filter.

(*e*) In cases where the hydroxypyrazole is less acidic the reaction was followed by careful removal of the solvent at 0.1 kPa and 40 °C. The residue was stirred for 10 min with 1M-aqueous potassium hydroxide (40 ml) and ether (10 ml). Filtration, separation of the ether, and successive washing of the precipitate and the aqueous solution with ether (2 × 10 ml) was followed by acidification of the combined precipitate and aqueous solution, and work-up was continued as in (*a*).

(*f*) When the potassium salt was slightly soluble, the solvent

was removed as in (*e*), followed by stirring with boiling 2N-potassium hydroxide (10 ml) for 2—3 min. Cooling to 0 °C, filtration, stirring with ether (20 ml), filtration, and washing with dichloromethane (3 × 5 ml) gave a residue which was stirred with boiling conc. hydrochloric acid (5 ml) for 2—3 min. Cooling to 0 °C, filtration, and washing with water (5 ml) afforded the crude product.

(*g*) Work-up was initiated as in (*a*), but since the hydroxypyrazole is relatively basic the acidification with conc. hydrochloric acid was stopped at pH 6. Then the water was removed and the residue was extracted with ethanol (3 × 5 ml). Removal of the ethanol left a residue which was triturated with boiling acetone (5 × 10 ml). Removal of the acetone, dissolution of the residue in methanol (10 ml), filtration through silica gel and activated carbon as in (*a*), removal of the methanol, and washing of the residue with hexane (2 × 10 ml) and ether (2 × 2.5 ml) gave the crude product.

(*h*) Work-up was initiated as in (*a*). The material which did not dissolve in sodium hydroxide was filtered off. Procedure (*a*) was continued for the filtrate which produced 4-hydroxy-3-methyl-1,5-diphenylpyrazole (**2**; $R^1 = R^3 = Ph$, $R^2 = Me$). The residue was stirred with ether and work-up continued as in (*f*) to give 3-benzoyl-4-hydroxy-1,5-diphenylpyrazole (**8**; $R^1 = R^2 = R^3 = Ph$).

(*i*) As in (*g*), but the washing with ether was followed by washing with ethyl acetate (2 × 1 ml) which left the crude product.

(*j*) The reaction mixture was extracted with dichloromethane (3 × 25 ml). Removal of the dichloromethane gave the crude product.

(*k*) As in (*j*), but the resulting material was worked up as in (*a*).

(*l*) As in (*k*). The material obtained was dissolved in ethyl acetate–hexane (1:4; 7.8 ml). The solution was filtered through silica gel (2 g) and the silica gel extracted twice with the eluant (2.5 ml). The filtrate was evaporated to dryness.

(*m*) The reaction mixture was diluted with water (60 ml) and 33% aqueous sodium hydroxide was added until the solution reached pH 6. The mixture was cooled to 0 °C and filtered. The residue was extracted with boiling ligroin (3 × 5 ml) and the product isolated as in (*c*).

(*n*) As in (*m*), but filtration was replaced by extraction with dichloromethane (4 × 25 ml) followed by removal of the dichloromethane.

(*o*) 33% Aqueous sodium hydroxide was added until pH 10 was reached, keeping the temperature below 30 °C. Filtration, washing with water (20 ml), acidification of the filtrate to pH *ca.* 2 (conc. hydrochloric acid), extraction with dichloromethane, and work-up as in (*n*) gave the crude product.

(*p*) Work-up was performed as in (*a*) with acidification to pH 6. The crude product was then flash-chromatographed (ethyl acetate–hexane, 1:1). The third fraction (R_F 0.19) contained the 4-hydroxypyrazole.

(*q*) Work-up was performed as in (*a*). Then flash chromatography (ethyl acetate–hexane 1:1) first gave 3-ethyl-4-hydroxy-5-methyl-1-phenylpyrazole (**2**; $R^1 = Ph$, $R^2 = Et$, $R^3 = Me$), then 4-hydroxy-5-methyl-1-phenylpyrazole (**2**; $R^1 = Ph$, $R^2 = H$; $R^3 = Me$).

(*r*) Similarly, flash chromatography (ethyl acetate–hexane 1:1) was used for separating the products (**2**; $R^1 = Ph$, $R^2 = Et$, $R^3 = Me$) and (**2**; $R^1 = Ph$, $R^2 = H$, $R^3 = Me$).

(*s*) Flash chromatography (ethyl acetate–hexane 1:2) served to separate 3-acetyl-4-hydroxy-5-methyl-1-phenylpyrazole (**8**; $R^1 = Ph$, $R^2 = R^3 = Me$), 4-hydroxy-5-methyl-3-propyl-1-phenylpyrazole (**2**; $R^1 = Ph$, $R^2 = Pr^n$, $R^3 = Me$), and compound (**2**; $R^1 = Ph$, $R^2 = H$, $R^3 = Me$).

(*t*) Procedure (*a*) was followed, but as the hydroxypyrazole was relatively basic the acidification was stopped at pH 6. Extraction with dichloromethane (2 × 10 ml), drying ($MgSO_4$), removal of the dichloromethane, and preparative t.l.c. [on plates kept for 0.5 h over conc. aqueous ammonia and then immediately eluted with ethyl acetate–hexane (1:1)] gave 4-hydroxy-3,5-dimethyl-1-phenylpyrazole (**2**; $R^1 = Ph$, $R^2 = R^3 = Me$) (R_F 0.21) as a yellow oil. Hydrochloride, m.p. 165—167 °C (propan-2-ol). O-*Acetyl derivative*, m.p. 55—56 °C (hexane) (Found: C, 68.0; H, 6.15; N, 12.15. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.15; N, 12.15%); δ ($CDCl_3$) 7.45—7.2 (5 H, m, Ph), 2.29 (3 H, s, $MeCO_2$), 2.17 (3 H, s, 3- or 5-Me), 2.16 (3 H, s, 5- or 3-Me). The next fraction contained 4-hydroxy-1,5-diphenylpyrazole (**2**; $R^1 = Ph$, $R^2 = H$, $R^3 = Ph$).

(*u*) The solvent was removed to give a residue which was flash-chromatographed (dichloromethane) to give 4-hydroxy-1,3,5-triphenylpyrazole (**2**; $R^1 = R^2 = R^3 = Ph$) (R_F 0.47).

Conversion of Compound (**8**; $R^1 = Ph$, $R^2 = H$, $R^3 = Me$) *into Compound* (**2**; $R^1 = Ph$, $R^2 = H$, $R^3 = Me$).—A solution of silver nitrate (5.2 g) in water (10 ml) was added to a solution of compound (**8**; $R^1 = Ph$, $R^2 = H$, $R^3 = Me$) (2.33 g) in 33% sodium hydroxide (5 ml). Heating of the mixture to 80 °C for 10 min, filtration, and extraction of the residue with water (2 × 20 ml) gave a filtrate which was acidified (conc. hydrochloric acid) to pH 2 and extracted with dichloromethane (50 + 10 ml). The organic solution was extracted with 4% aqueous potassium hydrogen carbonate (2 × 50 ml) and the aqueous solution was washed with dichloromethane (3 × 25 ml), acidified as above, and extracted with dichloromethane (3 × 50 ml). Removal of the dichloromethane gave 4-hydroxy-5-methyl-1-phenylpyrazole-3-carboxylic acid (**2**; $R^1 = Ph$, $R^2 = CO_2H$, $R^3 = Me$) (1.08 g, 43%) δ ($CDCl_3$) 7.88br (2 H, s, exchangeable, CO_2H and OH), 7.46 (5 H, s, Ph), and 2.26 (3 H, s, Me). The material was heated to 240—245 °C for 45 min, and the residue was extracted with dichloromethane (50 ml). The solution was extracted with 1M-sodium hydroxide (50 ml) and the aqueous extract was washed with dichloromethane (3 × 25 ml), acidified as above, and extracted with dichloromethane (2 × 50 ml). Removal of the dichloromethane gave a brown oil (0.30 g), which was flash chromatographed (ethyl acetate–hexane, 1:1) to give two unidentified compounds in minor amounts, followed by compound (**2**; $R^1 = Ph$, $R^2 = H$, $R^3 = Me$) (0.10 g, 12%), m.p. 136 °C (ethyl acetate) (lit.,[6] 137—138 °C). The mixed m.p. and the i.r., and ^1H and ^{13}C n.m.r. spectra were identical with those of an authentic sample.

Preparation of Hydrazones of the α-Oxoaldehydes.—(*a*) A mixture of water (200 ml), methanol (50 ml), acetic acid (20 ml), and 40% aqueous methylglyoxal (14.6 ml) was cooled to −15 °C. Methylhydrazine (10 ml) was added with stirring and the temperature kept below −12 °C. Stirring was continued for 30 min at −12 to −15 °C. 33% Sodium hydroxide was added until pH 6—7 was reached keeping the temperature below −9 °C. Rapid extraction with dichloromethane (200 + 2 × 75 ml) and removal of the dichloromethane gave a semicrystalline mass which was kept at −25 °C for 2 h and filtered to give yellow 2-*methylhydrazonopropanal* (**6**; $R^1 = R^2 = Me$) (4.26 g, 26%), m.p. 58—64 °C. Recrystallization (toluene–hexane, 1:4) raised the m.p. to 68—70 °C (Found: C, 47.15; H, 8.0; N, 27.35. $C_4H_8N_2O$ requires C, 48.0; H, 8.05; N, 28.0%); δ ($CDCl_3$) 9.29 (1 H, s, CHO), 6.18br (1 H, s; exchangeable, NH), 3.31 (3 H, d, *J* 3.8 Hz, collapses on irradiation at δ 6.18, NMe), and 1.78 (3 H, s, CMe); *m/z* 100 (100%, M^+).

(*b*) A solution of methylhydrazine (8.34 ml) and acetic acid (15 ml) in water (100 ml) was added with stirring during 15 min to a 1.0% aqueous solution of methylglyoxal (925 ml). The mixture was kept for 1 day at 20 °C and extracted with dichloromethane (4 × 150 ml). The organic solution was washed with water (4 × 40 ml), and the dichloromethane was

removed to give 1-*methylhydrazonopropanone* (7; R^1 = R^2 = Me) (4.16 g, 33%), as yellow crystals, m.p. 63—65 °C (toluene–ligroin, 1:2). After sublimation the m.p. was 67—69 °C (Found: C, 47.4; H, 8.05; N, 27.7. $C_4C_8N_2O$ requires C, 48.0; H, 8.05; N, 28.0%); δ ($CDCl_3$) 6.86 (1 H, s, HC), 6.61br (1 H, s, exchangeable, NH), 2.96 (3 H, dd, J_{HNMe} 4.4 and 0.7 Hz, MeN), and 2.31 (3 H, s, MeC); *m/z* 100 (100%, M^+).

(*c*) Water (200 ml), methanol (50 ml), acetic acid (20 ml), and 40% aqueous methylglyoxal (14.6 ml) were cooled to 0 °C. Phenylhydrazine (9.8 ml) was added during 1 min with stirring and cooling in an ice-bath. After being stirred at 0 °C for 10 min the mixture was extracted at 0 °C with dichloromethane (200 ml). The organic solution was washed with saturated aqueous sodium hydrogen carbonate (30 ml) and evaporated to dryness. The residue was washed with boiling hexane (3 × 50 ml) and recrystallized from toluene (29 ml), with cooling to −25 °C, producing 2-phenylhydrazonopropanal (**6**; R^1 = Ph, R^2 = Me) (7.62 g, 48%), m.p. 123—124 °C (lit.,[24] 126 °C); δ ($CDCl_3$) 9.45 (1 H, s, CHO), 8.0br (1 H, s, exchangeable, NH), 7.5—6.9 (5 H, m, Ph), and 1.98 (3 H, s, Me); *m/z* 169 (100%, M^+).

(*d*) 40% Aqueous methylglyoxal (7.7 ml) and then 1M-hydrochloric acid was added to a solution of phenylhydrazine (4.9 ml) in methanol (100 ml). The mixture was heated to reflux for 4 h and kept at 20 °C for 1 h. After filtration the residue was washed with 50% aqueous methanol (25 ml), 25% methanol (50 ml), and water (50 ml) to give 1-phenylhydrazonopropan-2-one (7; R^1 = Ph, R^2 = Me) (5.3 g, 65%), m.p. 134—142 °C. Recrystallization (toluene) gave m.p. 149 °C (lit.,[25] 148—149 °C).

(*e*) Phenylglyoxal (1.00 ml), methanol (50 ml), acetic acid (6 ml), methylhydrazine (0.51 ml), and water (50 ml) were mixed and kept for 1 day. Extraction with dichloromethane (3 × 20 ml), removal of the dichloromethane, and drying at 0.13 kPa over P_2O_5 produced light brown 1-*methylhydrazono*-2-*phenylethanone* (7; R^1 = Me, R^2 = Ph) (1.33 g, 93%) as a 3:1 mixture of the *Z*- and *E*-forms (Found: C, 66.45; H, 6.1; N, 16.35. $C_9H_{10}N_2O$ requires C, 66.65; H, 6.2; N, 17.25%); δ ($CDCl_3$) 8.0—7.7 and 7.55—7.2 (2 H, m, and 4 H, m; Ph and HC=N), 3.33 and 3.02 [3 H, two d (3:1), *J* 4.0 and 3.0 Hz, collapse upon exchange with D_2O, Me in the *Z*-and *E*-form, respectively]; *m/z* 162 (55%, M^+), 161 (30, $M-1$), 147 (45), 119 (75), 105 (60), 91 (100), and 77 (95).

(*f*) Methylhydrazine (8.34 ml), acetic acid (15 ml), and water (100 ml) were added during 15 min with stirring to 50% aqueous methylglyoxal (37.4 ml) in water (900 ml). After 1 day the mixture was washed with toluene (4 × 150 ml). Removal of the water at 20 °C gave a residue (9.72 g) which contained 1-[*N*-acetyl(hydroxy)methyl-*N*-methylhydrazono]propanone (**9**) (70% by ^1H n.m.r.) 1-methylhydrazonopropanone (7; R^1 = R^2 Me) (10%), and 1,1′-methylenebis(1-methyl-2-(2-oxopropylidene)hydrazine] (**10**) (20%). Attempts to purify compound (**9**) were unsuccessful. The n.m.r. spectrum of an unpurified specimen of (**9**) exhibited the following signals; δ ($CDCl_3$) 6.97 (1 H, q, *J* 0.9 Hz, HC=N), 5.21 (1 H, s, HCO), 4.4br (1 H, exchangeable, OH), 2.93 (3 H, d, *J* 0.9 Hz, NMe), 2.28 (3 H, s, MeCO), and 2.22 (3 H, s, OCMe); δ_C ($CDCl_3$) 202.5 (s, C=O), 197.1 (s, conj. C=O), 132.2 (d, *J* 167 Hz, HC=N), 89.9 (d, CO), 33.5 (q, NMe), 25.1 (q, Me), and 23.8 p.p.m. (q, Me).

Reactions between the Hydrazones of the α-Oxoaldehydes and Formaldehyde.—(*a*) 40% Aqueous formaldehyde (0.075 ml) and acetic acid (1.0 ml) were added to a solution of 1-methylhydrazonopropanone (7; R^1 = R^2 = Me) (0.10 g) in water (10 ml). After 2 h the mixture was extracted with dichloromethane (2 × 5 ml). Removal of the dichloromethane afforded *methylenebis*[1-*methyl*-2-(2-*oxopropylidene*)*hydrazine*] (**10**) (0.098 g, 92%), m.p. 106—107 °C. Recrystallization (toluene–ligroin, 1:5) did not change the m.p. (Found: C, 58.5; H, 8.8; N, 15.15. $C_9H_{16}N_4O_2$ requires C, 58.65; H, 8.75; N, 15.2%); δ ($CDCl_3$) 6.67 (2 H q, *J* 0.9 Hz, 2 CH=N), 5.03 (2 H, s, CH_2), 2.91 (6 H, d, *J* 0.9 Hz, 2 MeN), and 2.31 (6 H, s, 2 MeC=O), δ_C ($CDCl_3$) 197.1 (s, C=O), 130.0 (d, CH=N), 80.7 (t, CH_2), 34.4 (q, MeN), and 23.8 p.p.m. (q, MeC=O); *m/z* 212 (2%, M^+), and 113 (100).

(*b*) 2-Methylhydrazonopropanal (**6**; R^1 = R^2 = Me) (1.00 g) and 4% aqueous formaldehyde (10 ml) were kept for 3.5 h. Extraction with dichloromethane (2 × 50 ml), drying ($MgSO_4$), and removal of the dichloromethane gave 6-*hydroxy*-3,5-*dimethyl*-3,6-*dihydro*-2H-1,3,4-*oxadiazine* (**11**) (0.74 g), m.p. 94—101 °C. Recrystallization at 20 °C (dichloromethane–hexane, without heating) gave the pure product (0.40 g, 31%), m.p. 112—114 °C (Found: C, 46.35; H, 7.85; N, 21.3. $C_5H_{10}N_2O_2$ requires C, 46.15, H, 7.75; N, 21.55%); δ ($CDCl_3$) 4.92br (1 H, s, HC), 4.35 (1 H, d, *J* 7.8 Hz) and 4.03 (1 H, d, *J* 7.8 Hz) (CH_2), 3.13br (1 H, s, exchangeable, OH), 2.79 (3 H, s, MeN), and 1.99 (1 H, s, MeC); δ_C ($CDCl_3$) 146.1 (s, C=N), 85.6 (d, HC), 73.7 (t, CH_2), 40.2 (q, MeN), and 19.5 p.p.m. (q, MeC); *m/z* 130 (78%, M^+) and 113 (7%, M − OH).

Acknowledgements

Thanks are due to Dr. J. Øgaard Madsen for the mass spectra and to Prof. A. Kjaer for help with the manuscript. The ^{13}C n.m.r. spectrometer was provided by the Danish Natural Science Research Council and the mass spectrometer by the Danish Council for Scientific and Industrial Research.

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Received 10*th April* 1984; *Paper* 4/598