The Conversion of 5,6-Dihydro-4-methoxy-2-pyrones into 3-Alkyl-5-hydroxypyrazoles

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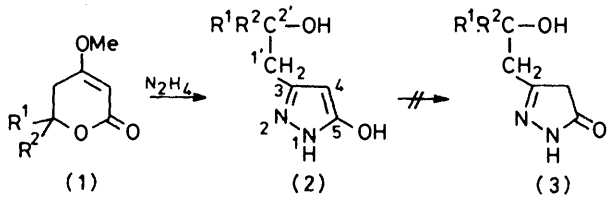
The production and characterisation of 3-[(2-aryl-2-hydroxy)ethyl]-5-hydroxy-1*H*-pyrazoles (2a—d) and 3-[(2-aryl-2-hydroxy-2-methyl)ethyl]-5-hydroxy-1*H*-pyrazole (2e) by the reaction of hydrazine with 6-substituted-5,6-dihydro-4-methoxy-2-pyrones is described. The products exist as 5-hydroxypyrazoles rather than pyrazolin-5-ones.

We have recently been interested in ring contraction of 5,6-dihydro-4-methoxy-2-pyrones to yield alkylidenetetronates, a presumed biosynthetic process.[1-4] We have investigated the preparation of 5,6-dihydro-6-substituted-4-methoxy-2-pyrones [5] (1) and now report that with hydrazine these compounds undergo a ring-contraction to give 5-hydroxypyrazoles (2) in excellent yields.



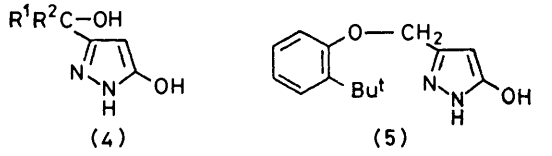
(1) (2) (3)

(a) $R^1 = H, R^2 = Ph$
(b) $R^1 = H, R^2 = 4\text{-MeO-}C_6H_4$
(c) $R^1 = H, R^2 = 3,4\text{-}(OCH_2O)\text{-}C_6H_3$
(d) $R^1 = H, R^2 =$ α-naphthyl
(e) $R^1 = Me, R^2 = Ph$

RESULTS AND DISCUSSION

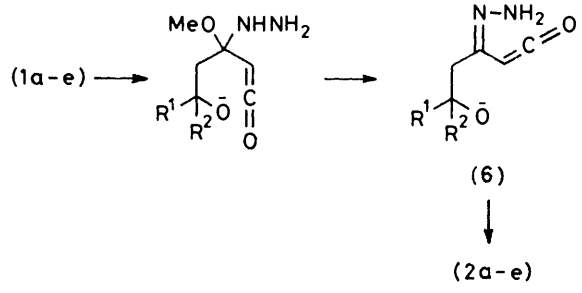
We anticipated the production of 5-hydroxypyrazoles by analogy with the report that tetronates themselves react with hydrazine to yield 5-hydroxypyrazoles (4a—c).[6]

In the event, when compounds (1a—e) were heated under reflux with methanolic hydrazine hydrate only the pyrazoles (2a—e) were obtained (for yields and properties see Table 1). Phenylhydrazine, however, did not react with dihydropyrones (1a—e) under the same conditions.



(4) (5)

(a) $R^1 = R^2 = H$
(b) $R^1 = H, R^2 = Me$
(c) $R^1 = R^2 = Me$



We were unable to isolate any intermediates, but it seems reasonable to suggest the intermediacy of the keten (6) (or its protonated form) possibly by the pathway shown, in some ways analogous to the route suggested for the reaction of hydrazine with butenolide.[6]

TABLE 1

Data for hydroxypyrazoles (2a—e)

Compound	M.p. (°C)	Yield (%)	$\nu_{max.}$/[a] cm^{-1}	$\lambda_{max.}$/[b] nm	Molecular formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(2a)	186—188	88	1 610	227	$C_{11}H_{12}N_2O_2$	64.81	5.82	13.69	64.70	5.88	13.72
(2b)	131—135	71	1 620	226	$C_{12}H_{14}N_2O_3$	61.42	5.83	11.88	61.53	5.98	11.96
(2c)	111—115	72	1 610	228	$C_{12}H_{12}N_2O_4$	58.17	4.89	11.41	58.06	4.83	11.29
(2d)	135—136	75	1 605	226	$C_{15}H_{14}N_2O_2$	70.78	5.49	11.23	70.86	5.51	11.02
(2e)	162—164	70	1 615	227	$C_{12}H_{14}N_2O_2$	66.16	6.47	12.52	66.05	6.42	12.84

[a] As KBr discs. [b] Spectra run in EtOH.

Furthermore it is known that certain 2-pyrones can react with hydrazine, with the loss of some of the ring-carbon atoms, to give 5-hydroxypyrazoles (pyrazolin-5-ones), but the reactions are quoted as being ' of little synthetic utility '.[7]

The ^1H n.m.r. spectra of (2a—e) (Table 2) were taken

in [$^2H_6$]DMSO and suggest that in this solvent, at least, they exist entirely in the hydroxypyrazole form (2) and not in the pyrazolone form (3). The spectra are in accord with those given for compounds (4),[6] in particular the signals at δ 4.66—5.2 are in accord with a vinylic proton on C-4.[8] The ^{13}C n.m.r. (Table 3) were in close accord with that recorded for (5).[9] The u.v.[10] and i.r.[11] spectra support the hydroxypyrazole formulation.

All the compounds underwent rapid H–D exchange not only of N–H, 2′-C–OH, and 5-C–OH, but also of 4-C–H to give (7a—e). The exchange of the 4-C–H must presumably proceed *via* a minute amount of (3).

gether with single-frequency off-resonance decoupled (s.f.o.r.d.) spectra and/or chemical shift values.[12] The signals at δ 145.67 and 160.81 for (4a) were singlets and therefore due to either C-3 or C-5. On deuteriation the singlet at δ 160.81 dropped in intensity and is therefore assigned to C-5, whilst that at δ 145.67 was not affected and was therefore due to C-3. Furthermore, the doublet at δ 88.04 had also diminished in intensity and this signal was therefore assigned to C-4. There was only one methylene signal (C-1′) as a triplet at δ 55.23 and no indication of a ring methylene due to a pyrazolin-5-one.

The ^1H and ^{13}C n.m.r. of the ring proton and carbon atoms of compounds (2a—e) were similar and were

TABLE 2

^1H N.m.r. data of hydroxypyrazoles [a,b]

Compound	H-4 [c]	H-1′	H-2′	2′-OH [c]	Ar-H	Others
(2a)	4.66 (1 H, s)	2.51 (2 H, d)	4.25 (1 H, m)	4.84 (1 H, d)	6.55 (5 H, s)	10.3 (br, NH, 5-OH) [c]
(2b) [d]	5.13 (1 H, s)	2.75 (2 H, d)	4.72 (1 H, t)	5.1 (br)	6.8 (2 H, d) 7.3 (2 H, d)	3.52 (3 H, s, OMe)
(2c) [d]	5.2 (1 H, s)	2.75 (2 H, d)	4.61 (1 H, t)	5.0 (br)	6.8 (2 H, s) 6.91 (1 H, s)	6.0 (2 H, s, OCH_2O)
(2d) [d]	4.76 (1 H, s)	2.62 (2 H, dd) (*J* 8 Hz)	4.9 (1 H, dd) (*J* 8 Hz)	4.5 (br)	7.1—7.5 (7 H, m)	
(2e) [d]	5.0 (1 H, s)	2.8 (2 H, s)		5.0 (br)	7.1—7.5 (5 H, m)	1.41 (3 H, s, Me)

[a] Chemical shifts given in p.p.m. from $SiMe_4$. [b] All spectra run in [$^2H_6$]DMSO. [c] Exchanged with D_2O. [d] NH and 5-OH protons are not observed.

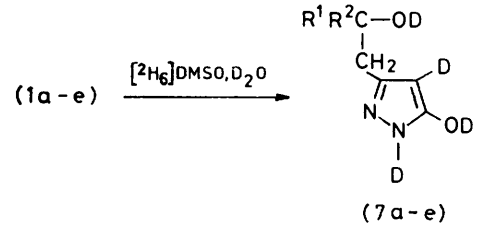
TABLE 3

^{13}C N.m.r. data of hydroxypyrazoles [a,b]

Carbon atom	(2a)	(2b)	(2c)	(2d)	(2e)	(4a)	(5) [9]
C-3	141.55	141.77	141.57	140.93	141.25	145.67	141.4
C-4	89.10	88.88	88.82	88.88	89.40	88.04	88.8
C-5	160.72	160.74	160.74	160.87	160.68	160.81	159.4
C-1′	36.14	36.38	36.38	35.80	40.99	55.23	62
C-2′	71.88	71.50	71.66	68.94	72.57		
Ar-C	125.89, 126.86, 127.90, 145.19	113.25, 127.02, 137.35, 158.21	106.29, 107.52, 119.09, 139.43, 145.93, 146.90	123.12, 123.38, 125.27, 125.78, 127.22, 128.52, 130.01, 133.26, 142.22	124.94, 125.92, 127.48, 148.7		
Others		54.96 (OMe)	100.58 (OCH_2O)		29.24 (Me)		

[a] Chemical shifts given in p.p.m. from $SiMe_4$. [b] All spectra run in [$^2H_6$]DMSO.

We decided to examine the ^{13}C n.m.r. in more detail in order to check both the exchange and the assignments of structure, and for this purpose prepared compound



(7a-e)

(4a) from methyl tetronate[3] by the literature method.[6] Except for C-3 and C-5 the assignments for (4a) (Table 3) follow directly from the noise-decoupled spectra, to-readily assigned by comparison with model compounds (4a) and (5) (Tables 2 and 3). The ^{13}C n.m.r. assignments are all backed by off-resonance spectra and the multiplicities are completely in accord with structures (2a—e) rather than (3a—e).[13]

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. U.v. absorption spectra were measured for solutions in ethanol with a Pye-Unicam SP 800 spectrophotometer. I.r. spectra were determined with Perkin-Elmer 127 and 237 spectrophotometers, in KBr. Proton, proton-decoupled, and complete spectra were obtained with a Bruker WH 90 DS spectrometer equipped with ASPECT 2000, 32K computer, operating at 22.63 MHz for C-13 n.m.r. with internal deuterium lock.

Methyl tetronate was prepared by the literature method [3] from ethyl 4-bromo-3-methoxybut-2-enoate.[14] 3-(1-Hydroxymethyl)-5-hydroxy-1*H*-pyrazole (4a) was prepared from methyl tetronate and hydrazine hydrate.[6] Compounds (1a—e) were synthesised from substituted benzaldehydes and ethyl 4-bromo-3-methoxybut-2-enoate.[5]

General Method for the Preparation of the 3-*Substituted*-5-*hydroxy*-1H-*pyrazoles* (2a—e).—A solution of the dihydropyrone (1a—e) (0.2 mol) and hydrazine hydrate (2 g, 0.4 mol) in absolute methanol (25 ml) was heated on a steam-bath for 1.5 h. The methanol and unreacted hydrazine were removed at 100 °C and 25 mmHg. The residue crystallised to a white mass on cooling. This was stirred with 10 ml of cold chloroform, filtered, and crystallised once from ethanol [for compounds (2a—c)] or from methanol–diethyl ether [for compounds (2d and e)] to give the pure title compounds (Table 1).

Attempted Reaction of Pyrones (4a—e) *with Phenylhydrazine*.—Solutions of pyrones (1a—e) (0.1 mol) and phenylhydrazine (2.16 g, 0.2 mol) in absolute methanol were heated on a steam-bath for 2 h. The solvent was removed and the residue crystallised from ethanol to give an almost quantitative recovery of starting materials.

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REFERENCES

[1] M. T. Ayoub., Ph.D. Thesis, University of Swansea, 1978.
[2] R. Hänsel, J. Schultz, A. Pelter, M. T. Ayoub, and R. Reinhardt, *Z. Naturforsch.*, 1978, **33b**, 1020.
[3] R. Hänsel, J. Schultz, A. Pelter, and M. T. Ayoub, *Z. Naturforsch.*, 1979, **34b**, 1576.
[4] A. Pelter, M. T. Ayoub, J. Schultz, R. Hänsel, and R. Reinhardt, *Tetrahedron Letters*, 1979, 1627.
[5] M. T. Ayoub, S. Ahmed, A. M. Dabbagh, and I. A. Taha, unpublished results.
[6] S. Gelin and P. Pollet, *J. Heterocyclic Chem.*, 1979, **16**, 505.
[7] R. H. Wiley and P. Wiley, ' Heterocyclic Compounds; Pyrazolones, Pyrazolidones and Derivatives,' p. 16. Interscience, New York, 1964.
[8] A. R. Katritzky and F. W. Maine, *Tetrahedron*, 1964, **20**, 299, 315; G. A. Newman and P. J. S. Pauwels, *ibid.*, 1969, **25**, 4605.
[9] G. Auzou, R. Rips, and J. Likforman, *Tetrahedron Letters*, 1976, 2245.
[10] H. Dorn, *J. prakt. Chem.*, 1973, 315, 382.
[11] C. Sabate-Alduy and J. Lematre, *Bull. Soc. chim. France*, 1969, 4159.
[12] J. B. Stothers, ' Carbon-13 N. M. R. Spectroscopy,' Academic Press, New York, 1972.
[13] J. Feeney, G. A. Newman, and P. J. S. Pauwels, *J. Chem. Soc.*, (*C*), 1970, 1842.
[14] B.P., 1967/1,137,466.