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THE TAUTOMERISM OF HETEROAROMATIC COMPOUNDS WITH FIVE-MEMBERED RINGS—V[1]

1-SUBSTITUTED 3-HYDROXYPYRAZOLES

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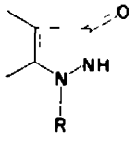
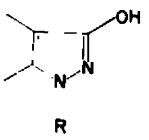
Abstract—Spectroscopic and basicity evidence shows that 3-hydroxy-1,5-dimethyl- and 3-hydroxy-5-methyl-1-phenyl-pyrazole exist in the hydroxy form in non-polar media and in the solid state. In aqueous solution the hydroxy- and oxo-forms co-exist in comparable amounts.



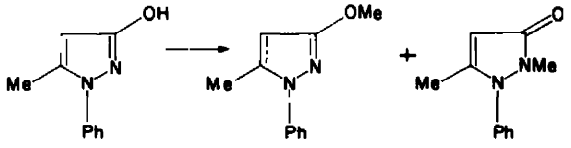
I



II

1-SUBSTITUTED pyrazolin-3-ones could exist either as such (I) or in the form of 3-hydroxypyrazoles (II). In contrast to the corresponding pyrazolin-5-ones[1] relatively little attention has been devoted to such tautomerism in the 3-series. In view of the interesting results found for the isoxazolinones, where compounds of the 3-series exist in the hydroxy form[2], we have compared the physical properties of two representative potentially tautomeric 3-hydroxypyrazoles/pyrazolin-3-ones with methylated derivatives of both forms.

Preparation of compounds was carried out by literature methods[3–6] as quoted in the experimental section except for 3-methoxy-5-methyl-1-phenyl- and 3-ethoxy-1,5-dimethyl-pyrazole. The former was prepared by the action of diazomethane on the 3-hydroxy analogue, a reaction which afforded approximately equal amounts of this and of 2,5-dimethyl-1-phenylpyrazolin-3-one (III → IV + V).



III IV V

[1] Part IV. A. R. Katritzky and F. W. Maine, preceding paper.
[2] A. J. Boulton, A. R. Katritzky, and S. Øksne, Unpublishd.
[3] A. Michaelis, *Liebig's Ann.* **338**, 274, (1904).
[4] C. A. Rojahn, *Ber. Dtsch. Chem. Ges.* **55**, 2968, (1922).
[5] R. Kitamura, *J. Pharm. Soc. Japan* **60**, 45, (1940); *Chem. Abstr.* **34**, 3737, (1940).
[6] L. Lederer, *J. Prakt. Chem.* (2), **45**, 91, (1892).

TABLE 1. INFRARED SPECTRA

Compound	Phase	Conc. M	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A
2,5-Dimethyl-1-phenylpyrazolin-3-one	$CHCl_3$	0·2	1644	500	1599	220	—		—		1501	220	1450	70	1417	145	1401	190	1373	130
3-Methoxy-5-methyl-1-phenylpyrazole	$CHCl_3$	0·2	—		1603	115	1570	410	—		1508	400	1461 1450	105 110	1420	370	—		1387	170
3-Hydroxy-5-methyl-1-phenylpyrazole	$CHCl_3$	0·2	—		1593	180	1575	360	1535	170	1508	310	1456	40	1412	80	—		1384	30
3-Hydroxy-5-methyl-1-phenylpyrazole	C_2Cl_4	0·02	—		1594	195	1576	300	1534	130	1508	270	—		1411	95	—		(C_2Cl_4)	
3-Hydroxy-5-methyl-1-phenylpyrazole	nujol	—	—		1594	s	1566	vs	1539	s	1505	vs	Nj		1407	m	—		—	
1,2,5-Trimethylpyrazolin-3-one	CCl_4	sat.	1667	vs	1587	m	—		—		—		1465 1443	m m	—		1406	5	1365	m
3-Ethoxy-1,5-dimethylpyrazole	CCl_4	0·2	—		—		1564	200	—		1501 1479	260 185	1447	100	—		—		1386	140
3-Hydroxy-1,5-dimethylpyrazole	$CHCl_3$	0·02	—		1603	150	1567	250	—		(—— $CHCl_3$ ——)								1384	40
3-Hydroxy-1,5-dimethylpyrazole	C_2Cl_4	<0·02	—		—		1570	vs	—		1508	s	—		—				(C_2Cl_4)	
3-Hydroxy-1,5-dimethylpyrazole	nujol	—	—		—		1560	vs	1530	s	1507	vs	1465	vs	1411	w			—	

Compound	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A
2,5-Dimethyl-1-phenylpyrazolin-3-one	1314	60	1294	75	—		1180	25	1137	35	1074	30	1043	40	1028	50	1000	25	—		918	15
3-Methoxy-5-methyl-1-phenylpyrazole	—		—		1202	75	1163	80	1135	30	1074	35	1047	130	1017	65	1000	60	967	40	911	15
3-Hydroxy-5-methyl-1-phenylpyrazole	1325	150	1293	30	1267	85	1169	40	1135	20	1073	20	1033	45	1013	55	980	25	—		911	20
3-Hydroxy-5-methyl-1-phenylpyrazole	1323	150	1293	35	1265	90	1166	40	(C_2Cl_4)		1073	25	1034	50	1012	40	(—— C_2Cl_4 ——)					
3-Hydroxy-5-methyl-1-phenylpyrazole	1323	m	1298	w	1262	m	1172	m	1137	w	1077	w	1034	m	1012	w	982	m	—		913	w
1,2,5-Trimethylpyrazolin-3-one	—		1315	w	1271	w	1200	m	1125	m	1095	m	—		1035	w	—		—		839	w
3-Ethoxy-1,5-dimethylpyrazole	1359	135	—		1288	30	1188	45	1154 1117	75 20	1092	25	1058	85	1038	55	972	10	—		897	25
3-Hydroxy-1,5-dimethylpyrazole	1330	110	1306	75	1292	70	(—— $CHCl_3$ ——)						—		1028	45	980	30	—		($CHCl_3$)	
3-Hydroxy-1,5-dimethylpyrazole	1326	s	1305	m	1293	m	1181	w	(—— C_2Cl_4 ——)				—		1022	w	(—— C_2Cl_4 ——)					
3-Hydroxy-1,5-dimethylpyrazole	1328	s	1314	m	1300 1287	m m	1177	m	1157	m	—		—		1028	m	982	w	—		850	m

However, in the 1-methyl series this reaction gave practically exclusively the 1,2,5-trimethyl derivative, as did methylation with methyl iodide-silver oxide. However, triethyl-oxonium fluoroborate[7,8] afforded the 3-ethoxy derivative in good yield, with a small amount of 1,5-dimethyl-2-ethylpyrazolin-3-one as a by-product (shown by NMR).

Infrared spectra

The IR spectra of a 0·2M solution of the potentially tautomeric 3-hydroxy-5-methyl-1-phenylpyrazole is compared in Fig. 1 with those of the two "fixed" methyl derivatives. The spectrum of the tautomeric compound closely resembles that of

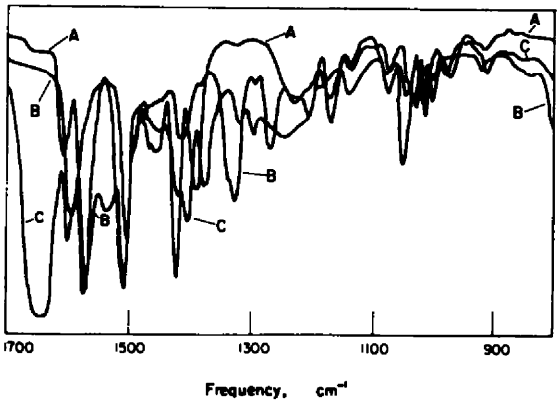
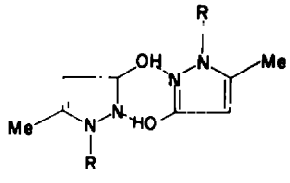


FIG. 1. Infrared spectra of 0·2M chloroform solutions (1700–800 cm^{-1}):
(a) 3-methoxy-5-methyl-1-phenylpyrazole
(b) 3-hydroxy-5-methyl-1-phenylpyrazole
(c) 2,5-dimethyl-1-phenylpyrazolin-3-one

the O-methyl-, and not that of the N-methyl analogue; the contrast is particularly marked in the 1700–1500 cm^{-1} region. This indicates that the tautomeric compound exists in the 3-hydroxy-form, and spectra of tetrachloroethylene and nujol mulls (cf. Table 1) indicate that the hydroxy form persists also in these media.

The results in the 1-methyl series (Table 1) parallel those in the 1-phenyl series.



VI

In the 3000 cm^{-1} region, the 3-hydroxy derivatives in the solid state or in concentrated solution show very strong absorption at 3200–2400 with many maxima in this range, indicating very strong hydrogen-bonding. Study of a 0·0004M chloroform solution of 3-hydroxy-5-methyl-1-phenylpyrazole in a 5 cm cell showed that most of

[7] H. Meerwein, G. Hinz, P. Hofmann, E. Kroning and E. Pfeil, *J. Prakt. Chem.* **147**, 268, (1937).
[8] A. V. Topchiev, S. V. Zavgozodnii, and Ya. M. Paushkin, *Boron Trifluoride and its Compounds as Catalysts in Organic Chemistry* p. 33. Pergamon Press, London (1959).

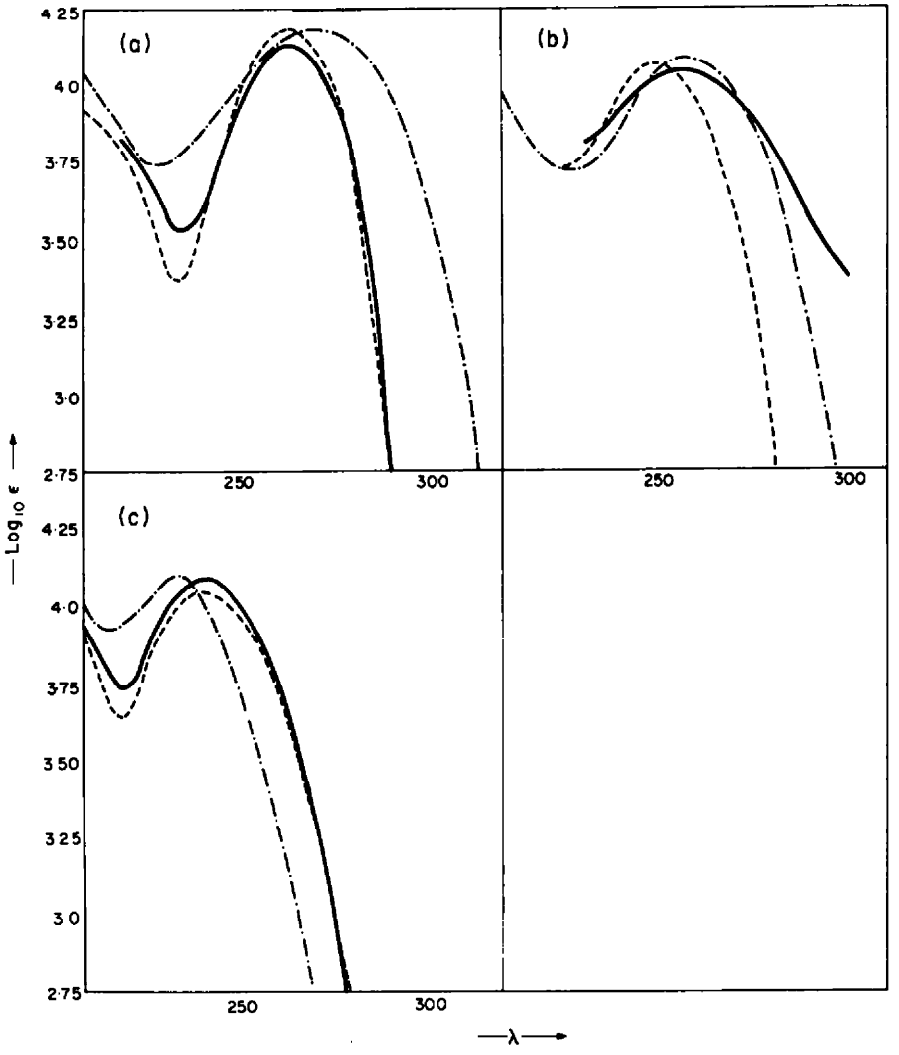


FIG. 2. Ultraviolet spectra of 3-methoxy- – – – –, and 3-hydroxy-5-methyl-1-phenyl-pyrazole———, and 2,5-dimethyl-1-phenylpyrazolin-3-one –·–·–·–.
(a) in cyclohexane, (b) in aqueous buffer (for pH see Table 2),
(c) in 20N sulphuric acid.

the compound still existed in the associated form (probably as dimer, VI), but a weak band was present at 3575 cm^{-1} indicating a small proportion of free hydroxy-compound: no peak was present in the 3500–3200 cm^{-1} indicating the absence of non-bonded NH-form. Dilute carbon tetrachloride solutions of this compound and of the 1-methyl analogue also gave evidence for the occurrence of small amounts of the free hydroxy-form.

IR spectra of the 1-series compounds in the solid state have been discussed by Refn[9] who concluded that the OH-form predominated.

[9] S. Refn, *Spectrochim. Acta* **17**, 40, (1961).

Ultraviolet spectra

For the 1-phenyl-series, a cyclohexane solution of the potentially tautomeric compound has a spectrum which is practically superposable on that of the 3-methoxy analogue (Fig. 2a) and appreciably differs from that of the N-methyl derivative. Hence the hydroxy-form is stable in cyclohexane. For aqueous solutions (Fig. 2b),

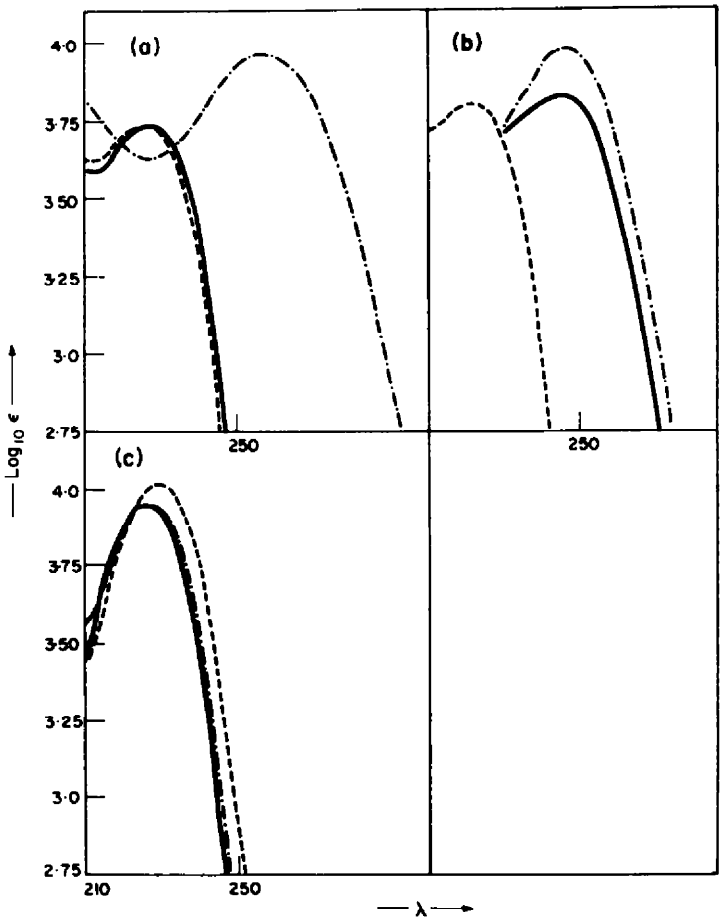
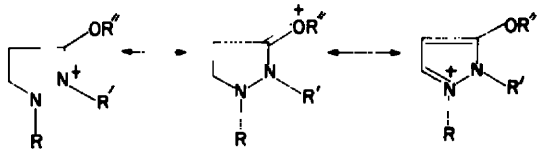


FIG. 3. Ultraviolet spectra of 3-ethoxy- – – – –, and 3-hydroxy-1,5-dimethylpyrazole ———, and 1,2,5-trimethylpyrazolin-3-one –.–.–.–.
(a) in cyclohexane, (b) in aqueous buffer (for pH see Table 2),
(c) in 20N sulphuric acid.

the spectra are all very similar and it is difficult to draw definite conclusions. Similar spectra (Fig. 2c) are also shown by the corresponding cations in 20N-sulphuric acid, as is expected.

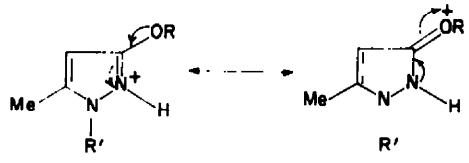
The differences between the spectra of the fixed derivatives are much larger in the 1-methyl series, and interpretation is consequently easier. In cyclohexane solution the potentially tautomeric compound clearly exists in the hydroxy form, as its spectrum closely resembles that of the methoxy compound. In aqueous solution, the spectrum of the tautomeric compound lies between the other two, and intensities indicate ca. 70% NH and 30% OH form. That all the compounds form mesomeric cations of type VII is confirmed by the mutual similarity of all the spectra in 20N-sulphuric acid (Fig. 3c).



VII

pK Measurements

The pK results (Table 3) show qualitatively that there is little difference in stability between the OH and NH forms. Quantitative interpretation is more difficult: the pK of the O–Me and N–Me derivatives are *lower* than those of the tautomeric compound in each series, hence, whatever the tautomeric composition of the latter, the O-methyl and N-methyl groups must exert a base-weakening effect. The basicities of methoxy- and hydroxy-anilines indicate[10] that whereas the inductive effects of OH and OMe are approximately equal, the mesomeric effect of OMe is stronger, by approximately 0·3 pK units in the aniline series.



VIII

In the present series, mesomerism involving the OMe or OH group is important, cf. structure VIII, explaining the base weakening effect observed.* Substitution of N–H by N–Me has usually been found to exert a base-strengthening effect unless steric effects intervened (cf. ref. 13). Especially in the 1-methyl series where the ΔpK between the O–Me and N–Me derivative is only 0·2 units we conclude that the OH form could well have the higher intrinsic basicity, and hence the NH form would predominate by a small factor. This is in good agreement with the UV results. For the 1-phenyl series, we conclude that basicity results may indicate that the OH-form predominates in aqueous solution but an appreciable quantity of the NH-form is certainly also present.

Refn[9] has discussed the tautomerism in the 1-phenyl series using pK_a results obtained in acetic acid solution. She concludes that the OH:NH ratio is ca. 8:1 in this medium.

Proton resonance spectra

Chemical shifts (τ units) are shown diagrammatically for structures IX–XIV. The peaks are singlets except: (i) complex multiplets occur for the phenyl groups, (ii) the ethyl peaks are split as expected, and (iii) signs of coupling ($J < 1$ c/s) are found

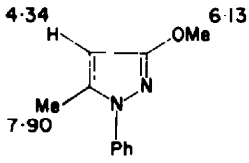
* The tautomerism of 4-hydroxypyridine-1-oxide is somewhat analogous; see refs. 11, 12.

[10] A. Albert and J. N. Phillips, *J. Chem. Soc.* 1294 (1956).

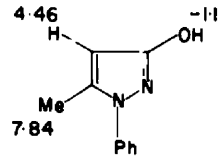
[11] J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.* 4375 (1957).

[12] R. A. Y. Jones, A. R. Katritzky and J. M. Lagowski, *Chem. & Ind.* 870 (1960).

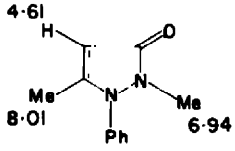
[13] For a review of the tautomerism of heterocyclic hydroxycompounds see A. R. Katritzky and J. M. Lagowski in *Advances in Heterocyclic Chemistry* 1, 312 and 341 (1963); 2, 3 and 28 (1963) in press.



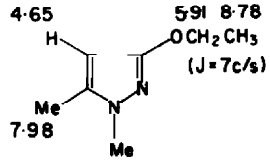
2·63
(Liquid)
IX



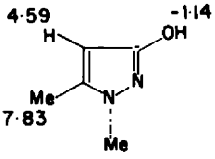
2·67
($CHCl_3$)
X



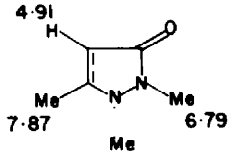
2·65
($CHCl_3$)
XI



6·58
(Liquid)
XII

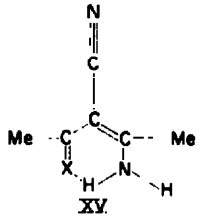


6·43
($CHCl_3$)
XIII



6·71
(Liquid)
XIV

for many of the compounds between the ring proton and the C-methyl group. Assignments are straightforward. The low fields at which the OH peaks absorb is a further indication of strong hydrogen bonding. The sharp character of the peaks is also



XV

better explained by the OH than an NH structure (the peaks for the hydrogen-bonded proton in XV, X = O and XV, X = NH are broad[14]). The other chemical shift values are unexceptional.

TABLE 2. ULTRAVIOLET SPECTRA

Substituents				Cyclohexane		Aqueous buffer			$20N$–H_2SO_4		$0{\cdot}1N$–NaOH	
1	2	3	5	λ_{max}	ε	pH	λ_{max}	ε	λ_{max}	ε	λ_{max}	ε
Ph	Me	—	Me	272	10,410	7	258·5	11,730	234	12,450	—	—
Ph	—	OMe	Me	263	14,650	7	250·5	11,250	241	11,170	—	—
Ph	—	—	Me	264	13,150	4·4	257	10,600	241	12,210	279	11,600
Me	Me	—	Me	257·5	9,310	5	246·5	9,570	227·5	8,800	—	—
Me	—	OEt	Me	225·5	5,470	7	221·5	6,310	229·5	10,100	—	—
Me	—	—	Me	227·5	5,530	5·5	245·5	6,710	226·5	8,830	239	5,440

[14] A. R. Katritzky and R. E. Reavill, unpublished work.

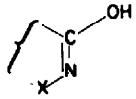
TABLE 3. pK_a VALUES*

Substituents 1	2	3	5	pK_a as base	pK_a (proton loss)
Ph	Me	—	Me	1·66 ± 0·03	—
Ph	—	OMe	Me	1·17 ± 0·06	—
Ph	—	—	Me	1·79 ± 0·06	8·23 ± 0·06
Me	Me	—	Me	2·22 ± 0·03	—
Me	—	OEt	Me	2·05 ± 0·08	—
Me	—	—	Me	2·60 ± 0·02	8·91 ± 0·03

CONCLUSIONS

The preceding evidence indicates that 3-hydroxypyrazoles exist as such in cyclohexane, tetrachloroethylene, chloroform, and in the solid phase. In aqueous solution, the hydroxy-forms co-exist with large amounts of the oxo-forms: the two forms are of comparable stability in aqueous media.

The 3-hydroxypyrazoles thus join an increasing group of heterocyclic compounds containing a hydroxyl group alpha to a ring nitrogen atom in the stable tautomeric form; this group includes also 3-hydroxyisoxazoles,[2] 3-hydroxy-1,2,4- and -1,2,5-oxadiazoles,[15] and some further compounds.[13] All these derivatives contain the structural element XVI, where X = O, N or S.



XVI

EXPERIMENTAL

3-Hydroxy-5-methyl-1-phenylpyrazole[3] formed needles (from ethanol), m.p. 171–173·5° (lit.,[3] m.p. 167°). 3-Hydroxy-1,5-dimethylpyrazole[4] formed plates (from ethanol), m.p. 180·5–183° (lit.,[4] m.p. 172–173°, lit.,[5] 174·5–176°).

2,5-Dimethyl-1-phenylpyrazolin-3-one[6] formed plates (from pet ether, b.p. 80–100°), m.p. 113–115° (lit.,[6] m.p. 113°). For the 1,2,5-trimethyl analogue (= 1,2,3-trimethylpyrazolin-5-one) see ref. 1.

3-Methoxy-5-methyl-1-phenylpyrazole. 3-Hydroxy-5-methyl-1-phenylpyrazole (20 g) was treated with diazomethane (ca. 9 g, from 64·5 g Diazald (Aldrich Chem. Co.)) in methanol–ether (1000 cc, 1:1). After 24 hr, solvents were evaporated off and the residue distilled at red. press. to yield the *methoxy derivative* (11·0 g, 50·7%) as a yellow oil, b.p. 92–92·5°/0·05 mm on redistillation (Found: C, 70·2; H, 6·4; N, 15·0; $C_{11}H_{12}N_2O$ requires: C, 70·2; H, 6·4; N, 14·9%). Later fraction from the distillation yielded 2,5-dimethyl-1-phenylpyrazolin-3-one (0·6 g, 2·8%) m.p. 113–115° (cf. above).

3-Ethoxy-1,5-dimethylpyrazole. 3-Hydroxy-1,5-dimethylpyrazole (15·7 g) was treated with freshly prepared triethyloxonium fluoroborate (60·4 g) in ethanol-free chloroform (1:1). After 12 hr at room temp, excess $NaHCO_3$aq. was added; the chloroform layer was separated and dried ($CaCl_2$). Evaporation of solvent and distillation of the residue gave the *ethoxypyrazole* (5·5 g, 28%) as an oil, b.p. 110°/15 mm. (Found: C, 59·6; H, 9·0; $C_7H_{12}N_2O$ requires: C, 60·0; H, 8·6%).

* For experimental details of pK_a detns. See F. W. Maine, Ph.D. thesis, Cambridge University.

[15] A. R. Katritzky and B. Wallis, unpublished work.