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1-HETEROARYL-PYRAZOLES : STABILIZATION OF THE 5-HYDROXY TAUTOMERIC FORM BY AN α-NITROGEN ATOM AND EFFECT ON SPECTRAL PROPERTIES

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We wish to report that the pyrazole derivatives (1 - 7) which are derived from the reaction of α-hydrazino-azaheterocycles with β-dicarbonyl compounds or acetylenic esters are true 5-hydroxypyrazoles (1 - 7 C), stabilized by hydrogen bonding (cf 10). They represent a significant exception to the usual rule that such compounds exist as 2H-(cf A) or 4H-pyrazolin-5-ones (B).

Our special attention was drawn to these compounds by the considerable difference in spectral properties that they show in comparison to the 1-phenyl and 1-(3-quinolyl) analogues (9 and 8), which exist as expected in the pyrazolone form (A and/or B). Compounds were indeed first assigned a triazepine structure but the pyrazole formulation for 16 was proved by the reaction of 2-iodoquinoline with 3,5-dimethylpyrazole to give 1-(2'-quinolyl)-3,5-dimethylpyrazole, identical with the product of the reaction between 2-hydrazinoquinoline and acetylacetone. Thus the difference in spectral properties should be related to the intramolecular hydrogen bond as in 10 and 11. All products[1] described here were prepared either by literature methods[2-4] or from the appropriate hydrazine and β-dicarbonyl compounds.

1-Phenyl-4-methylpyrazolin-5one (9) and the corresponding 1-(3-quinolyl) derivative (8) show no C=O frequency in KBr when they exist in the 2H-form (8A, 9A) while as the 4H-form (8B, 9B) in $CHCl_3$ solution they show an absorption at 1690 cm^{-1} (C=O) and the methylene protons at 3.30 ppm. The deshielded 2' and 6' protons in 9B (7.85 ppm) are restored to their normal region in 14 (7.40 ppm)[3] and 18 (7.39 ppm)[5] consequent to orthosubstitution. Similar behaviour is evident in going from 8B to 17. Also the two methyl signals in 17 and 18[5] appear almost at the same field (17 2.16, 18 2.26, 2.30 ppm).

The IR (KBr or $CHCl_3$) of 1, 2, 4 and 5 show no obvious CH or NH absorption. The NMR of 1 and 4 show no signals for methylene or for chelated OH. The vinyl proton signal (1 5.30, 4 5.43 ppm) indicates slow exchange, presumably due to the tautomeric equilibrium between CH, NH and OH forms (cf eqm 10 = 11 = 12). However, the other exchangeable signal in the region 7.10-7.50 ppm attributable to NH[6], suggests the prependerance of the NH form in

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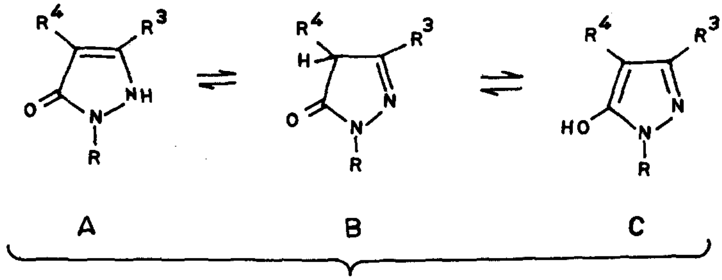
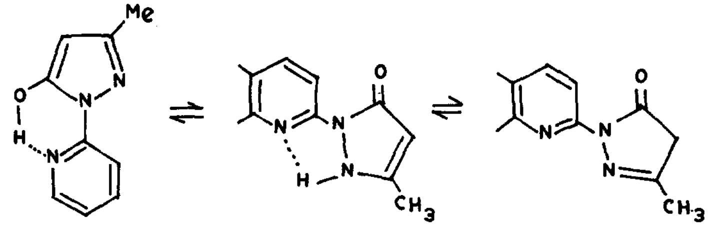
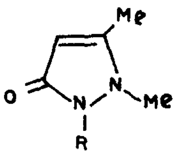


	1	2	3	4	5
R	2-pyridyl	2-pyridyl	2-pyridyl	2-quinolyl	2-quinolyl
R^3	Me	Me	CO_2Me	Me	Me
R^4	H	$CMe{:}CHCO_2Et$	H	H	$CMe{:}CHCO_2Et$

	6	7	8	9
R	2-quinolyl	1-isoquinolyl	3-quinolyl	phenyl
R^3	CO_2Me	Me	Me	Me
R^4	H	$CMe{:}CHCO_2Et$	H	H

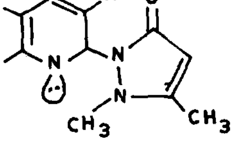


10 11 12

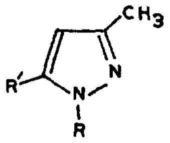


13 R = 2-quinolyl

14 R = phenyl



13a

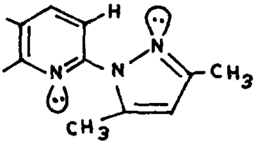


15 R = 2-quinolyl, R^1 = Cl

16 R = 2-quinolyl, R^1 = CH_3

17 R = 3-quinolyl, R^1 = CH_3

18 R = phenyl, R^1 = CH_3



16a

solution. In the solid state it is but reasonable that the hydrogen bond would be much more stable for the 5-hydroxy form than for the NH form. King and Reimlinger[7] postulated the OH form in the solid state for the pyrazolone obtained from 1-hydrazino-3-methyl isoquinoline and phenyl propiolate on the basis of X-ray analysis.

Proton Chemical Shifts[++] ($CDCl_3$)

Compound No.	4-H	$3-CH_3$	Other methyls	Aromatic and other protons
1	5.30	2.20	-	7.03^m(5'-H), 7.80^m (NH,3'H and 4'H), 8.13^m(6'-H)
4	5.43	2.30	-	7.00^d J = 8Hz, 8.22^d J = 8Hz (3'H and 4'H), $7.35-7.84^m$ (NH and other protons)
5	-	2.35	-	8.00^d J = 9Hz, 8.25^d J = 9Hz (3'H and 4'H), 6.01 (vinylic H), 2.56 (vinylic CH_3), 4.20^d ($COOC\underline{H}_2CH_3$), 1.31^t ($COOCH_2C\underline{H}_3$), $7.33-7.85^m$ (NH and other protons)
6	6.10	-	-	8.20^d J = 9Hz, 8.30^d J = 9Hz (3'H and 4'H), 3.93 ($COOCH_3$), $7.45-7.91^m$ (NH and others)
8B	-	2.20	-	3.40 ($-CH_2-$), 9.40^d $J_{2,4}$ = 2Hz (2'H), 8.60^d $J_{4,2}$ = 2Hz (4'H), 8.03^q (8'H), $7.40-7.93^m$ (other protons)
9B[3]	-	2.13	-	3.30 ($-CH_2-$), 7.85^q (2'H and 6'H), 7.10-7.50m (other protons)
13	5.30	2.21	3.38	8.13 (3'H and 4'H), $7.33-8.06^m$ (others)
14[3]	5.38	2.23	3.06	7.40 (phenyl protons)
15	6.25	2.38	-	8.01^d J = 9Hz, 8.20^d J = 9Hz (3'H and 4'H), $7.33-8.05^m$ (other protons)
16	5.99	2.30	2.80	AB quartet centered at 8.14 (3'H and 4'H) $7.40-8.03^m$ (other protons)
17	5.86	2.16	2.16	8.90^d $J_{2,4}$ = 2Hz (2'H), 7.96^m (4'H and 8'H), $7.25 - 7.71^m$ (other protons)
18[5]	6.01	2.26	2.30	7.39 (Phenyl protons)

The 3'H in 1 and 4 appear at 7.8 and 8.00 or 8.22 ppm respectively deshielded by the proximity of the C=O group which does not shift upfield in going from 4 to 16 or 13 (16 8.14, 13 8.13 ppm). In addition, 5-methyl in 16 (2.80 ppm) and 2-methyl in 13 (3.38 ppm) shifted downfield from the

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[++] expressed in δ ppm relative to TMS as internal standard.

corresponding phenyl derivatives 18 (2.3 ppm) and 14 (3.06 ppm). This persistent deshielding of 3'H and the preferential deshielding of 5-Me in 16 and 2-Me in 13 may be accounted for in the coplanar conformations 16a and 13a.

Two factors that influence the molecule to adopt the coplanar conformation are : (1) the tendency to attain *trans* coplanarity as in 2,2'-bipyridyl[8], to avoid repulsion between the nitrogen lone pairs, and (2) the repulsions between methyl and the nitrogen lone pair being less than that of methyl and 3'H.

In 13a, in addition to factor (2), the repulsions between the nitrogen lone pair and the C=O group may contribute to stabilize the planar conformation in which 3'H is deshielded by C=O and N-CH_3 by the nitrogen lone pair.

The upfield shift of 3'H in methanol and the downfield shift of the same in benzene (16 3'H, 7.52 (CH_3OH), 8.13 ($CDCl_3$) and 8.33 ppm (C_6D_6)) analogues to that of 2,2'-bipyridyl[8] substantiates the coplanar structure for 16.

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1. All the new compounds i.e., 2 (m.p. 247-49°), 5 (171°), 13 (106-08°), 7 (160-62°), 15 (54-55°), 16 (59-60°), 17 (liquid), and 8B (57-60°), gave proper analysis.
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