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Pyrazole Studies

XIII.* Oxidation by Air of 4-Substituted Pyrazole-5-ones and Stereochemistry of the Oxidation Products**

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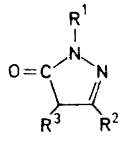
The stereochemistry of the substituted 4-(5′-oxopyrazolinyl)-pyrazol-5-ones formed by copper(II)-catalyzed air oxidation of the pyrazol-5-ones (I) has been studied. It has been found that



(I)

$R^1 = C_6H_5$, CH_3, or H
$R^2 = CH_3$, or C_6H_5
$R^3 = CH_3$, C_2H_5, C_4H_9, $C_6H_5CH_2$, or C_6H_5

the *meso* and racemate forms of the bis-pyrazol-5-ones can be separated by thin-layer chromatography and that NMR-spectroscopy can be used to distinguish between the isomers.

With R^1 and $R^2 = C_6H_5$ and $R^3 = CH_3$ the main oxidation product is the corresponding 4-hydroxypyrazol-5-one, with the bis-pyrazol-5-one as a by-product.

It is well known that many substituted pyrazol-5-ones are easily oxidised (*e.g.* by chromic acid, organic peroxides, or even atmospheric oxygen), forming the so-called 4,4′-bis-pyrazol-5-ones (4-(5′-oxopyrazolinyl)pyrazol-5-ones), a hydrogen atom at C^4 being removed and a C–C bond between the two C^4-atoms being established. Smith [1] showed that the oxidation of 1-phenyl-3,4-dialkylpyrazol-5-ones by means of atmospheric oxygen is catalysed by copper(II) ions. Veibel and Westöö [2] found that the oxidation is inhibited

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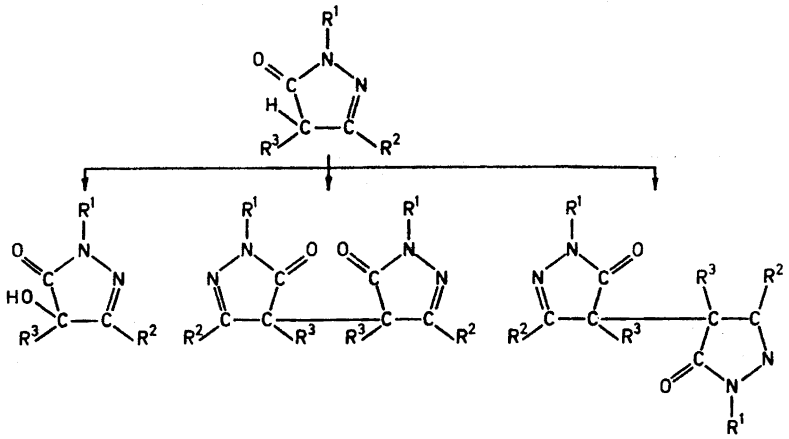
by hydrogen ions and that at neutral reaction a second oxidation product, a 4-hydroxypyrazol-5-one is formed. Small quantities of this hydroxy compound are also found when the crystalline pyrazol-5-one is left for longer periods exposed to atmospheric oxygen. Veibel and Linholt [3,4] showed that the hydroxy compound is the main product when the oxidation is catalysed by triethylamine, both with oxygen and with organic peroxides as oxidising agents. A radical mechanism was suggested for the oxidation.

The reactions are:



The hydroxy compound may exist in an (*R*) and (*S*) form, the bis-pyrazol-5-ones in a *meso*- and a racemic form. In the papers mentioned no attempt was made to investigate the stereochemistry of the reactions.

Hüttel and Authaler [5] have prepared bis-pyrazol-5-ones from 4-alkyl-substituted pyrazol-5-ones, either by nitrosation followed by heating or, as Westöö,[6] by reacting 4-alkylpyrazol-5-ones with 4-alkyl-4-bromo-pyrazol-5-ones. They were interested in the stereochemistry of the reaction, and with some of the pyrazol-5-ones studied they succeeded in separating the reaction product into two fractions with different m.p. They measured the dipole moments of the two fractions and identified the fraction with the lowest dipole moment as the *meso*-form, that with the highest dipole moment as the racemic form. A separation of the racemate in its optically active components was not tried since pyrazol-5-ones with two substituents at C^4 according to Veibel *et al.*[7] are unable to form salts with acids or bases.

As the separation by recrystallisation was rather cumbersome we examined the possibility of separating the two forms by thin-layer chromatography on silica gel plates and found a separation possible, for 1-phenyl substituted pyrazol-5-ones with benzene, for 1-methyl substituted and 1-unsubstituted pyrazol-5-ones with a benzene/ethyl acetate 3/1 mixture as the mobile phases.

Upon separation of the bis-1-phenyl-3,4-dimethylpyrazol-5-ones studied by Hüttel and Authaler [5] we obtained two fractions with m.p. 163 – 164°C and m.p. 140 – 141°C and R_F values 0.23 and 0.14. Hüttel and Authaler reported

Table 1.

				meso δ					racemic δ					
R^1	R^2	R^3	R_F	R^1	R^2		R^3	M.p. °C	R_F	R^1	R^2		R^3	M.p. °C
C_6H_5	CH_3	CH_3	0.23	—	2.00		1.70	163–164	0.14	—	2.20		1.60	140–141
						CH_3	0.60					CH_3	0.65	
C_6H_5	CH_3	C_2H_5	0.24	—	1.90	CH_2	2.25 2.05	160–162	0.14	—	2.20	CH_2	2.25 2.05	175–177
C_6H_5	CH_3	$C_6H_5CH_2$	0.50	—	2.00	CH_2	4.20 3.65	147–148	.20	—	2.45	CH_2	4.10 3.65	165–166
C_6H_5	CH_3	C_4H_9	0.56	—	1.90	CH_2	0.80	132–133	—	—	—	—	—	—
C_6H_5	C_6H_5	CH_3	0.30	—	—		1.60	204–205	—	—	—	—	—	—
CH_3	CH_3	$C_6H_5CH_2$	0.60	2.95	1.80	CH_2	4.15 3.35	186–188	0.34	2.90	2.20	CH_2	3.90 3.15	158–160
H	CH_3	$C_6H_5CH_2$	0.31	11.1	1.85	CH_2	4.05 3.25	220–221	0.14	10.8	2.20	CH_2	3.85 3.20	212–214

for their two fractions m.p. 162°C and m.p. 140°C, the higher melting compound having the lowest dipole moment, *i.e.* being the *meso* form, the lower melting the highest dipole mement, *i.e.* being the racemic form. This is in accordance with the R_F values found by us, the less polar *meso* form having a higher R_F value than the more polar racemic compound.

We then studied bis-1-phenyl-3-methyl-4-ethylpyrazol-5-one and bis-1-phenyl-3-methyl-4-benzylpyrazol-5-one. In both cases it was possible to separate two forms by thin-layer chromatography. The R_F values are indicated in Table 1. We have not measured the dipole moments but consider the forms with the highest R_F values to be the *meso*, those with lower R_F values the racemates. Contrary to what was found for the 4-methyl-derivatives the *meso* forms have m.p.'s lower than those of the racemic forms.

Starting from 1-phenyl-3-methyl-4-butylpyrazol-5-one and 1,3-diphenyl-4-methylpyrazol-5-one the bis-pyrazol-5-ones obtained after air oxidation could not be separated by thin-layer chromatography, each of them giving only one spot on the chromatograms. According to the R_F values (Table 1) it is most likely that *meso* forms have been formed.

From 1,3-dimethyl-4-benzylpyrazol-5-one and 3-methyl-4-benzylpyrazol-5-one we obtained, by copper(II) ion catalysed oxidation with air, the corresponding bis-pyrazol-5-ones which could be separated by thin-layer chromatography with benzene/ethyl acetate 3/1 as the mobile phase. Again, we consider the fractions with the higher R_F values to be the *meso*, those with lower R_F values the racemic forms. Here, as for the 1-phenyl-3,4-dimethyl derivatives, the *meso* forms have higher m.p.'s than the racemic forms.

Without giving details, Hüttel and Authaler [5] mention that the NMR-spectra of the two forms show different location of some of the signals. We, too, have studied the NMR-spectra of the bis-pyrazol-5-ones. The δ-values found are indicated in Table 1.

It is seen that in all cases where two forms have been isolated the signal of a methyl group at C^3 is displaced towards lower field, that of a hydrogen atom at N^1 towards higher field in the racemic form as compared with the *meso* form, whereas the signal of a methyl group at N^1 is of very nearly the same δ-values in the two forms. The difference between the signals for methyl groups at C^4 is smaller for the *meso* forms than for the racemic forms, substituents at C^3 being displaced more than substituents at C^4.

The signal of the methyl group in ethyl at C^4 is at an extremely high field value, the signals of the methylene groups in ethyl and benzyl at C^4 at almost normal values.

Table 1 shows that in the cases where only one form of the bis-pyrazol-4-one has been isolated, both the R_F and δ-values suggest that the form isolated is the *meso* form.

EXPERIMENTAL

All the pyrazol-5-ones studied were prepared by conventional methods and showed the m.p.'s indicated in the literature.

Oxidation procedure. 0.012 – 0.03 mol of the pyrazol-5-one was dissolved in ethanol (250 – 900 ml; just sufficient to form a nearly saturated solution). 5 – 10 ml of a 0.2 % aqueous solution of $CuSO_4.2H_2O$ were added and the beaker, covered by a watch-glass,

was left to stand for some days during which a precipitate of the bis-pyrazol-5-one-separated.

The precipitate was filtered off, the filtrate reduced to a small volume in vacuum on a rotation evaporator and the residue recrystallized from ethanol.

As the pyrazol-5-one nucleus may be opened during the long reaction time the yield of bis-pyrazol-5-one is in some instances rather low.

1-Phenyl-3,4-dimethylpyrazol-5-one. 5.7 g (0.03 mol) were dissolved in 300 ml ethanol and 7.5 ml copper(II) sulphate solution added. After 5 days 1.6 g prismatic crystals with m.p. 161 – 163°C (I) were isolated. From the filtrate 1.65 g with m.p. 143 – 147°C (II) were obtained.

1.6 g I were recrystallised from 60 ml ethanol. Yield 1.4 g with m.p. 162 – 163°C.

1.65 g II were recrystallised from 30 ml ethanol. Yield. 1.4 g with m.p. 143 – 147°C.

I was by thin-layer chromatography found to be homogeneous (mobile phase benzene, $R_F = 0.23$), whereas II even after several recrystallisations showed two spots on the chromatogram. It was then purified by preparative thin-layer chromatography. 0.45 g was applied to a 25 × 15 cm plate and chromatographed with benzene as the mobile phase. Two bands were located on the plate. That with the lowest R_F value was scraped off the plate, the silica gel extracted with ether, the ether evaporated, and the residue recrystallised from ethanol. M.p. 140 – 141°C. $R_F = 0.14$.

1-Phenyl-3-methyl-4-ethylpyrazol-5-one. From 6 g (0.03 mol) in 300 ml ethanol and 7.5 ml copper(II) sulphate solution were obtained, after 4 days, 4 g of a bis-pyrazol-5-one which by thin-layer chromatography (mobile phase benzene) was shown to be a mixture of two components. By preparative thin-layer chromatography two chromatographically pure substances were isolated, one with m.p. 161 – 162° C and $R_F = 0.24$, the other with m.p. 175 – 177°C and R_F 0.14 (mobile phase benzene).

1-Phenyl-3-methyl-4-benzylpyrazol-5-one. From 3.3 g (0.012 mol) in 145 ml ethanol and 5 ml copper(II) solution were isolated, after 5 days, 1.42 g with m.p. 147 – 148°C. From the filtrate 0.74 g with m.p. 143 – 149°C was isolated. Both crops were shown by thin-layer chromatography to be mixtures; by preparative thin-layer chromatography (mobile phase benzene) two chromatographically pure substances were isolated, one with m.p. 147 – 148°C and $R_F = 0.50$, the other with m.p. 165 – 166°C and $R_F = 0.20$.

1-Phenyl-3-methyl-4-butylpyrazol-5-one. From 6.9 g (0.03 mol) in 300 ml ethanol and 7.5 ml copper(II) sulphate solution were obtained, after 10 days, 2.5 g of a substance with m.p. 132 – 133°C. From the filtrate nothing crystallisable was obtained. The m.p. was not changed by recrystallisation, and the substance was shown to be chromatographically pure with $R_F = 0.56$, mobile phase benzene.

1,3-Diphenyl-4-methylpyrazol-5-one. From 5 g (0.02 mol) in 250 ml ethanol and 5 ml copper(II) sulphate solution was obtained, after 15 days, 1 g with m.p. 200 – 201°C. From the filtrate 2.8 g with m.p. 141 – 142°C were isolated. Recrystallised from ethanol the m.p.'s were raised to 204 – 205°C and 145 – 146°C. Both substances were chromatographically pure with R_F-values 0.30 and 0.14 (mobile phase benzene).

By IR-spectroscopy the lower melting compound was shown to contain a hydroxy-group and elemental analysis proved to be in accordance with 1,3-diphenyl-4-hydroxy-4-methylpyrazol-5-one. This means that for the substance investigated the oxidation to 4-hydroxypyrazol-5-one is more pronounced than the oxidation to the bis-pyrazol-5-one.

1,3-Dimethyl-4-benzylpyrazol-5-one. From 3.5 g (0.017 mol) in 200 ml ethanol and 10 ml copper(II) sulphate solution was isolated, after 20 days, 1.25 g with m.p. 180 – 182°C and from the filtrate 0.90 g with m.p. 158 – 160°C. Recrystallised from ethanol the m.p.'s were raised to 186 – 188°C and 160 – 161°C. Both fractions were chromatographically pure with R_F values 0.60 and 0.31 (mobile phase benzene/ethyl acetate 3/1).

3-Methyl-4-benzylpyrazol-5-one. A solution of 3.8 g (0.02 mol) in 900 ml ethanol and 10 ml copper(II) sulphate solution gave no precipitate after 11 days. It was concentrated in vacuum on a rotation evaporator and then left overnight in the ice-box. 1.2 g with m.p. 214 – 215°C was filtered off, the filtrate and washings (100 ml) were heated and water was added to 300 ml. After cooling 1.1 g with m.p. 174 – 176°C was filtered off. After several recrystallisations two chromatographically pure substances with m.p. 215 – 217°C and 174 – 176°C and R_F values 0.31 and 0.14 (mobile phase benzene/ethyl acetate 3/1) were obtained.

Elemental analyses of all compounds not described in the literature (from A. Bernhardt, Elbach) gave values within ± 0.4 % of the calculated.

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