

Pyrazole Studies

V. The Oxidation by Air of Some 3,4-Dialkylsubstituted 1-Phenylpyrazolones-5

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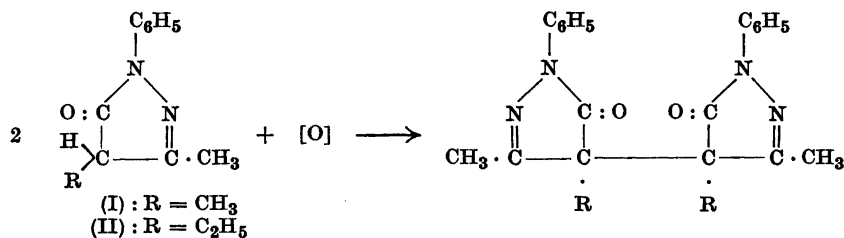
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In a previous paper¹ the potentiometrical titration of 5-pyrazolones with bases was described and it was mentioned that even when monosubstituted in position 4 the pyrazolones are sufficiently acid to give off a proton during the addition of sodium or barium hydroxide to their ethanolic solution.

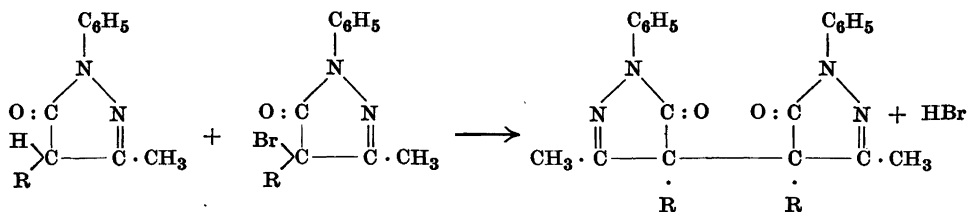
It was found, however, that if the ethanolic solution of a 4-monosubstituted pyrazolone had been kept for some days before titrating it, it would not consume the calculated amount of base, and if the solution was not too diluted it would, in the course of 8-14 days, deposit crystals of a new substance, less soluble in ethanol than the pyrazolone and absolutely neutral to sodium hydroxide. We have now examined more closely the behaviour of 1-phenyl-3-methyl-4-methyl- (or ethyl-)pyrazolone-5 by isolating and analysing the new substances.

First we thought them to be isomers of the ordinary pyrazolones as the nitrogen content of the new substances are, within the limit of the experiment, identical with the nitrogen content of the pyrazolones. A closer examination proved, however, that the neutral substances are oxidation-products of the pyrazolones, 4,4'-bis-pyrazolones. The oxidation is caused by the atmospheric oxygen and the reaction is strongly catalysed by cupric ions (*cf.* Smith²). If the ethanolic solutions are kept in completely filled flasks no oxidation takes place, not even if a trace of cupric sulfate is added to the solution.

The overall-reaction seems to be:



The structure of the neutral substances are proved by their preparation from 4-alkylsubstituted pyrazolone and 4-alkyl-4-bromopyrazolone (Westöö ³)



and by the fact that the ultraviolet absorption spectra of the substances prepared in this way are identical with the spectra of the oxidation products isolated.

An oxidation takes place not only in solution but in the solid state too. Preparations of 1-phenyl-3,4-dimethyl-pyrazolone-5 or 1-phenyl-3-methyl-4-ethyl-pyrazolone-5, kept in cork-stoppered flasks for some months were found to have been partially oxidised, and when heated for 3—4 days to 100° oxidation also takes place. Treated in the last mentioned way two different oxidation products of the pyrazolones may be isolated. By recrystallisation of the heated pyrazolone from ethanol the bis-pyrazolone may easily be isolated as a slightly soluble substance. M.p. for the two pyrazolones mentioned 165° and 161—162° respectively. When the mother liquors from the bis-pyrazolones are slowly concentrated at room temperature two other substances with m.p. 113° and 117° respectively may be isolated. These substances, too, are neutral to sodium hydroxide. By elementary analysis we found that they contain one atom of oxygen more than the pyrazolones, and it may be shown that this oxygen is contained in a hydroxyl group, as the substances with *m*-nitrobenzazide form *m*-nitrophenylcarbamic esters (*cf.* Veibel and Lillelund ⁴). At room temperature only the lower melting oxidation products seem to be formed.

As for the position of the hydroxyl group the only possibility seems to be at C₄. The low-melting neutral substances are therefore considered to be 1-phenyl-3-methyl-4-methyl-(or ethyl-)4-hydroxy-pyrazolone-5. In agreement with this assumption the substance formed by oxidation of (I) is transformed into 1-phenyl-3,4-dimethyl-4-chloro-pyrazolone-5 by treatment with phosphorous trichloride.

A comparison of the ultraviolet absorption spectra of the hydroxy-compounds and of the corresponding 4-chloro- and 4-bromo-substituted pyrazolones (these spectra have been examined by Westöö ⁵) corroborates the assumption of the hydroxy compounds being 4-hydroxypyrazolones.

EXPERIMENTAL PART

(I) and (II) were prepared as indicated by Knorr and Blank ⁶ and showed the physical properties indicated in the literature.

1. *Oxidation by air of the pyrazolones in ethanolic solution.* A solution of (II) in ethanol was placed in a thermostat at 30°. The flask was stoppered with a cork-stopper. At intervals samples to 50 ml were titrated with barium hydroxide.

In a parallel experiment smaller flasks with ground glass-stoppers were completely filled with the solution, placed in the thermostat and a new flask opened for each sample. In this series, the air had no access to the solution (Table 1).

Table 1.

Sample taken after hours	a) Access of air ml Ba(OH) ₂	b) No access of air ml Ba(OH) ₂
0	7.60	—
168	6.50	6.90
336	5.60	6.75
480	4.80	6.75
672	4.00	6.75

The experiment proves that the oxidation is caused by the air, not by *e. g.* acetaldehyde or other impurities in the ethanol.

2. *Catalytic action of cupric ions on the oxidation of the pyrazolones.* The following solutions were prepared. At intervals samples to 50 ml were titrated with barium hydroxide (Table 2).

- c) 20 ml water, filled up to 250 ml with a 0.033 *M* ethanolic solution of (II).
- d) 20 ml 1.176 *N* hydrochloric acid, filled up to 250 ml with the same solution as in c.
- e) 20 ml 0.01 % CuSO₄ · 5H₂O in water, filled up to 250 ml with the same solution as in c.
- f) 20 ml 0.1 % CuSO₄ · 5H₂O in water, pyrazolone as in c—e.

These solutions are seen to be about 0.03 *M* with regard to pyrazolone.

Table 2.

Sample taken after hours	50 ml solution consume ml Ba(OH) ₂ , 0.2144 <i>N</i>			
	c	d	e	f
0	7.17	7.17	7.17	7.17
120	6.65	6.50	4.2	1.8
192	—	—	1.5	—
336	5.10	5.35	—	—

The amount of barium hydroxide used by hydrochloric acid subtracted.

The catalysis caused by cupric ions is seen to be strong. It increases with the concentration of cupric ions. Hydrogen ions up to a concentration about 0.1 *N* are seen to have only a slight decreasing effect upon the oxidation of the pyrazolone, but if the concentration of hydrogen ions is increased to 1.6 *N* the oxidation is completely suppressed, both in the absence and in the presence of cupric ions (Table 3). The amount of barium hydroxide used by the sulfuric acid subtracted.

Table 3. *g*) 100 ml 4 *N* sulfuric acid, 5 ml 0.1 % $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ in water, 0.06 *M* ethanolic solution of (II) to 250 ml.

Sample taken after hours	ml $\text{Ba}(\text{OH})_2$
0	8.55
72	8.35
144	8.33
216	8.63

When the figure for the sample after 216 hours is greater than for the previous samples it is due to the fact that when the sulfuric acid has been neutralised, the oxidation is strongly catalysed by the cupric ions. During the titration air is introduced into the solution by mechanical stirring, and the oxidation is therefore much faster than when air is only accessible by diffusion. The titration of the 3 first samples was carried out slowly, but for the last one, where the consumption of barium hydroxide was known, it was possible to reduce the time used for the titration to a minimum.

That the copper-catalysed oxidation is caused by air is shown in the experiment recorded in Table 4.

Table 4. *h*) 15 ml 0.1 % $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ in water; Ethanolic solution of (II) to 250 ml; 4 Flasks with ground glass-stoppers were filled completely with this solution and placed in the thermostat at 30°. One flask was opened for each titration.

Sample taken after hours	ml $\text{Ba}(\text{OH})_2$
0	11.5
48	11.8
96	12.0
144	12.1

The increase in the figures means, as above, that the titration is carried through in a shorter time when the total amount of barium hydroxide necessary has been determined by previous titrations.

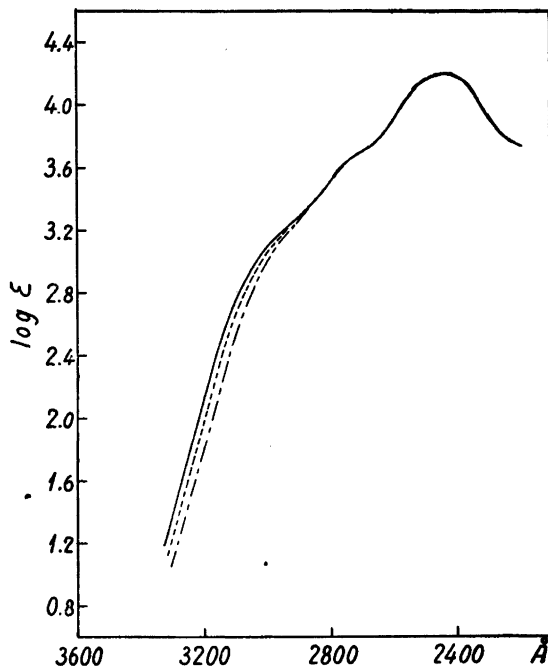


Fig. 1. Ultraviolet absorption spectra of bis-(I) (---), bis-(II) (—), and bis-1-phenyl-3,4-dimethylpyrazolone-5 (.....).

3. Identification of the substances obtained by the oxidation in ethanolic solution. Not too diluted ethanolic solutions of (I) and (II), kept at room temperature for some time will deposit crystals, from (I) with m.p. 165°, from (II) crystals sintering at 152° and melting with slight decomposition at 161–162°. A substance with m.p. identical with that of the substance deposited from (I) has been prepared by reaction between (I) and brominated (I), bromine entering in position 4 (Westöö³), and mixed melting point of the isolated and the synthesised substance does not show depression. From this it may be concluded that the substances deposited from the ethanolic solutions are the bis-pyrazolones. Knorr⁷ indicates for the bis-pyrazolones from (I) and (II) m.p. 164° and 160°. The bis-pyrazolone of (II) may possibly exist in dimorphous forms, a phenomenon not unknown in the pyrazolone-group. Elementary analyses agree with the assumption of bis-pyrazolones.

bis-I. $C_{22}H_{22}N_4O_2$ (374.4)	Calc. C = 70.6 %, H = 5.9 %
	Found C = 70.5 %, H = 5.9 %
bis-II. $C_{24}H_{26}N_4O_2$ (402.5)	Calc. C = 71.6 %, H = 6.51 %, N = 13.92 %
	Found C = 71.7 %, H = 6.45 %, N = 13.85 %

The identity of the two substances isolated in the way described with the bis-pyrazolones was further proved by comparison of their ultraviolet absorption spectra, meas-

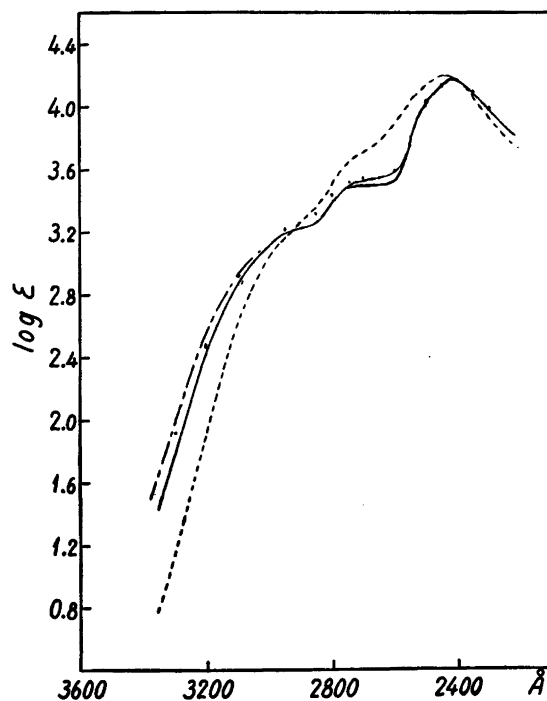


Fig. 2. Ultraviolet absorption spectra of (III), (—), (IV) (-----), bis-1-phenyl-3,4-dimethylpyrazolone-5 (.....), and some determinations of the absorption of (III) in acid ethanolic solution (· · · ·)

ured with a Beckman-U.V.-spectrograph, with the absorption spectrum of a sample of bis-(I), prepared and measured by Westöo³. The absorption curves are given in Fig. 1.

No doubt the oxidation in ethanolic solution leads to the formation of the bis-pyrazolone. As mentioned above the reaction is catalysed by cupric ions. Further investigation of the cupric-ion catalysed reaction has shown that also the substances (III) and (IV) mentioned below may be formed.

4. *Identification of the substances obtained by keeping the pyrazolones at 100° for some days.* (I) and (II) are both practically insoluble in ether, but when they have been kept for some months at room temperature or for a couple of days at 100° they have been partially transformed into ether-soluble substances. The hydrobromide of (I), on the other hand, may be kept at least for a year at room temperature without transformation. Parallel to the transformation the amount of sodium or barium hydroxide used to neutralise the pyrazolone is reduced. The transformation products are evidently neutral substances in distinction to the pyrazolones. By evaporation the ethereal solution leaves crystals which by fractionated crystallisation from ethanol may be separated into two fractions, one, sparingly soluble in cold ethanol, being the above mentioned bis-pyrazolone, the other, easily soluble in both ethanol and ether, being neutral as the bis-pyrazolone but containing per pyrazolone-nucleus one atom of oxygen more than the bis-

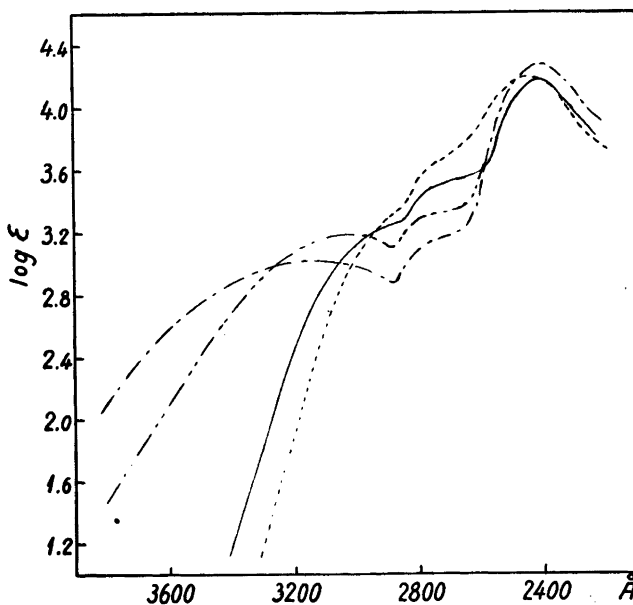


Fig. 3. Ultraviolet absorption spectra of 1-phenyl-3,4-dimethyl-4-bromo-pyrazolone-5 (-----), 1-phenyl-3,4-dimethyl-4-chloro-pyrazolone-5 (- · - · - · -), 1-phenyl-3,4-dimethyl-4-hydroxy-pyrazolone-5 (—————), and bis-1-phenyl-3,4-dimethyl-pyrazolone-5 (·····).

pyrazolone. M. p. of the substance from (I) 113°, from (II) 117°. Elementary analyses give the formulas $C_{11}H_{12}O_2N_2$ (III) and $C_{12}H_{14}O_2N_2$ (IV).

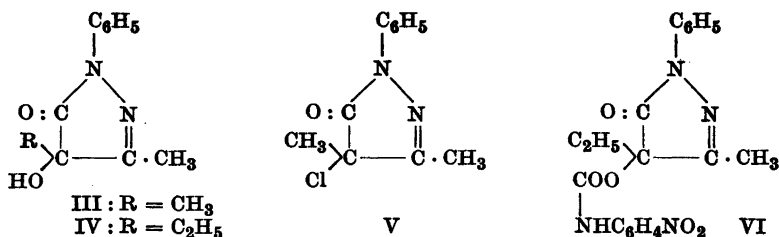
III. $C_{11}H_{12}O_2N_2$ (204.2)	Calc.	C = 64.68 %	H = 5.92 %	N = 13.72 %
	Found	C = 64.9 »	H = 5.95 »	N = 13.88 »
IV. $C_{12}H_{14}O_2N_2$ (218.2)	Calc.	C = 66.04 »	H = 6.47 »	N = 12.84 »
	Found	C = 65.8 »	H = 6.38 »	N = 12.91 »

The extra oxygen atom is contained in a hydroxyl group. By treatment with PCl_3 (III) was transformed into 1-phenyl-3,4-dimethyl-4-chloro-pyrazolone-5 (V), identified through analysis, m.p. (68°) and mixed m.p. with an authentic sample of V which showed no depression.

V. $C_{11}H_{11}O N_2Cl$ (222.7)	Calc.	C = 59.3 %	H = 5.0 %
	Found	C = 59.5 »	H = 5.2 »

A further proof of the presence of a hydroxyl group was obtained by reaction of (IV) with *m*-nitrobenzazide. Hereby a substance (VI) was isolated, the elementary analysis of which corresponds to a *m*-nitrophenylcarbamic ester of (IV):

VI. $C_{19}H_{18}O_5N_4$ (382.4), m.p. 139°	Calc.	C = 59.6 %	H = 4.7 %	N = 14.7 %
	Found	C = 59.7 »	H = 4.5 »	N = 14.9 »



The only other possible position of an oxygen atom seems to be at *N* in position 2, transforming (I) and (II) into amine oxides or into *N*-hydroxy compounds. Such compounds will hardly be of neutral character, and the absorption curves, shown in Fig. 2 and Fig. 3, corroborate the formulas (III) and (IV). In Fig. 2 is shown that the absorption of (III) is the same in acid as in neutral solution. This behaviour is shown by pyrazolones with two substituents at C₄, *e. g.* 4-alkyl-4-halogeno-5-pyrazolone (Westö⁵), whereas antipyrine, with a substituent at N₂, shows another absorption spectrum in acid than in neutral solution (Valyashko and Bliznyukov⁶).

In Fig. 3 the absorption spectra of the hydroxy-compounds are compared with the absorption spectra of 4-alkyl-4-halogeno-5-pyrazolones. For all compounds an absorption band with maximum $\sim 2400 \text{ \AA}$ is found. For the halogeno-compounds the absorption in the region $2500 \text{ \AA} - 2900 \text{ \AA}$ is diminished, most pronounced for the bromo-compound, and a broad secondary maximum about $2900 \text{ \AA} - 3300 \text{ \AA}$ may be seen. Our substances (III) and (IV) now fit well into this series, in accordance with the slightly electronegative character of OH as compared with Cl and Br. From the broad absorption band about $2900 \text{ \AA} - 3300 \text{ \AA}$ only a shoulder at 2900 \AA remains, which in the bis-pyrazolone is further reduced to an inflexion point. The decrease in absorption in the region $2500 \text{ \AA} - 2900 \text{ \AA}$ is only $1/3$ of that of the bromo-compound, $1/2$ of that of the chloro-compound. For further discussion of the spectra see Westö⁵.

Knowing that substances of the general formula (V) with I or Br instead of Cl are able to couple with (I) and (II) with formation of the bis-pyrazolone (*cf.* Smith²) it would be natural to postulate that the formation of the hydroxy-compounds (III) and (IV) are intermediate steps in the formation of the bis-pyrazolones. This assumption has, however, to be abandoned, as solutions of (I) and (III) or (II) and (IV) in ethanol may be kept for a long time without formation of bis-pyrazolones if the access of air is prohibited, whereas the formation of bis-pyrazolones starts as soon as air is admitted. This, too, fits well into the series of the halogeno-compounds as the velocity of coupling diminishes in the order $I > Br > Cl$, the difference in velocity between the bromo- and the chloro-compound being considerable. We, therefore, have to admit two reactions, proceeding simultaneously, one leading to the formation of bis-pyrazolones, the other to the formation of the hydroxy-compound. Both reactions take place in the solid phase as well as in solution, and at all events in solution both reactions are catalysed by cupric ions, the first mentioned very strongly. The oxydation is inhibited by hydrogen ions.

SUMMARY

Solutions of 3,4-dialkylsubstituted 5-pyrazolones in ethanol were found to be oxidised by air with formation of two different oxidation products, one being the corresponding 3,4-dialkylsubstituted bis-pyrazolones, the other

being the 3,4-dialkyl-4-hydroxypyrazolones. The formation of the bis-pyrazolones is strongly catalysed by cupric ions, the catalysis being inhibited by hydrogen ions. Also the formation of the hydroxy-compounds is catalysed by cupric ions.

In the solid phase the oxidation proceeds more slowly than in solution. The influence of cupric ions upon the velocity of oxidation in the solid state has not been investigated.

The ultraviolet absorption spectra of the bis-pyrazolones and the hydroxypyrazolones have been determined and compared with the absorption spectra of an authentic sample of the bis-pyrazolone and of 4-bromo- and 4-chloro-substituted 3,4-dialkylpyrazolones.

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