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Pyrazole Studies

VIII *. Oxidation of 4-Alkylsubstituted Pyrazol-5-ones with Tertiary Butylhydroperoxide

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The preparation of 4-alkyl-4-hydroxysubstituted pyrazol-5-ones in anhydrous alkaline-alcoholic solution containing ca. 70 % of tert. butanol with tert. butylhydroperoxide is described. The presence of water causes a decrease in the yield of hydroxy compound. When the pyrazolone is unsubstituted at N_1, only unidentified, oily products have been isolated in experiments with water containing solvents.

In neutral anhydrous solution N_1-substituted 4-alkylpyrazol-5-ones are oxidised by tert. butylhydroperoxide to the corresponding bis-pyrazolones whereas pyrazolones unsubstituted at N_1 are oxidised to unidentified oily substances.

In the preceding paper in this series was shown that 4-alkylsubstituted pyrazol-5-ones dissolved in methanol are oxidised by oxygen in the presence of an excess of triethylamine, forming a 4-alkyl-4-hydroxysubstituted pyrazol-5-one and triethylamine oxide, 1 mole of oxygen being consumed per mole of pyrazolone. The stoichiometry of this reaction was found to correspond to the following sequence of reactions (Py meaning a pyrazol-5-one molecule minus the two hydrogen atoms at C_4):

$$\mathrm{PyRH} + (\mathrm{C_2H_5})_3\mathrm{N} \rightleftharpoons \mathrm{PyR^-} + (\mathrm{C_2H_5})_3\overset{+}{\mathrm{N}}\mathrm{H} \quad (1)$$

$$\mathrm{PyR^-} + \mathrm{O_2} \rightleftharpoons \mathrm{PyROO^-} \quad (2)$$

$$2\ \mathrm{PyROO^-} + 2\ (\mathrm{C_2H_5})_3\overset{+}{\mathrm{N}}\mathrm{H} \rightleftharpoons \mathrm{PyROH}\ldots\bar{\mathrm{O}}\ldots\mathrm{HORPy} + (\mathrm{C_2H_5})_3\mathrm{NO} \quad (3)$$

$$\mathrm{PyROH}\ldots\bar{\mathrm{O}}\ldots\mathrm{HORPy} + \mathrm{H_2O} \rightarrow 2\ \mathrm{PyROH} + (\mathrm{C_2H_5})_3\mathrm{N(OH)_2} \quad (4)$$

The substance presumed as the result of reaction (2) is a hydroperoxide ion. The formation of hydroperoxides is well known from investigations of the oxidation by air of aliphatic or alicyclic unsaturated hydrocarbon systems

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(*cf. e. g.* Bolland [1]), hydrogen atoms in α-position to the double bond being attacked by an oxygen molecule, resulting in the formation of a hydroperoxide group. In the pyrazol-5-one the hydrogen at C_4 is in α-position both to the C = N double bond in the pyrazolone nucleus and to the C = O double bond outside the nucleus and is therefore strongly activated. This applies to both 4-unsubstituted and to 4-monosubstituted pyrazol-5-ones, but only in the latter case has it been possible to isolate oxidation products of definite structure after treatment of the primary reaction product with water or hydrochloric acid.

In order to get some evidence as to the possibility of alkylhydroperoxide ions to react with alkylpyrazolone ions we investigated the reaction between 4-alkylsubstituted pyrazol-5-ones and tertiary butylhydroperoxide in alcoholic solution containing sodium ethoxide. This method proved to be an excellent method for preparing 4-alkyl-4-hydroxysubstituted pyrazol-5-ones. Here, no doubt, the reaction is:

$$PyR^- + (CH_3)_3COO^- \rightarrow PyRO^- + (CH_3)_3CO^-$$

or

$$PyRH + (CH_3)_3COOH \rightarrow PyROH + (CH_3)_3COH$$

followed by:

$$PyRO^- + Na^+ \rightarrow PyRONa$$

or

$$PyROH + C_2H_5ONa \rightarrow PyRONa + C_2H_5OH$$

We are inclined to adopt the first mentioned of these possibilities as the oxidation of 4-alkylsubstituted pyrazolones in neutral ethanolic solution, at any rate in some cases, leads to the bis-pyrazolone:

$$2\ PyRH + (CH_3)_3COOH \rightarrow PyR{-}RPy + (CH_3)_3COH + H_2O.$$

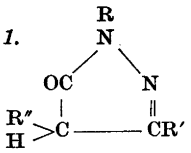
The readiness with which the pyrazolones are oxidised according to the proposed scheme is dependent on substituents present at N_1, at C_3 and at C_4, and besides on the solvent, the reactions proceeding more unambiguously with sodium ethoxide in anhydrous ethanol or in tertiary butanol than in 90 % ethanol. In the latter case pyrazolones alkyl- or arylsubstituted at N_1 (and besides substituted at C_3 and C_4) react normally, forming the 4-hydroxy-substituted pyrazolones, whereas pyrazolones unsubstituted at N_1 consume tertiary butylhydroperoxide, but the oxidation products are heavy oils which cannot be purified by distillation in vacuo (*ca.* 1 mm Hg). These oils were not further investigated; they possibly are the result of an oxidative or a hydrolytic cleavage of the pyrazole-ring.

In anhydrous neutral solution the oxidation of pyrazol-5-ones with tert. butylhydroperoxide results in the formation of bispyrazolones when the pyrazolone is substituted at N_1 whereas oils are formed when the pyrazolone is unsubstituted at N_1.

EXPERIMENTAL PART *

The pyrazolones investigated in this paper are tabulated in Table 1 which records at the same time yield, m.p. and analysis of the 4-hydroxypyrazolones formed.

* All m. p.'s uncorrected; all microanalyses by Mr. W. Egger or Mr. P. Hansen, Department of Organic Chemistry, The University, Copenhagen.

Table 1.  *Oxidation of pyrazolones with tert. butyl hydroperoxide and analysis of the 4-hydroxypyrazolones*

	R	R′	R″	Yield %	M. p. °C	Hydroxypyrazolone · Formula	Analysis	% C	% H	% N
I[2]	C_6H_5	CH_3	CH_3	44[a]	105	$C_{11}H_{12}O_2N_2$	Calc.	64.68	5.93	13.72
							Found	64.72	5.86	13.89
II[2]	C_6H_5	CH_3	C_2H_5	70	130	$C_{12}H_{14}O_2N_2$	Calc.	66.04	6.47	12.84
							Found	66.17	6.59	12.77
III[3]	C_6H_5	CH_3	*n*-C_3H_7	65	116—117	$C_{13}H_{16}O_2N_2$	Calc.	67.20	6.94	12.06
							Found	67.32	7.21	11.96
IV[3]	C_6H_5	CH_3	*n*-C_4H_9	65	95	$C_{14}H_{18}O_2N_2$	Calc.	68.27	7.37	11.38
							Found	68.34	7.18	11.50
V[4]	C_6H_5	CH_3	$C_6H_5CH_2$	95—100[b] 43[c]	145	$C_{17}H_{16}O_2N_2$	Calc.	72.85	5.75	10.00
							Found	72.81	5.64	10.23
VI[5]	C_6H_5	*Cyclo*hexano		33	140	$C_{13}H_{14}O_2N_2$	Calc.	67.81	6.13	12.17
							Found	68.08	6.03	12.26
VII[6]	CH_3	CH_3	C_2H_5	50	39	$C_7H_{12}O_2N_2$	Calc.	53.84	7.70	17.94
							Found	53.93	7.81	18.05
VIII[7]	CH_3	CH_3	$C_6H_5CH_2$	80	155—156	$C_{12}H_{14}O_2N_2$	Calc.	66.04	6.47	12.84
							Found	66.24	6.32	12.89
IX[8,9]	H	CH_3	CH_3	d	96—97	$C_5H_8O_2N_2$	Calc.	46.89	6.29	21.87
							Found	46.94	6.21	21.70
X[9,10]	H	CH_3	C_2H_5	77	128—130	$C_6H_{10}O_2N_2$	Calc.	50.67	7.09	19.71
							Found	50.20	7.19	19.70
XI[9,11]	H	CH_3	*n*-C_3H_7	65	117—118	$C_7H_{12}O_2N_2$	Calc.	53.84	7.70	17.94
							Found	53.75	7.78	17.83
XII[12]	H	CH_3	C_3H_5	65	103—104	$C_7H_{10}O_2N_2$	Calc.	54.53	6.53	18.18
							Found	54.28	6.43	17.93
XIII	H	CH_3	*n*-C_4H_9	65	101—102	$C_8H_{14}O_2N_2$	Calc.	56.47	8.29	16.47
							Found	56.63	8.24	16.43
XIV	H	CH_3	C_6H_{11}	86	140	$C_{10}H_{16}O_2N_2$	Calc.	61.20	8.22	14.28
							Found	61.36	8.32	14.36
XV[13]	H	CH_3	$C_6H_5CH_2$	60	143—144	$C_{11}H_{12}O_2N_2$	Calc.	64.68	5.93	13.72
							Found	64.73	6.03	13.70
XVI[6]	H	CH_3	C_6H_5	70	190	$C_{10}H_{10}O_2N_2$	Calc.	63.15	5.30	14.73
							Found	63.23	5.20	15.13
XVII[5]	H	*Cyclo*hexano		15	195—197	$C_7H_{10}O_2N_2$	Calc.	54.53	6.53	18.18
							Found	54.70	6.81	18.28
XVIII[14]	H	C_6H_5	$C_6H_5CH_2$	95	185—186	$C_{16}H_{14}O_2N_2$	Calc.	72.17	5.30	10.52
							Found	72.04	5.15	10.74

a) Methanolic solution
b) Anhydrous solution
c) 10 % of water present
d) Obtained only by oxidation by air, not with tert. butylhydroperoxide

All the pyrazolones were prepared by current methods and showed the m.p.'s indicated in the literature. For XIII and XIV no indications were found and we, therefore, indicate in Table 2 yield, m.p. and analyses of these substances, prepared from hydrazine hydrate and the corresponding *a*-substituted ethyl acetoacetate as indicated by Veibel *et al.*[6].

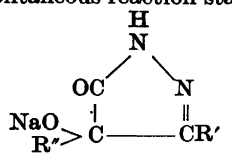
Table 2. Data for the pyrazolones XIII and XIV.

	R	R′	R″	Yield %	M.p.	Formula	Analysis	% C	% H	% N
XIII	H	CH_3	C_4H_9	95	197–98°	$C_8H_{14}ON_2$	Calc.	62.30	9.15	18.17
							Found	62.50	9.18	18.35
XIV	H	CH_3	C_6H_{11}	95	225–26°	$C_{10}H_{16}ON_2$	Calc.	66.63	8.95	15.55
							Found	66.86	9.09	15.67

1. Oxidation with tert. butylhydroperoxide in anhydrous solution in the presence of sodium ethoxide

As examples the oxidation of 3-methyl-4-ethylpyrazol-5-one (X) and of 3-phenyl-4-benzylpyrazol-5-one (XVIII) are described.

6.3 g (0.05 mole) of X, 30 ml of 2 *N* sodium ethoxide in ethanol (0.06 mole), 75 ml of tertiary butanol and 7.5 ml (0.08 mole) of tert. butylhydroperoxide, prepared as indicated by Milas and Surgenor [15], are mixed at room temperature. A spontaneous reaction starts which causes a slow increase of temperature of the mixture, 35–40° being reached after *ca.* 30 minutes and maintained there for a further hour during which the flask is shaken at intervals. A precipitate separates which after cooling is filtered off and dried over night in a vacuum desiccator. Yield 6.6 g. From the mother liquor further 0.8 g were obtained. Total yield 7.4 g = 90 %, the substance presumed to be XIX, M = 164.1.



XIX: R′ = CH_3, R″ = C_2H_5
XX: R′ = C_6H_5, R″ = $C_6H_5CH_2$

Dissolved in glacial acetic acid the substance may be titrated with perchloric acid, 0.1642 g using up 9.90 ml 0.1000 *N* perchloric acid. M calc. 164.1, found 165.7, *i.e.* purity of the substance 99 %.

The value of pK_B cannot be estimated from the titration curve, the hydroxypyrazolone ion being so strong a base that acetate ions are quantitatively liberated when the sodium salt is dissolved in glacial acetic acid so that the titration curve is practically that of the acetate ion, not that of the hydroxypyrazolone ion (*cf.* Fritz [16]). In Table 3 are recorded the potentiometer readings by titration of the sodium salts of the oxidation products of X and XIV and of acetic acid, one millimole being titrated in each case. It is seen that the figures obtained are identical within the limit of error (purity of the anhydrous sodium acetate and of the sodium salt of the oxidation product of XIV 98 %, of the oxidation product of X 99 %).

The hydroxypyrazolone itself is, as are all the other 4,4-disubstituted pyrazol-5-ones investigated, too weak a base to be titratable with perchloric acid in glacial acetic acid. It is, on the other hand, too weak an acid to be titrated with sodium hydroxide, even if its sodium salt may be isolated in the manner indicated.

The sodium salt is soluble in methanol. Excess methanolic hydrochloric acid is added, sodium chloride precipitated and filtered off. From the filtrate the solvent is removed *in vacuo* (bath temperature *ca.* 40°). The residue crystallises and is purified by recrystallisation from an ethyl acetate-petroleum ether mixture. Yield 85 % m.p. 128–130°. The substance is rather soluble in water, readily soluble in alcohols. For analysis, see Table 1.

The overall yield of the 4-ethyl-4-hydroxypyrazolone from 4-ethyl-pyrazolone is 77 %.

7.5 g (0.03 mole) of XVIII are dissolved in a mixture of 18 ml of 2 *N* sodium ethoxide (0.036 mole) and 40 ml of tert. butanol by heating. 5 ml (0.055 mole) of tert. butylhydroperoxide are added and the mixture kept for 5 minutes at 70° when a solid suddenly precipitates. The mixture is kept at 70° for a further quarter of an hour and shaken at intervals, and then left for a couple of hours at room temperature. When cold the sodium salt is filtered off with suction and dried in a stream of air. Yield quantitative.

0.2902 g of XX are dissolved in 50 ml of glacial acetic acid and titrated with 0.1 *N* perchloric acid in glacial acetic acid. M calc. 288.3, found 290. As for XIX the titration

Table 3. Titration of the sodium salts of the oxidation products of X and XIV and of acetic acid with perchloric acid in glacial acetic acid.

ml 0.1000 *N* perchloric acid in glacial acetic acid	Sodium salts of the oxidation products of X	Sodium salts of the oxidation products of XIV	Sodium acetate
	MV	MV	MV
0.0	93	92	93
1.0	102	101	102
2.0	110	110	109
3.0	117	117	116
4.0	124	124	123
5.0	132	133	131
6.0	141	141	140
7.0	151	152	150
8.0	164	165	165
9.0	188	192	190
9.5	213	231	224
10.0	333	353	355
10.5	369	376	377
11.0	381	386	387
13.0	401	402	404

curve is not that of the hydroxypyrazolone ion but that of the acetate ion. The sodium salt is readily soluble in methanol.

When the salt (8.4 g) is dissolved in water (50 ml) with slight heating another solid suddenly separates out. Evidently the sodium salt is hydrolysed by water. The solution is neutralised with acetic acid, the precipitate filtered off and dried in a vacuum desiccator. Yield 7.5 g (95 %); m.p. 185–86°. Recrystallised from aqueous acetone (50 %) the hydroxypyrazolone is obtained as fine felted needles, from water as a microcrystalline powder; m.p. unchanged 185–86°. For analysis see Table 1.

The sodium salt may also be prepared by oxidation with tert. butylhydroperoxide in ethereal solution. 0.01 mole of the pyrazolone is dissolved in 6 ml of 2 *N* sodium ethoxide. 25 ml of ether are added and a clear solution obtained by shaking. Then 2 ml (0.02 mole) of tert. butylhydroperoxide are added and the solution refluxed for 6 hours on an infra-bath. The sodium salt of the 4-hydroxypyrazolone is precipitated in a more easily filterable form than by the procedure described above. Yield 80 %.

When the sodium salt is treated with acetic anhydride a diacetate is obtained. 2 g of the sodium salt are dissolved in 10 ml of acetic anhydride by heating. The solution is kept over night at room temperature. The next day ether is added to precipitate sodium acetate which is filtered off. The filtrate is distilled *in vacuo* to remove ether and excess acetic anhydride. An oily residue is left which readily crystallises. The crystals are dissolved in ethyl acetate and precipitated with petroleum ether. Yield 1 g (40 %); m.p. 122–23°. (Found: C 68.35; H 5.59; N 7.89. Calc. for $C_{20}H_{18}O_4N_2$: C 68.57; H 5.14; N 8.00.)

2. Oxidation with tert. butylhydroperoxide in aqueous-alcoholic solution in the presence of sodium ethoxide

Here the oxidation of 1-phenyl-3-methyl-4-benzylpyrazol-5-one (V) is described as an example.

13.2 g (0.05 mole) of V, 12 ml 5 *N* aqueous potassium hydroxide (0.06 mole), 50 ml of tert. butanol and 5 ml (0.055 mole) of tert. butylhydroperoxide are mixed and kept at room temperature for 24 hours. The solution assumes a faint yellow colour after 3–4 hours No evolution of heat is observed.

After 24 hours the mixture is acidified with conc. hydrochloric acid and *ca.* 50 ml of water are added. The solution is concentrated *in vacuo* (bath temp. *ca.* 50°) to remove the organic solvent. Hereby a somewhat sticky precipitate is formed which is filtered off and dried in a vacuum desiccator. Yield 11.3 g with m.p. *ca.* 90° which dissolved in ethyl acetate and precipitated with petroleum ether yield 6 g (43 %) of the pure substance with m.p. 145°.

Recrystallised from methanol the hydroxy compound is obtained in long rhombic crystals; m.p. unchanged. For analysis see Table 1.

When methanol is used as solvent instead of tert. butanol a yield of only 30 % is obtained. In anhydrous solution the yield is 95—100 % when the procedure outlined above is followed.

3. Oxidation with tert. butylhydroperoxide in neutral anhydrous solution

5 g (0.025 mole) of II are dissolved in 50 ml of ethanol. 5 ml (0.055 mole) of tert. butylhydroperoxide are added and the mixture refluxed for one hour after which 25 ml of water are added. A precipitate is formed which after 48 hours at room temperature is filtered off and dried. Yield 4.5 g (90 %) of 4,4'-bis(1-phenyl-3-methyl-4-ethylpyrazol-5-one), m.p. 160—165° (*cf.* Veibel and Westöö [17]).

When X is oxidised in this manner no bis-pyrazolone is obtained but only heavy oils which so far have not been further investigated.

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