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Pyrazole Studies

VII *. The Kinetics of Oxidation by Air of 4-Alkylsubstituted Pyrazol-5-ones to 4-Alkyl-4-hydroxysubstituted Pyrazol-5-ones

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The oxidation of some 4-alkylsubstituted pyrazol-5-ones by oxygen has been investigated. With methanol as solvent and triethylamine present in excess the oxidation follows a first order scheme when the concentration of oxygen is kept constant. This means that the velocity of oxidation for a series of pyrazolones may be compared by comparing the time necessary for 50 % oxidation, 1 mole of oxygen being consumed per mole of pyrazolone.

The reaction products, isolated in almost quantitative yield, are the 4-hydroxysubstituted pyrazolone and triethylamine oxide. It has been shown that a substance composed of 2 moles of 4-hydroxysubstituted pyrazolone and 1 mole of triethylamine oxide is formed as a preliminary product which, when treated with water or dilute hydrochloric acid, is decomposed into the hydroxysubstituted pyrazolone and triethylamine oxide.

Veibel and Westöö [1] showed that 4-alkylsubstituted pyrazol-5-ones are spontaneously oxidised by air and that both the corresponding bis-pyrazolone and the 4-hydroxysubstituted pyrazolone could be isolated from the oxidationproducts. The reaction was found catalysed by cupric ions (*cf.* Smith [2]) but no attempt to determine the kinetics of the reaction was made.

By a closer investigation of the reactions we found that they may proceed with measurable velocity also in the absence of cupric ions, the product obtained being dependent on the reaction of the solution. In alkaline solution the 4-hydroxysubstituted pyrazol-5-one may be the only isolable reaction product whereas in neutral solution the bis-pyrazol-5-one is the main product and often the only isolable reaction product.

The reaction seems to proceed most regularly in organic solvents, organic bases being present in great excess, and in this paper only such reactions are investigated. The following technique was applied:

0.01 mole of the pyrazolone was dissolved in methanol. 0.05 moles of triethylamine were added and the solution made up to 25 ml with methanol

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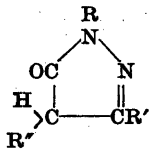
in a 100 ml flask. The air in the flask was expelled by oxygen and the flask was connected with an oxygen-reservoir, formed as a gas-burette, allowing the direct reading of the oxygen absorbed. The flask was mechanically stirred during the experiment in order to secure constant saturation of the solution with oxygen, the concentration of which therefore may be regarded as constant. The reaction proceeds at room temperature but no measures for keeping the temperature strictly constant were taken so that deviations of $\pm$ 3° may have occurred.

The absorption of oxygen was observed. It proceeds regularly, approaching asymptotically 240 ml or 0.01 mole of oxygen per mole of pyrazolone Straight lines are obtained when log (240 — x) is plotted against time (x being ml of oxygen absorbed), showing that the reaction follows a first order scheme (*i.e.* the velocity is proportional to the concentration of pyrazolone, the concentration of oxygen being regarded as constant), so that the velocity of the reaction may be given as the time required for 50 % oxidation.

In Table 1 a summary of the pyrazolones investigated and their velocity of oxidation is recorded.

Table 1. Oxidation of different pyrazolones with oxygen.



R	R′	R″	pK_B	Time for 50 % oxidation	Yield %	M.p. of the hydroxy-pyrazolone
I C_6H_5	CH_3	CH_3	11.3	26 h	95—100	105°
II C_6H_5	CH_3	C_2H_5	11.4	20 h	95—100	130°
III C_6H_5	CH_3	C_3H_7 *n*	11.4	26 h	95—100	116°
IV C_6H_5	CH_3	C_4H_9 *n*	11.4	32 h	95—100	95°
V C_6H_5	CH_3	C_3H_7 *iso*	11.6	22.5 h	95—100	115°
VI C_6H_5	CH_3	C_6H_{11}	11.6	9 h	95—100	110°
VII C_6H_5	CH_3	$C_6H_5CH_2$	11.8	72 h	95—100	145°
VIII CH_3	CH_3	C_2H_5	10.5	7 h	65	38—39°
IX CH_3	CH_3	$C_6H_5CH_2$	10.9	23.5 h	95—100	156°
X C_6H_5	*Cyclo*hexano		11.4	13.5 h	90	145°

When the reaction is finished the solvent is removed by evaporation, leaving an oil which, on treatment with water, is converted into a crystalline 4-hydroxy derivative of the pyrazolone examined. From the aqueous layer trimethylamine oxide may be isolated, most conveniently as the hydrochloride.

In one case, X (Table 1), the oil left on evaporation of the reaction mixture crystallised on standing to a mass of colourless crystals, contaminated by a small amount of oil which could be removed (see below), and the pure substance XI was obtained as colourless leaves of m. p. 120°, *i. e.* another sub-

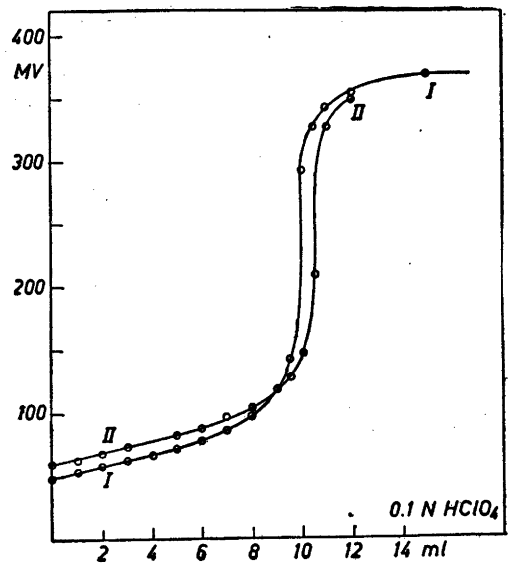
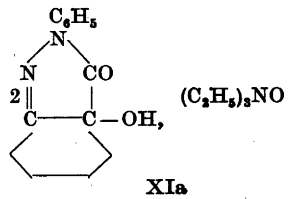


Fig. 1. Titration of XI (curve I) and of triethylamine oxide (curve II) with 0.1 N *perchloric acid. I: 0.5770 g; M = 577.7. II: 0.1237 g; M = 117.2.*

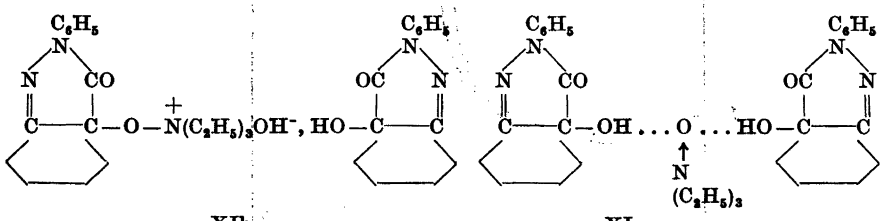
stance than the hydroxypyrazolone. The composition of this substance corresponds to the empirical formula $C_{32}H_{43}O_5N_5$, M = 577.7 (see elementary analysis below). Titrated with perchloric acid in glacial acetic acid (Veibel *et al.*[3]) the molecular weight was found to be 582, the form of the titration curve (Fig. 1, I) showing that the substance is a rather strong base ($pK_B < 9$). Treated with water the crystalline compound behaves as do the oils isolated from the other pyrazolones investigated, *i. e.* the crystals are decomposed into a 4-hydroxy derivative of X and triethylamine oxide, the latter being most conveniently isolated as its hydrochloride when an equivalent amount of hydrochloric acid is added to the substance with M = 577 together with the water. The hydroxy compound separates out and from the filtrate the triethylamine oxide hydrochloride is obtained on evaporation *in vacuo*. The ratio of hydroxy compound to triethylamine oxide isolated is approximately 2 : 1. From this is deduced that the composition of the substance first isolated is:



XIa

The substance is readily soluble in non-polar solvents and in alcohols but is, as mentioned, decomposed by water. The titration curve mentioned above is very similar to the titration curve of triethylamine oxide (Fig. 1, II), and possibly the substance is decomposed by glacial acetic acid into the hydroxy compound and triethylamine oxide.

The m. p. of the substance (120°), its solubility in non-polar solvents and its hydrolysis by water to a substance, the acidic properties of which cannot be detected, and a base, seems to indicate that the substance is not a salt. The following formulations may be discussed, but XI b must be rejected, being too strongly polar to be reconcilable with the properties of the substance.



XIb XIc

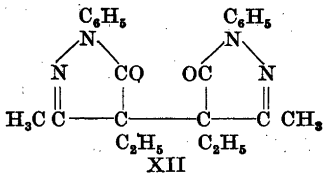
The triethylamine used should be freshly distilled. Incidentally, it was discovered that a sample of triethylamine which had been kept in a glass-stoppered bottle for a long time (1—2 years), thereby being slightly coloured, caused a much faster oxidation than the same sample freshly distilled. With VI as the pyrazolone investigated the time for 50 % oxidation was with the freshly distilled amine 9 hours, with the not purified sample 1.5 hours. In both cases a first order reaction was found by plotting log (240—x) against time, and the 4-hydroxy substituted pyrazolone could be isolated in a nearly quantitative yield.

It was examined whether a sample of distilled triethylamine, kept for one and a half month in a glass-stoppered flask, during which time it had assumed a slight colour and had deposited a trace of an oily substance, would cause a more rapid oxidation than a freshly distilled sample. In this experiment the pyrazolone I was oxidised. The time for 50 % oxidation was with freshly distilled triethylamine 26 hours, with the other sample of triethylamine 27 hours, this difference not exceeding the limit of error in the determination.

The nature of the impurity causing the strong acceleration of the velocity of oxidation when very old samples of triethylamine are used has not been further investigated so far.

Cupric ions accelerate the oxidation very strongly but the result of the oxidation is different from that obtained in absence of cupric ions. To a standard experiment with oxidation of the pyrazolone II (time for 50 % oxidation 20 hours) was added one drop of a 0.1 N solution of cupric sulphate, *i. e.* $c_{Pyrazolone} = 0.4\ M$, $c_{Cu^{++}} \leqq 0.0004\ N$. No appreciable absorption of oxygen occurred during the first half hour, but then suddenly absorption of oxygen started, accompanied by a recognisable evolution of heat. After 10 minutes the reaction was over, 100 ml of oxygen having been absorbed against the calculated 240 ml. The reaction products were dark coloured and obviously

more than one substance had been formed. The only substance which we succeeded in isolating in a state of purity was the bis-pyrazolone XII:



XII

4-Substituted pyrazolones may be oxidised to 4-substituted 4-hydroxy-pyrazolones by tert. butylhydroperoxide too. The stoichiometry of this reaction will be described in a subsequent paper. The result may, however, indicate that peroxides are taking part in the oxidation investigated here, a possible course of the reaction being the following where PyRH means a 4-monoalkylsubstituted pyrazol-5-one, possibly alkyl- or arylsubstituted at N_1 and at C_3.

$$PyRH + (C_2H_5)_3N \rightleftharpoons PyR^- + (C_2H_5)_3\overset{+}{N}H \quad (1)$$

$$PyR^- + O_2 \rightarrow PyROO^- \quad (2)$$

$$2\ PyROO^- + 2\ (C_2H_5)_3\overset{+}{N}H \rightarrow PyROH\ldots\underset{\displaystyle N(C_2H_5)_3}{\underset{|}{O}}\ldots HORPy + (C_2H_5)_3NO \quad (3)$$

$$PyROH\ldots\underset{\displaystyle N(C_2H_5)_3}{\underset{|}{O}}\ldots HORPy + H_2O \rightarrow 2\ PyROH + (C_2H_5)_3N(OH)_2 \quad (4)$$

This sequence of reactions covers the stoichiometry of the reaction. Examples of oxygen atoms acting as receptors for two hydrogen bonds are given by Pauling [4], who mentions substances where a carbonyl oxygen with only two lone electron pairs acts as receptor for two hydrogen bonds, whereas the oxygen atom in the amine oxide presumed in the present paper has three lone electron pairs and therefore should be still more liable to act as receptor for hydrogen bonds than the carbonyl oxygen.

As to the kinetics of the reaction it has to be presumed that (2) is the velocity determining step as the reaction follows a first order scheme when the concentration of oxygen is kept constant.

The velocity of the reaction is dependent on substituents present both at N_1 and at C_4. Table 1 gives a record of the time necessary for 50 % oxidation of the pyrazolones investigated. It is seen that an aryl group at N_1 decreases the velocity as compared with 1-alkylsubstituted pyrazolones.

The 4-alkylsubstituted pyrazolones examined are oxidised at nearly the same rate when the substituent at N_1 is kept constant. When a *cyclo*hexyl-radical is substituted for an alkyl-radical the velocity is considerably increased whereas the substitution of an alkyl group with a benzyl group decreases the velocity sensibly. For the pyrazolones investigated the following expressions hold good:

$$\left[\frac{t^{C_2H_5(C_4)}_{50\ \%}}{t^{C_6H_5CH_2(C_4)}_{50\ \%}}\right]_{C_6H_5(N)_1} = \left[\frac{t^{C_2H_5(C_4)}_{50\ \%}}{t^{C_6H_5CH_2(C_4)}_{50\ \%}}\right]_{CH_3(N_1)} = 0.30$$

$$\left[\frac{t^{CH_3(N_1)}_{50\ \%}}{t^{C_6H_5(N_1)}_{50\ \%}}\right]_{C_6H_5(C_4)} = \left[\frac{t^{CH_3(N_1)}_{50\ \%}}{t^{C_6H_5(N_1)}_{50\ \%}}\right]_{C_6H_5CH_2(C_4)} = 0.34$$

or: *the relation between the time for 50 % oxidation of pyrazolones with different substituents at C_4 is independent of the substituent at N_1*, and *the relation between the time for 50 % oxidation of pyrazolones with different substituents at N_1 is independent of the substituent at C_4.*

Table 1 records the pK_B-values of the pyrazolones too, most of them taken from a preceding paper (Veibel *et al.*[5]). It is seen that there is no direct dependency of the rate of oxidation on the pK_B of the pyrazolone.

The investigation on the oxidation of pyrazolones is continued.

EXPERIMENTAL PART *

The pyrazolones investigated were prepared by current methods. For I—III, V—VI, and VIII see Veibel *et al.*[5], for IV, VII, and X see [6-8], respectively. The pK_B values recorded in Table 1 were determined as indicated by Veibel *et al.*[5].

1,3-Dimethyl-4-benzylpyrazol-5-one (IX). A mixture of 66 g (0.3 mole) of ethyl α-benzylacetoacetate, 100 ml of methanol and 300 ml of *N* methylhydrazine solution (Veibel *et al.*[5]) are stirred mechanically at 70° for 8 hours. Methanol and most of the water are then removed *in vacuo* (bath temperature 50°), the pyrazolone crystallising from the residue on cooling. It may be recrystallised from water, aqueous ethanol or ethyl acetate. Yield 70 %; m.p. 155°. (Found: C 71.17; H 7.03; N 13.83. Calc. for $C_{12}H_{14}ON_2$ (202.2): C 71.27; H 6.98; N 13.86.)

Oxidation of pyrazolones. The technique applied has been described above. The experiment is interrupted when oxygen is not absorbed longer. The solvent is removed *in vacuo* (bath temperature ca. 40°). The oily residue is dissolved in a minimum amount of methanol, water is added and the mixture shaken mechanically for half an hour during which an oil separates out. The oil is extracted with ether and the ethereal layer is extracted twice with water. The ether is removed at room temperature leaving a solid colourless or slightly coloured substance usually in a nearly quantitative yield. The substance may be recrystallised from ligroin (b.p. 100—140°) or purified by treatment of its methanolic solution with absorption carbon, removing the solvent *in vacuo* after filtration.

From the aqueous layer triethylamine oxide may be isolated as its hydrochloride after addition of the equivalent amount of hydrochloric acid and evaporation on the steam bath.

As an example the isolation and purification of the hydroxy compound in an experiment with 5 times the standard amount of pyrazolone shall be described.

7 g (0.05 mole) of 1,3-dimethyl-4-ethylpyrazol-5-one and 35 ml (0.25 mole) of triethylamine were diluted with methanol to 125 ml in a flask. The flask was connected with an oxygen-reservoir and shaken mechanically for 24 hours during which 1 100 ml of oxygen were absorbed (calculated 1 200 ml of oxygen). The solvents were removed *in vacuo* (bath temperature 40—50°), leaving a viscous oil which was shaken for 1 hour with 15—20 ml of water and 0.05 mole of concentrated hydrochloric acid. Then 200 ml of ether were

* All m.p.s uncorrected; microanalyses by Mr. W. Egger, Department of Organic Chemistry, University of Copenhagen.

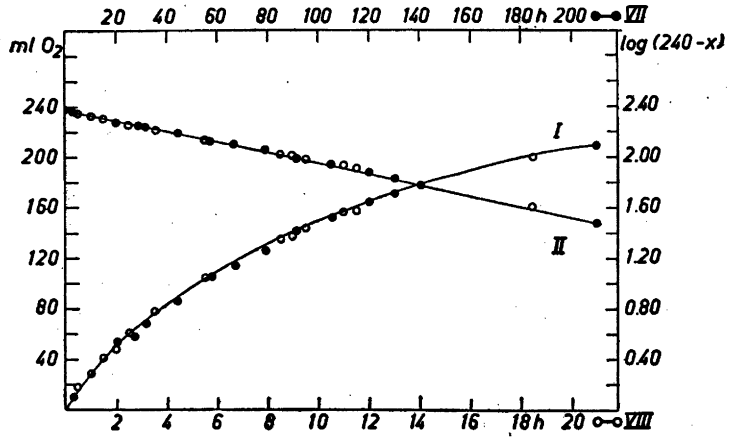


Fig. 2. Uptake of oxygen (curve I) and log (240−x) (curve II) for the pyrazolones VII (○——○) and VIII (●——●).

added and sufficient anhydrous calcium chloride to absorb the water. After 5—6 hours the solution was filtered and the ether removed from the filtrate *in vacuo*, leaving a viscous oil which eventually crystallised. M.p. *ca.* 30°, yield 7 g, calculated for 1,3-dimethyl-4-ethyl-4-hydroxypyrazol-5-one 7.8 g, *i. e.* a yield of 90 %. The hydroxy compound may be distilled *in vacuo*, b.p. 140°$_{15\ mm}$. It may be purified by recrystallisation from ethyl acetate-petroleum ether, using absorption carbon to decolourise the solution. The filtrate is chilled to −40°i n order to improve the yield which was 5 g or 65 % with m.p. 38—39°. (Found: C 53.93; H 7.81; N 18.05. Calc. for $C_7H_{12}O_2N_2$ (156.2): C 53.84; H 7.70; N 17.94.)

When 1-phenyl-3,4-*cyclo*hexanopyrazol-5-one (X) is oxidised it is possible to isolate an intermediate compound in a crystalline state:

10.7 g of X and 35 ml of triethylamine were dissolved in methanol to 125 ml, the flask connected with the oxygen-reservoir and shaken mechanically for 48 hours, 1 150 ml of oxygen being absorbed during this time (calculated 1 200 ml). The solvents were removed *in vacuo*, leaving a viscous oil which crystallised when left for some time (or during the evaporation of the solvents). Yield 16.95 g, m.p. 95—100°. The crystals include some oil which, however, is insoluble in warm hexane in which the crystals are soluble. The solution is decolourised with absorption carbon and filtered, the filtrate depositing colourless crystal leaves on cooling. M. p. 120°.

Another way of removing the oil is by dissolving the crystals in ethyl acetate and slowly adding petroleum ether or low boiling ligroin. The oil is first precipitated; the supernatant solution is decanted from the oil and on further addition of petroleum ether the pure substance XI is obtained. Yield of pure substance 12 g = 80 %.

This substance is readily soluble in acetone, chloroform, methanol and other alcohols, benzene and ethyl acetate, somewhat soluble in ether from which solvent it may be recrystallised. It is slightly soluble in petroleum ether. Its composition corresponds to the formula $C_{32}H_{43}O_5N_5$ or two moles of the hydroxy compound and one mole of triethylamine oxide. (Found: C 66.68; H 7.60; N 12.29. Calc. for $C_{32}H_{43}O_5N_5$ (XI) (577.7): C 66.53; H 7.50; N 12.12).

2.9 g of this substance (0.005 mole) was dissolved in 25 ml 0.2 *N* hydrochloric acid (0.005 mole) and heated to boiling for a few minutes. On cooling 2.2 g of a substance (XIII) with m.p. 145° was precipitated. The filtrate was evaporated to dryness *in vacuo*, leaving a substance XIV with m. p. ca. 150°, containing ionogenic chlorine.

The same two substances were obtained by shaking 2.9 g of XI mechanically with 6 ml *N* hydrochloric acid (20 % excess) for half an hour. The crystal leaves of the original compound were converted into a finegrained crystal powder which was filtered off, washed

Table 2. Absorption of oxygen.

Pyrazolone																			
I		II		III		IV		V		VI		VII		VIII		IX		X	
Time h	O_2 ml	Time h	O_2 ml	Time h	O_2 ml	Time h	O_2 ml	Time h	O_2 ml	Time h	O_2 ml	Time h	O_2 ml	Time h	O_2 ml	Time h	O_2 ml	Time h	O_2 ml
1	7	1	7	0.5	4	1	5	1	10	0.25	4	3	10	0.5	19	0.5	3	0.5	5
2	14	2	13	1	6	2	8	2	14	0.5	10	6	21	1	29	1	5	1.75	11
3	21	2.5	16	7.5	44	2.5	12	2.5	18	0.75	15	8	23	1.5	42	8	45	3	30
4	26	3	20	9	47	3	13	3.5	22	1	20	9	25	2	54	10.5	56	4	39
8	46	4	26	19.5	88	3.5	14	4.5	30	1.5	30	20	48	2.5	62	11.5	63	5	50
9	52	8	53	21.5	95	7	31	5.5	38	2	38	27	58	3.5	77	12.5	69	9	85
21	101	10	67	24	105	13	57	6	43	3	56	29	63	5.5	104	15.5	86	12	111
26	118	11	73	30	131	23.5	87	6.5	45	3.5	64	31.5	66	8.5	134	16.5	92	13	117
31	138	13.5	93	32	137	27.5	100	7	49	4	71	44	85	9	138	17.5	98	14	123
45	178	23	127	44	168	29	104	10	70	5.5	90	57	105	9.5	143	33.5	154	23	170
		27	140	49	180	35	127	11	75	6	94	66.5	113	10.5	151	35.5	156	25	178
		31.5	156	53	191	47	152	13	85	12.5	147	79	126	11	154	39.5	164	26	183
		37.5	175	69	220	51.5	162	24	123	20	180	91	139	11.5	157	57	190	28	187
		47.5	195			57.5	177	26	130			105	152	18.5	199	61	193	29	190
		52	204			59.5	181	28	135			120	164					46	221
								30	143			130	170					49	223
								33	154			140	178					51	226
								35	158			210	210						
								37	163										
								47.5	185										
								60.5	211										
								70	220										

with water and dried in a vacuum-desiccator. Yield 2.20 g with m. p. 140° which could be raised to 145° by recrystallisation from a minimum amount of ethyl acetate or an ethyl acetate-petroleum ether mixture. The filtrate was extracted with ether. The colourless aqueous layer was evaporated to dryness *in vacuo*, the residue dissolved in methanol and precipitated with ether, yielding 0.7 g of a compound with m. p. 152—153° (dec.). For the hydrochloride of triethylamine oxide is indicated m. p. 154° (dec.), for the hydrochloride of triethylamine m. p. 253—254°, and the m. p. of XIV was not depressed by admixture of an authentic sample of triethylamine oxide hydrochloride.

$$\underset{\text{XI}}{C_{32}H_{43}O_5N_5} + HCl \rightarrow 2\ \underset{\text{XIII}}{C_{13}H_{14}N_2O_2} + \underset{\text{XIV}}{(C_2H_5)_3N\langle^{OH}_{Cl}}$$

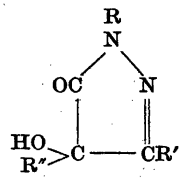
(Found: C 68.08; H 6.03; N 12.26. Calc. for $C_{13}H_{14}N_2O_2$ (XIII) (230.2): C 67.81; H 6.13; N 12.17.)

Further investigation of XI showed that it may be titrated with perchloric acid in glacial acetic acid and that the titration curve is practically identical with that of triethylamine oxide. In Fig. 1, curve I is the titration curve of XI, curve II that of triethylamine oxide.

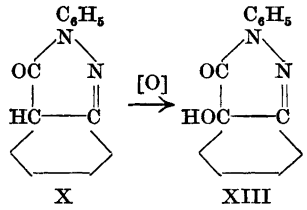
If XI was a salt of triethylamine oxide (which is hardly possible when its behavior towards solvents is taken into consideration) triethylamine oxide picrate should be precipitated on addition of a methanolic solution of XI to a saturated solution of picric acid in methanol. No such precipitation takes place.

Evidently XI is decomposed by hydrochloric acid into two new compounds, one of which is triethylamine oxide hydrochloride. The other one is a hydroxy derivative of the pyrazolone X, a hydroxy group being substituted for a hydrogen atom at C_4:

Table 3. Analyses of some pyrazolones



	R	R′	R″	Formula		% C	% H	% N
I ox	C_6H_5	CH_3	CH_3	$C_{11}H_{12}O_2N_2$	Calc.	64.68	5.93	13.72
					Found	64.72	5.86	13.89
II ox	C_6H_5	CH_3	C_2H_5	$C_{12}H_{14}O_2N_2$	Calc.	66.04	6.47	12.84
					Found	66.17	6.59	12.77
III ox	C_6H_5	CH_3	C_3H_7 *n*	$C_{13}H_{16}O_2N_2$	Calc.	67.20	6.94	12.06
					Found	67.32	7.21	11.96
IV ox	C_6H_5	CH_3	C_4H_9 *n*	$C_{14}H_{18}O_2N_2$	Calc.	68.27	7.37	11.38
					Found	68.34	7.18	11.50
V ox	C_6H_5	CH_3	C_3H_7*iso*	$C_{13}H_{16}O_2N_2$	Calc.	67.20	6.94	12.06
					Found	67.42	6.96	12.28
VI ox	C_6H_5	CH_3	C_6H_{11}	$C_{16}H_{20}O_2N_2$	Calc.	70.57	7.40	10.29
					Found	70.70	7.23	10.41
VII ox	C_6H_5	CH_3	$C_6H_5CH_2$	$C_{17}H_{16}O_2N_2$	Calc.	72.85	5.75	10.00
					Found	72.81	5.64	10.23
VIII ox	CH_3	CH_3	C_2H_5	$C_7H_{12}O_2N_2$	Calc.	53.84	7.70	17.94
					Found	53.93	7.81	18.05
IX ox	CH_3	CH_3	$C_6H_5CH_2$	$C_{12}H_{14}O_2N_2$	Calc.	66.02	6.47	12.84
					Found	66.24	6.32	12.89
X ox	C_6H_5	*Cyclo*hexano		$C_{13}H_{14}O_2N_2$	Calc.	67.81	6.13	12.17
					Found	68.08	6.03	12.26



X XIII

By the titration of XI with perchloric acid the molecular weight of XI was found to be 582 (0.5770 g of substance require 9.9 ml of 0.1 *N* perchloric acid in glacial acetic acid). This and the amounts of XIII and XIV isolated indicate that XI is composed of two moles of XIII and one mole of XIV. For XI the structure indicated above (XI c, p. 1010) is proposed.

When other pyrazolones were oxidised we did not succeed in isolating the primary oxidation product in a crystalline form but only as oils which upon treatment with hydrochloric acid were decomposed into the corresponding hydroxy-substituted pyrazolone and triethylamine oxide or its hydrochloride. In Table 1 is indicated the yield and the m.p. of the different hydroxy-substituted pyrazolones. In Fig. 2 the absorption of oxygen is plotted against time for two typical pyrazolones and in Table 2 the oxygen uptake of all the pyrazolones investigated is recorded. Finally, Table 3 is a summary of the analyses of all the 4-hydroxy-substituted pyrazolones prepared.

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