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Pyrazole Studies

XI.* Oxidation by Air of 1:4-Disubstituted Pyrazolidine-3:5-diones

STIG VEIBEL, S. LINHOLTER and P. SØRENSEN

Department of Organic Chemistry, University of Technology, Copenhagen, Denmark

Previously reported studies on the triethylaminecatalysed oxidation by air of 4-alkylsubstituted pyrazol-5-ones have been extended to embrace 1:4-disubstituted pyrazolidine-3:5-diones. These substances are oxidised to the corresponding 4-hydroxysubstituted compounds considerably faster than the pyrazolones, and the scheme followed is another, no triethylamine oxide being formed simultaneously and further oxidation to unidentified products taking place more readily than in the case of the pyrazolones.

The identity of a substance mentioned by Gagnon *et al.* as 1:4-diphenylpyrazolidine-3:5-dione with phenylacetic acid phenylhydrazide has been suggested and the genuine 1:4-diphenylpyrazolidine-3:5-dione has been prepared.

In a previous communication [1] we were able to show that 4-alkylsubstituted pyrazol-5-ones in methanolic solution are oxidised by air to 4-alkyl-4-hydroxysubstituted pyrazol-5-ones, this oxidation, in the presence of triethylamine in excess and at constant concentration of oxygen, following a first order scheme, one molecule of oxygen being absorbed per molecule of pyrazolone and one molecule of triethylamine oxide being formed simultaneously.

In view of the growing significance of substituted pyrazolidine-3:5-diones we decided to investigate the oxidation of these substances under conditions similar to those being in force in the investigations mentioned. We found that the pyrazolidine-3:5-diones are oxidised extremely readily under these conditions, but the scheme is not so clear-cut as in the instance of the pyrazol-5-ones where a first order scheme was followed usually at least up to 80 % completion and the hydroxy-compound could be isolated in 95—100 % yield. With the pyrazolidine-3:5-diones the absorption of oxygen usually comes to an end when about 66—75 % of the calculated volume of oxygen has been absorbed, presuming the absorption of one mole of oxygen per mole of pyrazolidinedione. The velocity with which oxygen is absorbed is considerably greater

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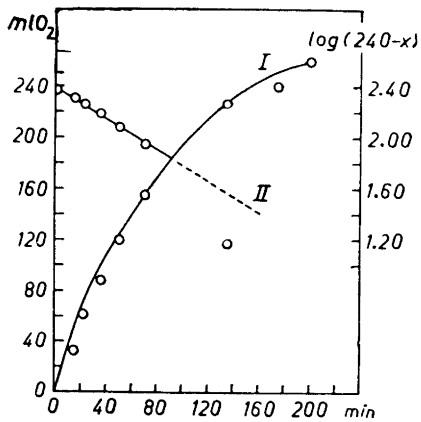


Fig. 1. Oxidation of a 0.02 M solution of 4-butylpyrazolidine-3:5-dione.
Curve I (ordinates left): Uptake of oxygen.
Curve II (ordinates right): log(240—x).

in the case of the pyrazolidinediones than in the case of the pyrazolones, and no triethylamine oxide can be isolated from the reaction products.

This means that only one *atom* of oxygen per molecule of pyrazolidinedione is demanded for the oxidation to the hydroxy compound, and the total consumption of oxygen is thus somewhat greater than calculated. As, however, the yield of hydroxy compound isolated is only some 50—75 %, and as the formation of oily products is always observed, we are of the opinion that the formation of the hydroxy compound is followed by a hydrolytic cleavage of the pyrazolidine-nucleus and possibly an oxidation of the substituted tartronic acid monophenylhydrazide formed (compare the following paper), this oxidation being responsible for the excess of oxygen consumed. As seen from Fig. 1, which is representative for all the oxidations, a first order scheme is followed up to some 60 % oxidation, presuming that only 1 atom of oxygen is used per molecule. This means that we here as in the case of the pyrazolones may compare the velocities of oxidation by indicating the time necessary for the absorption of 50 % of the calculated volume of oxygen.

A possible sequence of reactions might be:

$$\mathrm{PyRH} + (\mathrm{C_2H_5})_3\mathrm{N} \rightleftharpoons \mathrm{PyR^-} + (\mathrm{C_2H_5})_3\mathrm{NH^+}$$

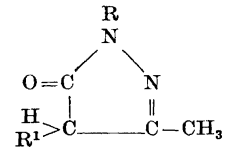
$$\mathrm{PyR^-} + \mathrm{O_2} \rightleftharpoons \mathrm{PyROO^-}$$

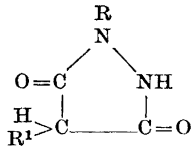
$$\mathrm{PyROO^-} + \mathrm{PyR^-} \longrightarrow 2\ \mathrm{PyRO^-},$$

PyRH meaning a 4-substituted pyrazolidine-3:5-dione.

The difference between the oxidation of pyrazolones and pyrazolidinediones should, thus, depend on the oxidation potentials of the pyrazolone anion, the triethylammonium ion and the pyrazolidinedione anion, decreasing in this order if the explanation given here is the correct one.

Table 1. Oxidation of different pyrazolones and pyrazolidine-diones with oxygen.





R	R^1	Time for 50 % oxidation	R	R^1	Time for 50 % oxidation
C_6H_5	CH_3	26 h	C_6H_5	CH_3	2 min
C_6H_5	C_2H_5	20 h	C_6H_5	C_2H_5	2.5 min
C_6H_5	C_3H_7*iso*	22.5 h	C_6H_5	C_3H_7*iso*	14 min
C_6H_5	C_4H_9	32 h	C_6H_5	C_4H_9	50 min
C_6H_5	C_6H_{11}	9 h	C_6H_5	C_6H_{11}	60 min
C_6H_5	$C_6H_5CH_2$	72 h	C_6H_5	$C_6H_5CH_2$	14 min
			C_6H_5	C_6H_5	4 min
			C_6H_5	$(C_6H_5)_3C$	—

The technique applied was that described previously [1]. Table 1 summarises the results obtained and gives a comparison of oxidation rates for corresponding pyrazol-5-ones and pyrazolidine-3:5-diones.

It is seen from Table 1 that we extended the investigation to the oxidation by air of 1:4-diphenylpyrazolidine-3:5-dione and of 1-phenyl-4-triphenylmethylpyrazolidine-3:5-dione. The former of these two substances was oxidised readily, the latter was not oxidised at all.

A comparison of columns 3 and 6 of Table 1 shows that not only are the rates of oxidation much higher for the pyrazolidinediones than for the pyrazolones, but the influence of the substituent present at C^4 is quite different in the two series. The 4-*cyclo*hexylpyrazolone is the one most rapidly oxidised, whereas the 4-*cyclo*hexylpyrazolidinedione is the one most slowly oxidised in the series of pyrazolidinediones investigated. So far, we have found no explanation covering this difference, but the mechanism followed in the two series is, as mentioned, quite different.

The presence of a phenyl group (or possibly also other substituents) at N^1 seems to be essential for the oxidisability of the pyrazolidinediones. 4-Benzylpyrazolidine-3:5-dione was not oxidised when the usual technique was applied. By addition of some crystals of cupric acetate, however, the absorption of oxygen was started and some 60 % of the volume calculated for the formation of the hydroxy compound was absorbed during 2 h. We did not succeed in isolating a definite oxidationproduct. Evidently an oxidative degradation of the cyclic compound takes place.

On the other hand, we succeeded, when oxidising 4-benzylpyrazolidine-3:5-dione in the absence of triethylamine, in isolating after 13 h, when 1 mole of oxygen per mole of pyrazolidinedione had been absorbed, a small quantity of a substance with m.p. 159—161° which contained 9.33 % of nitrogen, calculated for the 4-hydroperoxide of the pyrazolidinedione 9.28 % N. The main product was, however, an oil which was not further investigated but which,

in analogy to results obtained with butazolidine (see the following paper) might be impure benzyltartronic acid monophenylhydrazide or the free benzyltartronic acid.

EXPERIMENTAL PART *

The pyrazolidine-3:5-diones were prepared by current methods [2,3]. The yields obtained and the m. p.'s found as well as those indicated in the literature are tabulated in Table 2, whereas Table 3 contains the corresponding figures for the 4-hydroxypyrazolidine-3:5-diones.

Table 2. 1-Phenyl-4-alkyl-pyrazolidine-3:5-diones.

	Alkyl	Yield %	M. p.	M. p. Literature		C %	H %	N %
I	CH_3	70	168–170°	—	calc.	63.15	5.26	14.73
					found	62.90	5.42	14.76
II	C_2H_5	75	108–109°	108° [4,5]		—	—	—
III	C_3H_7*iso*	70	114–115°	110° [6]		—	—	—
IV	C_4H_9	75	94–95°	94° [5]		—	—	—
V	C_6H_{11}	80	154–156°	—	calc.	69.76	7.00	10.85
					found	69.70	6.99	10.75
VI	$C_6H_5CH_2$	75	183–185°	—	calc.	72.14	5.26	10.45
					found	72.95	5.37	10.44
VII	$(C_6H_5)_3C$	90	225–235°	—	calc.	80.00	5.42	6.89
					found	79.55	5.54	6.48
VIII	C_6H_5	*ca.* 5	218–220°	—	calc.	71.43	4.71	11.11
					found	70.80	5.14	10.95

Table 3. 1-Phenyl-4-alkyl-4-hydroxypyrazolidine-3:5-diones.

	Alkyl	Yield %	M. p.		C %	H %	N %
I	CH_3	70	207–208°	calc.	58.25	4.89	13.58
				found	58.15	4.92	13.48
II	C_2H_5	50	175–176°	calc.	60.00	5.49	12.72
				found	60.20	5.73	12.56
III	C_3H_7*iso*	50	175°	calc.	61.54	6.00	11.95
				found	61.81	6.21	12.12
IV	C_4H_9	75	174–175°	calc.	62.90	6.41	11.30
				found	62.70	6.39	11.39
V	C_6H_{11}	75	148°	calc.	65.70	6.61	10.21
				found	65.95	6.86	10.36
VI	$C_6H_5CH_2$	75	225°	calc.	68.09	5.00	10.00
				found	68.10	5.20	9.80
VIII	C_6H_5	75	210–212°	calc.	67.10	4.47	10.40
				found	66.90	4.38	10.26

The substance VII, 1-phenyl-4-triphenylmethylpyrazolidine-3:5-dione, was prepared in analogy to 1-phenyl-3-methyl-4-triphenylmethylpyrazol-5-one [7] by refluxing 1.95 g of triphenylcarbinol and 1.50 g of 1-phenylpyrazolidine-3:5-dione dissolved in 10 ml of glacial acetic acid and 3 drops of concentrated hydrochloric acid. After 45 min refluxing a substance precipitated which was not redissolved by addition of glacial acetic acid. After cooling some ml of water were added and the substance was isolated by suction, washed on the filter with methanol and dried.

* All microanalyses by Mr. Preben Hansen, Department of Organic Chemistry, University of Copenhagen.

In preparing VIII the yield was very poor, only some few (5) % of a substance with m. p. 218—220° and the composition calculated for 1:4-diphenylpyrazolidine-3:5-dione, $C_{15}H_{12}O_2N_2$ (252.3) as indicated in Table 2. This substance is soluble in alkali, leaving behind a substance insoluble in alkali. The alkali-insoluble substance was recrystallised from ethanol and isolated in a yield of 90 % with m. p. 166—167° (uncorr.). It was recognised as phenylacetic acid phenylhydrazide, $C_6H_5CH_2CONHNHC_6H_5$, $C_{14}H_{14}ON_2$ (226.3). (Found C 74.10; H 6.40; N 12.42. Calc. C 74.34; H 6.22; N 12.40.) The hydrazide has been prepared by Schott [8] who indicates m. p. 168—170°. Gagnon *et al.*[9] report the preparation of 1:4-diphenylpyrazolidine-3:5-dione which they describe as an alkali-insoluble substance with m. p. 172—173°, containing 11.60 % N. We think it reasonable to regard this substance as the phenylhydrazide, the cyclisation evidently taking place less readily in this instance than in the instance of alkylsubstituted malonic esters.

The formation of minor amounts of alkaliinsoluble substances was observed in the preparation of most of the substances I—IV. In one instance we isolated the alkali-insoluble substance which showed a composition in accordance with the corresponding phenylhydrazide, the formation of which may be explained by the scheme:

$$RCH{<}^{COOE}_{COOE} + C_6H_5NHNH_2 \longrightarrow RCH{<}^{CONHNHC_6H_5}_{COOE} \xrightarrow{NaOE}$$

$$RCH{<}^{CONHNHC_6H_5}_{COONa} + EOH \xrightarrow{HCl} RCH_2CONHNHC_6H_5 + CO_2 + EOH + NaCl.$$

Accordingly, we observed a slight liberation of carbon dioxide upon acidification of the reaction mixture when alkylmalonic esters were reacted with phenylhydrazine, but in the case of phenylmalonic ester the liberation of carbon dioxide was much stronger than usually.

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