

## Pyrazole Studies

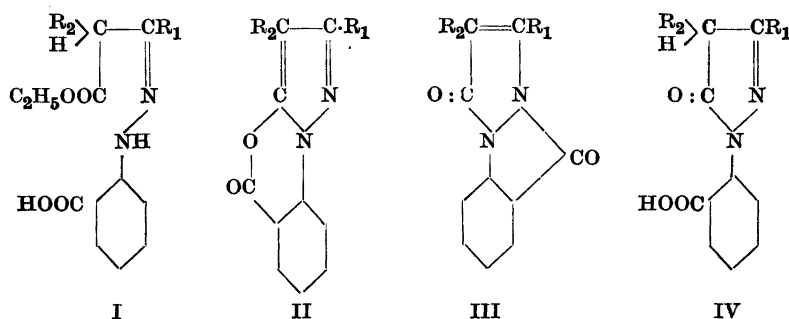
### III. Further Investigations on the $\alpha$ - and $\beta$ -Lactones of some 1-(2'-Carboxyphenyl)-pyrazolones-5 (Pyrazoisocoumarazones)

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In two previous papers<sup>1,2</sup> one of us have described the preparation of some *o*-carboxyphenylhydrazones of esters of  $\beta$ -ketoacids and has shown that such *o*-carboxyphenylhydrazones (I), as first described by Michaelis<sup>3</sup>, by heating above their melting point not only, as other phenylhydrazones of  $\beta$ -ketoacids, form pyrazolones (IV) by ring closure, but that the 1-(2'-carboxyphenyl)-pyrazolones-5 thus formed by further ring closure loose 1 mol of water and form anhydrides which by Michaelis and by us were considered as lactones of the enolised form of the pyrazolones (II) and by Michaelis were termed pyrazoisocoumarazones.

So far nothing unusually is to be seen in the formation of these lactones. But Michaelis was able to show that with  $R_1 = \text{CH}_3$ , and  $R_2 = \text{H}$  (II) exists in two different modifications,  $\alpha$  and  $\beta$ , which are mutually interconvertible



and are not dimorphous forms of the lactone, as bromination leads to two different monobromocompounds. With  $R_1 = \text{C}_6\text{H}_5$ ,  $R_2 = \text{H}$  Michaelis did

not succeed in preparing two modifications of the lactone, but in one of the above mentioned papers <sup>2</sup> we were able to show that not only with  $R_1 = C_6H_5$ ,  $R_2 = H$ , but also with  $R_1 = CH_3$ ,  $R_2 = C_2H_5$  two modifications of the lactones may be prepared.

A simple explanation of the existence of two substances with the composition as an anhydride of IV would be that one is the lactone II, the other the lactim III. This explanation, however, we found it necessary to abandon as we found that the  $\beta$ -series of the anhydrides may be titrated in ethanolic solution as monobasic acids, whereas the  $\alpha$ -series cannot be directly titrated, but only with delay, caused by a previous rearrangement of the  $\alpha$ -modifications to the  $\beta$ -modifications.

The natural explanation that the different velocity with which the two modifications is titrated is due to a difference in velocity of opening of the lactone-ring and the lactim-ring had to be abandoned as we were able to show that the acids IV resulting from such a ring-opening are titrated as dibasic acids (with the exception of the acid with  $R_1 = CH_3$ ,  $R_2 = C_2H_5$  which is titrated as a monobasic acid).

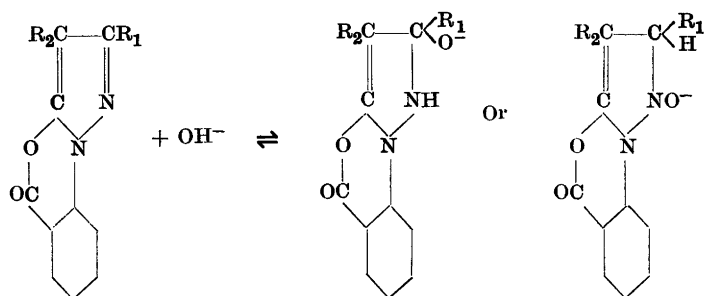
So far, the proof that the  $\alpha$ -modifications are rearranged to the  $\beta$  modifications before or during the titrations has been only indirect, but now we think that we have been able to produce a direct proof of this transformation. We have neutralised the two modifications with 1 equivalent of base and then added the equivalent amount of hydrochloric acid, whereupon we have isolated the substances resulting from these operations. In both series it is the  $\beta$ -modification which may be isolated after these treatments.

We then examined the possibility that the two series of anhydrides were due to polymerism so that the  $\alpha$ -lactones were dimeres or polymeres of the  $\beta$ -lactones. But cryoscopic determinations of the molecular weights of the  $\alpha$ - and the  $\beta$ -lactones proved that both series are monomeres with molecular weights corresponding to the formulas II or III so that this possibility, too, had to be abandoned. With  $R_1 = CH_3$  and  $R_2 = H$  or  $C_2H_5$  the  $\alpha$ -modification shows a higher melting point than the  $\beta$ -modification whereas with  $R_1 = C_6H_5$ ,  $R_2 = H$  the opposite is the case. But in all three cases it is the  $\beta$ -modification which may be titrated directly. In order to find a further proof of the analogous structure of the 3  $\alpha$ -lactones on one hand, the 3  $\beta$ -lactones on the other hand, we determined the dipole moments of the 6 lactones and found that the 3  $\alpha$ -lactones have relatively small dipole moments ( $\mu = 1.33$ — $1.89$ ), the 3  $\beta$ -lactones relatively great dipole moments ( $\mu = 2.53$ — $2.80$ ). These results show with practically absolute certainty that the structure of all 3  $\alpha$ -lactones on one hand and the 3  $\beta$ -lactones on the other hand are analogous. It may further be concluded that the possibility mentioned in one

of the previous papers <sup>2</sup>, namely that the acidic properties of the  $\beta$ -lactones was due to a repartition of the electrical charges on the carbon atoms of the pyrazolone ring facilitating the splitting off of the hydrogen atom at  $C_4$  as a proton, cannot be correct as such a repartition of the charges would implicate a dipole moment much greater than the dipole moments found for the  $\beta$ -lactones. These measurements thus corroborate the conclusions arrived at in the previous papers, where it was the fact that even with  $R_2 = C_2H_5$  the  $\beta$ -modification may be titrated which was not reconcilable with the assumption, but if the dipole moment of the  $\alpha$ -lactone with  $R_2 = C_2H_5$  did not fit in with the dipole moments of the other  $\alpha$ -lactones the assumption might still be valid if  $R_2 = H$ , and another explanation had to be found for lactones with  $R_2$  different from H.

From the values of the dipole moments of the two series it may be concluded that the  $\beta$ -modifications correspond to formula II, the dipole moment being determined principally by the carbonyl-groups, from which II contains one, and III two acting in opposite directions.

From the two formulas proposed II is the only one which may possibly be able to neutralise bases. It contains a  $C = N$ -double bond to which a hydroxyl ion may be added as  $O^-$  and H:



Different mesomeric (or tautomeric) formulas may be considered, too. By addition of acid (hydrogen ion) the hydroxyl ion is eliminated and the  $\beta$ -modification is reformed.

The  $\alpha$ -modification, on the other hand, does not contain a  $C = N$ -double bond and is, therefore, not able to add a hydroxyl ion. As a delayed titration of the  $\alpha$ -modification is possible, accompanied by a rearrangement of the  $\alpha$ -modification into the  $\beta$ -modification, the open acid IV not being an intermediate, an intramolecular rearrangement, catalysed by hydroxyl ions, may be anticipated. The mechanism of this rearrangement is not clear yet, but its investigation is continued.

## EXPERIMENTAL PART

a. Proof that the  $\alpha$ -modifications are rearranged to the  $\beta$ -modifications during titration

1.  $\beta$ -Methyl-pyrazo*isocoumarazone* (II,  $R_1 = \text{CH}_3$ ,  $R_2 = \text{H}$ ). M. p. 136°. 0.5272 g were dissolved in ethanol and neutralised with 27.4 ml 0.0962 *N* Ba(OH)<sub>2</sub> (1 equivalent), followed by 30.0 ml 0.0848 *n* HCl (1 equivalent). The solution was evaporated to dryness in a vacuum, the residue extracted with ethanol and the ethanolic solution evaporated in a vacuum dessicator. M. p. of the  $\beta$ -lactone regained 125—127°.

2.  $\alpha$ -Methyl-pyrazo*isocoumarazone*. M. p. 168°. 0.4225 g dissolved in ethanol were neutralised with 21.4 ml 0.0962 *N* Ba(OH)<sub>2</sub> (1 equivalent). Phenolphthalein was added. When the colour had faded ( $\frac{1}{2}$  hour) 24.3 ml 0.0848 *N* HCl (1 equivalent) were added and the lactone recovered as above.

M. p. of the substance recovered	131—132°
Mixed with equal parts of $\alpha$ -lactone	110—130°
Mixed with equal parts of $\beta$ -lactone	132—134°

Evidently the  $\alpha$ -lactone has been rearranged to the  $\beta$ -lactone during the neutralisation.

3—6. Quite analogous experiments were carried out with the  $\alpha$ - and  $\beta$ -modifications of 3-methyl-4-ethyl-pyrazo*isocoumarazone* (II,  $R_1 = \text{CH}_3$ ,  $R_2 = \text{C}_2\text{H}_5$ ) and of 3-phenyl-pyrazo*isocoumarazone* (II,  $R_1 = \text{C}_6\text{H}_5$ ,  $R_2 = \text{H}$ ). The melting points of the substances recovered and, if necessary, of mixtures of these with the authentic  $\alpha$ - and  $\beta$ -lactones are indicated below.

	M. p. of pure substance	M. p. of substance recovered	M. p. of mixture with $\alpha$ - lactone	M. p. of mixture with $\beta$ - lactone	M. p. of mixture of $\alpha$ - and $\beta$ -lactone
$\beta$ -3-Methyl-4-ethyl- pyrazo <i>isocoumarazone</i>	107—108°	105—108°	—	—	—
$\alpha$ - —→	144—145°	95—104°	95—130°	96—105°	94—134°
$\beta$ -3-Phenyl-pyrazo- <i>isocoumarazone</i>	201—202°	197—198°	—	—	—
$\alpha$ - —→	144—145°	195—198°	—	—	—

As the m. p. of the acid resulting from an opening of the lactonering of 3-phenyl-pyrazo*isocoumarazone* is 196—197°, that of the  $\beta$ -lactone 201—202°, the m. p. 197—198° of the substance recovered might mean that the lactone ring had been opened during the titration. As, however, the acid is titrated as a dibasic acid, the lactone as a monobasic acid, and the substance recovered could use 1 equivalent of base only, we think it quite obvious that in this case, too, the  $\alpha$ -lactone is rearranged to the  $\beta$ -lactone during the titration.

b. Cryoscopical determination of the molecular weight

The melting points of solutions of the different lactones in benzene were determined. All determinations are double determinations, the difference between the two determinations for a given solution being 0.001° or less. For the molecular depression of the freezing point of benzene we have used the value 49.0°. The benzene used was a Kahlbaum-preparation, c. p. for molecular weight determinations. The m. p. of the pure benzene on the Beckmann-thermometer used was 1.309°.

	Weight of substance <i>a g</i>	Weight of benzene <i>b g</i>	M. p. (Beckmann)	<i>t</i>	<i>M</i>	<i>M</i> calc.
3-Methyl-pyrazo <i>isocoumarazone</i>						
<i>a</i>	0.1140	14.431	1.112	0.197	197	200.2
	0.1162	14.101	1.093	0.216	187	200.2
<i>β</i>	0.1565	14.502	1.034	0.275	192	200.2
	0.1565	18.948	1.095	0.214	198	200.2
3-Methyl-4-ethyl-pyrazo <i>isocoumarazone</i>						
<i>a</i>	0.1882	17.743	1.074	0.235	221	228.2
<i>β</i>	0.1807	10.950	0.933	0.376	215	228.2
3-Phenyl-pyrazo <i>isocoumarazone</i>						
<i>a</i>	0.1238	12.566	1.121	0.188	257	262.2
<i>β</i>	0.1945	28.867	1.178	0.131	252	262.2

From these determinations may be concluded with absolute certainty that all the modifications are monomers.

c. Dipole measurements

The measurements of the dielectric constants were carried out with a precision-apparatus from Kipp and Zonen<sup>4</sup>.

The lactones were dissolved in benzene (Kahlbaum, c. p.). The specific gravity of the solutions were determined by means of a flask-pyknometer, enabling determinations with an exactitude of 0.00001, which is sufficiently exact for the present purpose.

	Mol fraction of substance	Sp. gr. of solution	$\epsilon$	P	
3-Methyl-pyrazo <i>isocoumarazone</i> . <i>M</i> = 200.190					
<i>a</i>	0.00265	0.87632	2.2851	(104.91)	$P_E$ (calc.) = 44
	0.00778	0.88049	2.3002	93.92	$P_\infty$ = 97
	0.01550	0.88668	2.3235	90.83	$\mu$ = 1.60
<i>β</i>	0.00429	0.87733	2.3156	189.28	$P_E$ (calc.) = 44
	0.00564	0.87837	2.3287	188.44	$P_\infty$ = 190
	0.00980	0.88013	2.3665	187.30	$\mu$ = 2.66

3-Methyl-4-ethyl-pyrazoisocoumarazone.  $M = 228.242$ 

$\alpha$	0.00198	0.87546	2.2775	88.94	$P_E$ (calc.) = 52.6
	0.00603	0.87893	2.2873	87.73	$P_\infty = 89$
	0.00764	0.87997	2.2912	88.96	$\mu = 1.33$
$\beta$	0.00206	0.87549	2.2912	(186.62)	$P_E$ (calc.) = 52.6
	0.00472	0.87755	2.3140	181.90	$P_\infty = 185$
	0.00838	0.88013	2.3462	182.63	$\mu = 2.53$

3-Phenyl-pyrazoisocoumarazone.  $M = 262.256$ 

$\alpha$	0.00259	0.87721	2.2850	127.62	$P_E$ (calc.) = 58
	0.00418	0.87877	2.2926	123.43	$P_\infty = 132$
	0.00165	0.87608	2.2802	(117.00)	$\mu = 1.89$
$\beta$	0.00468	0.87807	2.3232	219.52	$P_E$ (calc.) = 58
	0.00311	0.87715	2.3070	218.53	$P_\infty = 220$
	0.00337	0.87755	2.3100	217.61	$\mu = 2.80$

Most of the experiments described here were carried out in the Laboratory of Organic Chemistry, the University, Copenhagen.

## SUMMARY

By further investigation of the anhydrides of some 3- and 4-substituted 1-(2'-carboxyphenyl)-pyrazolones-5, each existing in 2 modifications,  $\alpha$  and  $\beta$ , it has been proved that the  $\alpha$ -modifications are transformed into the  $\beta$ -modifications by titration with standard base.

Cryoscopical determinations of the molecular weights of the different modifications show that they are all of them monomers.

Measurements of the dipole-moments show that the 3  $\alpha$ -modifications examined on one hand and the 3  $\beta$ -modifications on the other hand are ranged in two series with different dipole-moments, the moments of the  $\beta$ -modifications (the modifications which may be titrated without rearrangement) being considerably greater than those of the  $\alpha$ -modifications.

## REFERENCES

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