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Pyrazole Studies

II. Anhydrides of 1-(2′-Carboxyphenyl)-3-phenyl-pyrazolone-5 and 1-(2′-Carboxyphenyl)-3-methyl-4-ethyl-pyrazolone-5

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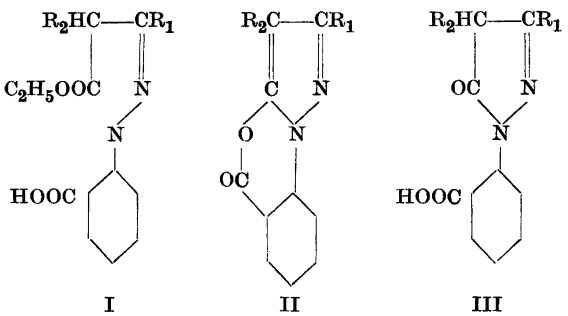
In the first paper of this series [1] we were able to show that from the 3 modifications of the anhydride of 1-(2′-carboxyphenyl)-3-methyl-pyrazolone-5 postulated by Michaelis [2] only 2 of them are pure compounds, the third being a mixture of the two others. Michaelis mentions that the anhydride of 1-(2′-carboxyphenyl)-3-phenyl-pyrazolone-5, by him named 3-phenyl-pyrazo*iso*-coumarazone, seems to exist in one modification only.

Pyrazolones substituted both in position 3 and in position 4 were not examined by him.

We now have examined the formation of anhydrides of the *o*-carboxyphenylhydrazones of ethyl benzoylacetate (I, $R_1 = C_6H_5$, $R_2 = H$) and of ethyl ethylacetoacetate (I, $R_1 = CH_3$, $R_2 = C_2H_5$). In both cases the anhydrides, possibly of structure as II, are formed by heating the *o*-carboxy-

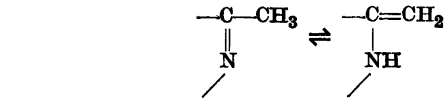


I II III

phenylhydrazones above their melting points. After treatment with conc. sulphuric acid these anhydrides may be isolated in modifications similar to the

β-modification of 1-(2'-carboxyphenyl)-3-methyl-pyrazolone-5-anhydride (the 3-methyl-pyrazo*iso*coumarazone of Michaelis), whereas treatment with anhydrous zink chloride at elevated temperature transforms the anhydrides to modifications with properties similar to the α-modification of the previously investigated anhydride. In all 3 cases we thus have 2 series of anhydrides, one with weakly acidic properties, the other neutral. Both modifications may be titrated in ethanolic solution with standard base as monobasic acids, the α-modification, however, only after rearrangement to the β-modification. The acidic properties are, therefore, not due to an opening of the lactone ring, as the pyrazolone-carbonic acids III by titration claim 2 equivalents of base to their neutralisation. (An exception is III with $R_1 = CH_3$, $R_2 = C_2H_5$, this acid claiming only one equivalent of base).

We still are not able to indicate at what place of the molecule the acidic properties are located or which hydrogen atom may be split off as a proton. With $R_1 = CH_3$ the possibility seems to exist that a transformation



might take place and that the imino-hydrogen was the one which showed acidic properties but with $R_1 = C_6H_5$ this explanation seems impossible. When $R_2 = H$ the acidic properties might be located at the carbon atom 4 in the pyrazolone-ring, if the bond to the hydrogen atom is sufficiently loosened, thus allowing the hydrogen atom to be removed as a proton, but with $R_2 = C_2H_5$ no such possibility exists. And even if the acidic properties might be explained in such ways there would be no explanation of the existence of two different modifications of the lactones, at all events not if the acidic properties were located at C_4, as the difference of the two modifications would be only the place of an electron and this difference may cause a case of mesomerism, not one of tautomerism or isomerism.

In pyrazolones of simpler structure, too, we have found similar cases of isomerism between an acidic and a neutral modification. Possibly the explanation of the isomerism mentioned in this paper may be understandable when the explanation of the simpler case has been found. The investigations on the simpler case will be published later.

EXPERIMENTAL PART

1. Ethyl benzoylacetate-o-carboxyphenylhydrazone (I, $R_1 = C_6H_5$, $R_2 = H$). $C_{18}H_{18}O_4N_2 = 326.3$. 13 g *o*-carboxyphenylhydrazine hydrochloride were dissolved in 500 ml water. The solution was stirred mechanically and 0.9 g ethyl benzoylacetate were added. The precipitate formed was filtered off and discarded. The filtrate was stirred mechanically and 9.6 g ethyl benzoylacetate were added and well emulgated in the

solution. A precipitate was formed soon, but to complete the reaction the mixture was heated on steam bath for some two hours. After refrigeration the precipitate was filtered off, washed chlorine-free and dried. Yield 11 g = 67 %. M. p. 165° (on a metal block, heated with the block), but the instantaneous m. p. (block Maquenne) was 175°. Michaelis (*l. c.* p. 179) indicates m. p. 166—167°. Recrystallised from 10 parts of ethanol the m. p. was raised to 173—175° when the substance was slowly heated or 184—185° (block Maquenne). Further recrystallisation did not alter the m. p.

0.4111 g were dissolved in ethanol and titrated with 0.0927 *N* $Ba(OH)_2$. After addition of 16 ml the end point seemed to be reached as the solution turned red, but the colour faded very fast and only after the addition of 26.9 ml $Ba(OH)_2$ the colour persisted for 1 hour (CO_2-free nitrogen athmosphere) and with further 0.3 ml the colour persisted for 1 ½ hour. The equivalent weight is thus between 164.8 (26.9 ml) and 163.0 (27.2 ml), *i. e.* the *o*-carboxyphenylhydrazone is titrated as a dibasic acid (*M* calculated 326.3, found $329.6 > M > 326.0$.

The *o*-carboxyphenylhydrazone of ethyl acetoacetate was titrated as a monobasic acid [1] and we therefore examined if the present *o*-carboxyphenylhydrazone had been transformed into another substance during the titration.

1 g of the *o*-carboxyphenylhydrazone was dissolved in ethanol and neutralised with the calculated amount of $Ba(OH)_2$ (2 equivalents of base pr. mol of *o*-carboxyphenylhydrazone). The barium salt which separated out as a precipitate during the addition of base, was filtered off and dissolved in water. By acidification with hydrochloric acid a precipitate was formed, which was filtered off, washed Cl^--free with water and dried. Yield 0.8 g of a substance with m. p. about 200°, *i. e.* different from the starting material. By titration 0.1732 g claimed 13.47 ml 0.0927 *N* $Ba(OH)_2$, which corresponds to an equiv. wt. of 138.7 or a mol. wt. of 277.4. Both the m. p. and the equiv. wt. is concordant with m. p. and equiv. wt. of 1-(2'-carboxyphenyl)-3-phenyl-pyrazolone-5 described below. During the titration of the *o*-carboxyphenylhydrazone, therefore, a saponification of the ester and ring-closure of the acid to a pyrazolone has taken place.

2. *1-(2'carboxyphenyl)-3-phenyl-pyrazolone-5-lactone* (II?, $R_1 = C_6H_5$, $R_2 = H$). $C_{16}H_{10}O_2N_2 = 262.2$. Michaelis [2] indicates that the ethyl benzoylacetate-*o*-carboxyphenyl-hydrazone by heating above the melting point over direct flame is transformed into a lactone with the composition $C_{16}H_{10}O_2N_2$, named by him 3 phenyl-pyrazo*iso*coumarazone. M. p. of the lactone is 198—200°, dependent on the medium from which it is recrystallised. Michaelis states that neither by treatment with sulphuric acid nor by melting with anhydrous zink chloride is the lactone transformed into other modifications as was the case with the 3-methyl-pyrazo*iso*coumarazone.

We prepared the lactone after the indications of Michaelis and obtained a substance with m. p. 201—202°, very sparingly soluble in ethanol. It may, however, be recrystallised from ethyl acetate. The substance was titrated in hot ethanolic solution with standard $Ba(OH)_2$ in a stream of CO_2-free nitrogen. 0.1196 g claimed 9.80 ml 0.0927 *N* $Ba(OH)_2$. To this corresponds an equiv. wt. 131.7. Under the circumstances of the experiment the lactone ring is opened during the titration, the lactone thus claiming 2 equivalents of $Ba(OH_2)$.

When titrated at room temperature only a little more than 1 equivalent of base is used to neutralisation. 0.1614 g claimed 6.92 ml 0.0962 *N* $Ba(OH)_2$. *M* found 243.1, calc. 262.2. As was the case with the β-3-methyl-pyrazo*iso*coumarazone [1] the mol. wt. is found to be 6—7 % lower than calculated, most likely due to a partial opening of the

lactone ring. When more $Ba(OH)_2$ is added the colour fades very slowly, an excess of 0.5 ml base claiming some 6 hours to be used. At room temperature, therefore, the opening of the lactone ring is a very slow proces.

β-Modification. 20 g of the lactone were heated on the steam bath for 1 ¼ hours with 100 ml conc. sulphuric acid. The solution was cooled and poured into 1 l of water. The precipitate was filtered off, washed with water and dried. Yield 19 g with m. p. 192—193°, recrystallised from ethyl acetate m. p. 201—202°. The lactone prepared by direct heating of the ethyl benzoylacetate-*o*-carboxy-phenylhydrazone, therefore, is the β-modification.

The β-modification is not volatile with steam and its solution gives no colour reaction with ferric chloride.

α-Modification. 13 g β-lactone were mixed with 13 g anhydrous zink chloride and heated for 3 hours in a metal bath to 250°, protected against the humidity of the air. A sublimate of β-modification was from time to time pushed back in the melt. When cooled the dark coloured solidified melt was dissolved in 100 ml absolute ethanole. The ethanolic solution was poured into 500 ml *N*/1 HCl. A dark tar was precipitated which solidified to an amorphous pitchy mass. The pitch was repeatedly boiled with 1 liter portions of water. When the solution was filtered as hot as possible through a funnel with a plate of sintered glass 0.2 g yellowish crystals separated out from each portion on cooling. 1.6 g of these crystals were gained, which recrystallised from 35 ml ethanol gave 1.2 g yellow crystals with m. p. 140° (on a metal block) or 144—145° (in capillary tube). Further recrystallisation with treatment of the solution with absorption coal did not alter the colour or the m. p. Yield 9—10 %.

0.0925 g were dissolved in ethanol and titrated (in CO_2-free nitrogen atmosphere) with 0.1234 *N* $Ba(OH)_2$ (indicator phenolphthalein). Each drop of $Ba(OH)_2$ provoked a colour which faded slowly. 2.00 ml were used in 20 minutes, further 0.55 ml in 10 min, 0.30 ml in 10 min, 0.05 ml in 20 min, 0.03 ml in 50 min. When heated the colour faded very fast.

To 2.95 ml corresponds an equivalent weight of 254.1, calculated 262.2. The α-modification is thus titrated at room temperature as a monobasic acid, but as was the case with the α-3-methyl-pyrazo*iso*coumarazone, not directly. In warm solution the lactone ring is opened during the titration.

The ethanolic solution does not give any colour reaction with ferric chloride.

3. *1-(2'-Carboxyphenyl)-3-phenyl-pyrazolone 5* (III, $R_1 = C_6H_5$, $R_2 = H$). $C_{16}H_{12}O_3N_2$ = 280.3. As mentioned above the β-lactone may be titrated in warm ethanolic solution as a dibasic acid. From the neutralised solution the open phenyl-pyrazolone-carbonic acid may be isolated after acidification. The α-lactone behaves itself in the same manner.

The 1-(2'-carboxyphenyl)-3-phenyl-pyrazolone-5 is more soluble in ethanol than the lactones. The ethanolic solution is coloured brown by ferric chloride. Heated on a metal block it melts at 196—197° with evolution of gas (vapour?), then solidifies and melts by further heating at 201°. This means that it is very easily transformed into the β-lactone.

0.0894 g dissolved in ethanol claims 5.17 ml 0.1234 *N* $Ba(OH)_2$. The titration is easy and the end-point is sharply determined. The equiv. wt. is 140.1.

Melting point and titration show that this substance is identical with the substance isolated after complete neutralisation of the ethyl benzoylacetate-*o*-carboxyphenyl-hydrazone.

4. *Ethyl ethylacetoacetate-o-carboxyphenylhydrazone* (I, $R_1 = CH_3$, $R_2 = C_2H_5$). $C_{15}H_{20}O_4N_2 = 292.3$. The preparation of this substance was completely analogous to the preparation of the ethyl benzoylacetate-*o*-carboxyphenylhydrazone. The raw product (m. p. 141—145°) was purified by dissolving it in ethanol, treating the ethanolic solution with adsorption coal and precipitating the hydrazone by addition of water. The pure ethyl ethylacetoacetate-*o*-carboxyphenylhydrazone melts at 148—149°. Yield of pure substance 16.5 g = 57 %.

0.3712 g dissolved in ethanol claim 12.97 ml 0.1000 *N* $Ba(OH)_2$. Equiv. wt. found 289.8, calc. 292.3.

5. *1-(2'-Carboxyphenyl)-3-methyl-4-ethyl-pyrazolone-5-lactone* (II?, $R_1 = CH_3$, $R_2 = C_2H_5$. $C_{13}H_{12}O_2N_2 = 228.2$.

β-Modification. From our experience with the preparation of the β-3-methyl-pyrazo-*iso*coumarazone [1] we prepared the β-lactone in the following way.

17 g ethyl ethylacetoacetate-*o*-carboxyphenylhydrazone were placed in a fractionating flask and heated in oil bath for 3 hours to 160—180°. 3.1 g distillate were collected (calculated for loss of 1 mol ethanol and 1 mol water 3.7 g). The residue in the flask was heated on steam bath for 2 hours with 15 ml conc. sulphuric acid. When cooled the sulphuric acid solution was poured into 200 ml of water. The white precipitate was filtered off, washed with water and dried. Yield 12.7 g with m. p. 98—100° or 95 %.

By repeated recrystallisations from ethanol the m. p. was raised to 107—108°.

Dissolved in ethanol 0.2171 g claimed 10.18 ml 0.0927 *N* $Ba(OH)_2$. Equiv. wt. found 230.2, mol. wt. calculated 228.2, *i. e.* the β-lactone is titrated as a monobasic acid. The originally colourless solution assumes as the solution of the β-3-methyl-pyrazo*iso*coumarazone a faint yellow-green colour during the titration.

The lactone-ring in 3-methyl-4-ethyl-pyrazo*iso*coumarazone seems to be more resistant than the lactone-ring in the lower homologue. The loss of substance during the treatment with sulphuric acid is not as great in the former as in the latter case. The 4-ethyl-lactone, like its lower homologue, is volatile with water-vapour, and the lactone separates out from the distillate on cooling. The acid which would be formed from the lactone if the lactone-ring was opened during the distillation cannot be isolated from the distillate, whereas in the case of the lower homologue most of the lactone was transformed into the acid during the distillation with water-vapour [1].

The ethanolic solution gives no colour-reaction with ferric chloride.

α-Modification. 5 g β-lactone were mixed with 5 g of anhydrous zink chloride. The mixture was heated to 170° for 1 hour in an oil bath. When cool, the solidified melt was dissolved in 50 ml ethanol. The solution was poured into 400 ml of water acidified with 5 ml conc. hydrochloric acid. The brown precipitate was filtered off and dried. Yield 3.6 g with m. p. 130—133°. Recrystallised from 20 parts of ethanol (treatment of the ethanolic solution with adsorption coal) the yield was 2.0 g faint yellow crystals with m. p. 144—145° or 40 %. Neither the colour nor the m. p. was altered by further recrystallisation.

As in the case of the other α-lactones, the titration of the ethanolic solution of the α-lactone with standard $Ba(OH)_2$ was very delayed. A solution of 0.2021 g used 9.50 ml 0.0927 *N* $Ba(OH)_2$ in 90 minutes. Further 0.10 ml were used in 20 minutes and still further 0.10 ml were not used in 30 minutes. From this is found 229.5 > equiv. wt. > 227.1. The calculated mol. wt. is 228.2, which shows that the α-lactone is titrated with delay as a monobasic acid. Its solutions do not give colour reaction with ferric chloride.

6. *1-(2'-carboxyphenyl)-3-methyl-4-ethyl-pyrazolone-5* (III, $R_1 = CH_3$, $R_2 = C_2H_5$). $C_{13}H_{14}O_3N_2 = 246.2$. By treatment with excess alcali both the α-and the β-lactone are transformed into the open acid. 0.5 g α-lactone were treated with an excess of NaOH. When dissolved the solution was acidified with hydrochloric acid. A crystalline precipitate was filtered off. Yield 0.26 g with m. p. 153—155°. By titration of its ethanolic solution with 0.1234 *N* $Ba(OH)_2$ 0.0711 g claimed 2.33—2.40 ml, *i. e.* 247 > equiv. wt. > 240. The calculated mol. wt. being 246.2 this means that the acid is titrated as a monobasic acid, in disagreement with the two other pyrazolones investigated, which both of them were titrated as dibasic acids. Another difference from the two other pyrazolones is that the pyrazolone examined here does not give a colour reaction with ferric chloride, at least at room temperature, whereas the two others give a colour reaction. The hot aqueous solution does give a faint colour reaction, but it disappears by addition of hydrochloric acid. The tendency of enolisation of the pyrazolone is evidently diminished by the substitution of a hydrogen atom for an ethyl group at C_4.

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

SUMMARY

It has been shown that contrary to the statement of Michaelis the anhydride of 1-(2'-carboxyphenyl)-3-phenyl-pyrazolone-5 does exist in 2 modifications from which one may be titrated directly with standard base, the other only after rearrangement.

From 1-(2'-carboxyphenyl)-3-methyl-4-ethyl-pyrazolone-5 too, not examined previously, two modifications of an anhydride may be prepared.

REFERENCES

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