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Pyrazole Studies

I. On the Pyrazo-*iso*coumarazones of A. Michaelis

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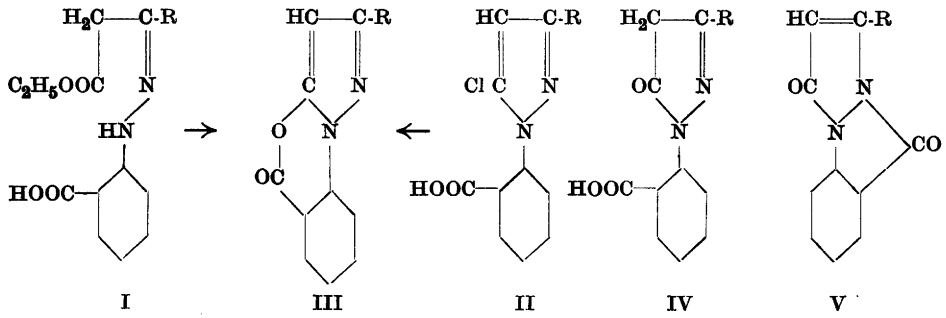
In the years 1904—1910 Michaelis and his pupils [1-7] investigated some substances obtained either by condensation of *o*-carboxyphenylhydrazine with esters of acylacetic acids and distillation of the *o*-carboxyphenylhydrazones primarily formed (I) or by heating of 1-(2'-carboxyphenyl)-3-alkyl-(or aryl-)5-chloropyrazole (II) to some 200°.



I III II IV V

The unsubstituted substance (III), R = H, Michaelis termed pyrazo-*iso*-coumarazone.

With R = CH_3 Michaelis and collaborators claim to have isolated 3 different substances, α, β and γ, all of them having the empirical formula corresponding to (III) and regarded by the authors as 3 modifications of one compound. Treated with bromine they yielded 3 different monobromosubstituted substances which too were regarded as modifications of one compound.

The γ-compound was obtained by distillation of the *o*-carboxyphenylhydrazone of ethylacetoacetate. The β- and the γ-compound could be transformed into the α-compound by heating them for some time to 160° with an-

hydrous zink chloride or by boiling them for some hours with water, the α- and the γ-compounds could be transformed into the β-compound by dissolving them in 10 parts of concentrated sulphuric acid and after 20 hours at room temperature pouring them slowly into 100 parts of water.

All 3 modifications were soluble in sodium hydroxide. By acidification of the alkaline solutions one and the same 1-(2′carboxyphenyl)-3-methyl-pyrazolone-(5), (IV), R = CH_3), with m. p. 195° could be isolated in all 3 instances.

Michaelis *et al.* were not able to propose structural formulas for the 3 modifications mentioned, but into their opinion polymorphism could be excluded. A closer study of these compounds, therefore, seemed useful.

In the course of our investigations we could show that the γ-compound of Michaelis *et al.* is not a pure compound but a mixture of the α- and the β-compound. The same holds good for the γ-modification of the monobromo-substituted compounds. We, no more than Michaelis, so far have been able to put forward proposals for structural formulas for the 2 series of compound but the investigation is continued.

Both modifications are showing weakly acidic properties. An alcoholic solution of the β-compound may be titrated with standard sodium- or barium-hydroxide as a monobasic acid. The equiv. wt. is found to be some 2—3 % lower than that calculated for the lactone (III). From the neutralized solution the β-compound may be isolated after acidification.

The α-compound, too, may be titrated, but only very slowly, and the equiv. wt. found is some 5 % lower than that calculated for (III). When the neutralized solution of the α-compound is acidified the β-compound and not the α-compound may be isolated. The neutralisation of the α-compound thus seems to be preceeded by, or accompanied by, a rearrangement into the β-compound.

The alcoholic solutions of both modifications are colourless. Enolisation does not seem to occur, as none of the solutions give colour-reaction with ferric chloride. When titrated with sodium hydroxide, however, the solutions assume a faint greenish-yellow colour during the titration.

Michaelis [7] proposed as structural formulas for two of the three modifications found by him the lactone-formula (III) and the lactim-formula (V). This proposal cannot, however, be maintained on account of the results of the titrations. A rearrangement of (III) to (V) or vice-versa cannot possibly occur without the opening of the lactone- or the lactim-ring and by this opening of the ring the acid (IV) is formed. This acid, as mentioned above, is a stable compound, and in alcoholic solution it is titrated with standard alcali as a dibasic acid, the solution of which remains colourless during the titration. Moreover, the alcoholic solution of (IV) gives a typical reddish colour-reaction

with ferric chloride, evidently due to an enolisation of the 5-keto-group in the pyrazolonering.

It is possible that during the titration an opening of the lactone- or lactimring occurs to a very limited extent. This would explain that the equivalent weights are found a little too low by titration. As a matter of fact, however, neither of the formulas (III) and (V) seem to contain a hydrogen atom able to be split off as a proton.

EXPERIMENTAL PART

Ethylacetoacetate-*o*-carboxyphenylhydrazone

(Formula I, R = CH_3), $C_{13}H_{16}O_4N_2$ = 264.3

This compound is easily precipitated if the ethylacetoacetate is added to an aqueous solution of *o*-carboxyphenylhydrazine hydrochloride. The purification of the substance is, however, facilitated by following procedure:

25 g *o*-carboxyphenylhydrazine hydrochloride are dissolved in 1000 ml of hot water. The solution is stirred mechanically and 1 ml of ethylacetoacetate is added. A yellow to brown precipitate is formed which after some minutes is filtered off and discarded. To the filtrate is added, under efficient mechanical stirring, 13 ml ethylacetoacetate and the stirring is continued for 2 hours. The cream-coloured precipitate is then filtered off by suction, washed free of chlorine with water and dried, first at room temperature, then at 95—100°. Yield 22.8 g = 87 %.

Prepared in this way the substance is pure. Michaelis [7] indicates m. p. 125°, Blockmann [1] 135°. We found in different preparations m. p. between 123 and 136° and were able to show that the substance exists in two dimorphous forms, with m. p. 123.5 and 136° respectively. The two forms may be transformed mutually by recristallisation from ethanol-water mixtures and inoculation with the form desired. By titration of ethanolic solutions of both forms with standard barium hydroxide the equiv. wt. calculated for a monobasic acid $C_{13}H_{16}O_4N_2$ is found within the limits of error.

0.2610 g claim 9.52 ml 0.1048 *N* $Ba(OH)_2$ (indicator phenolphthalein). *M* found 261.7, calc. 264.3.

3-Methyl-pyrazoisocoumarazone or 1-(2′-carboxyphenyl)-3-methyl-pyrazolone-5-lactone

(Formula III or V ?, R = CH_3) $C_{11}H_8O_2N_2$ = 200.2.

»*γ-Modification.*» According to Michaelis [7] the γ-modification of the lactone (with m. p. 112°) is formed by distillation of the phenylhydrazone mentioned above at atmospheric pressure, whereas distillation under reduced pressure leads to the β-modification with m. p. 132°. These results we have not been able to reproduce. By distillation at atmospheric pressure we obtained distillates which melted very unsharply, with intervals from 125 to 145°, and by distillation in vacuum we only once obtained a distillate with m. p. 109—110°, corresponding to the γ-modification of Michaelis, in other cases the interval of melting was from 115 to 150°. As, however, the substances obtained could be

transformed into the pure α- and β-modifications we did not continue the investigations on the preparation of the γ-modification, which later could be shown to be a mixture of the α- and the β-modifications.

β-Modification. According to Michaelis [7] and to Ziesel [6] the β-modification is obtained by treatment of the γ-modification with concentrated sulphuric acid. Our distillates, too, treated in this manner, yielded the β-lactone, but as the yield of distillate is not very great the overall yield of β-lactone is poor. It may be considerably improved by treating the carboxyphenylhydrazone with sulphuric acid without previous distillation. Boiling with glacial acetic acid, too, leads, as indicated by Michaelis [7] and Brockmann [1], to the formation of β-lactone, but the yield is better when treated with sulphuric acid.

10 g ethylacetoacetate-*o*-carboxyphenylhydrazone are heated on the steam bath for 15 minutes with 12 ml conc. sulphuric acid. The mixture is cooled and poured into 120 ml of ice-water. The white, flocculous precipitate is filtered with suction, washed with water and recrystallised from ethanol, the ethanolic solution being decolorized with adsorption coal. Yield 3.1 g = 41 % of colourles needles with m. p. 135°, unaltered by further recrystallisation. (Michaelis indicates m. p. 132° for the pure β-compound).

Micro-determination of N *: Calc. 14.00 %, found 14.08 %.

0.2056 g dissolved in ethanol were titrated with 0.1234 *N* $Ba(OH)_2$ (indicator phenolphthalein). During the titration the original colourless solution assumed a faint yellow-green colour which somewhat disturbed the observation of the end point, reached when 8.60 ml had been added. When the substance is regarded as a monobasic acid *M* is found to 194, calculated 200.2.

α-Modification. Michaelis [7] obtained the α-modification by melting the γ-modification with anhydrous zink chloride. On treatment of the β-modification with zink chloride we obtained a substance which evidently was identical with the α-modification of Michaelis.

5 g of β-lactone are mixed with 5 g anhydrous zink chloride in a conical flask equipped with a cork stopper with a glass tube as air condenser. The mixture is heated in an oil bath to 165° for 4 hours. After cooling the solidified mixture is dissolved in ethanol, forming a dark brown solution, which is poured into water acidified with HCl. The brown precipitate is filtered off and recristallised from ethanol, the ethanolic solution being decoloured with adsorption coal. Yield 2 g = 40 % of a light yellow substance with m. p. 166—168°. Michaelis indicates for the α-lactone m. p. 165°.

Micro-determination of N: Calc. 14.00 %, found 13.97 %.

An ethanolic solution of 0.0319 g was titrated with 0.1000 *N* $Ba(OH)_2$ (indicator phenolphthalein). After the addition of some few drops of $Ba(OH)_2$ the solution assumed a pink colour, but the colour disappeared after few minutes, even if the admission of CO_2 was prevented by a stream of CO_2-free nitrogen. In this way the titration could be continued till 1.68 ml had been added. The red colour which till then had disappeared in few minutes after the addition of one drop of $Ba(OH)_2$ now persisted for at least ½ hour. During the titration the solution had assumed the same faint yellow-green colour as the solution of the β-lactone. From the titration result *M* is found to be 190 (monobasic acid), calculated 200.2.

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* We are indebted to Mr. O. Rosenlund Hansen, Civil engineer, for the carrying out of the micro-N-determinations.

Identification of the γ-modification as a mixture of the α- and the β-modification

The velocity with which the α- and the β-modification were neutralised by standard alkali was found so different that it was natural to investigate the velocity of neutralisation of the γ-modification too. 0.2614 g were dissolved in ethanol and titrated with 0.1000 *N* $Ba(OH)_2$, a stream of CO_2-free nitrogen being passed through the solution in order to exclude the action of carbon dioxide from the air. When 9.0 ml had been added the end point was apparently reached, but the colour faded and only after the addition of 13.0 ml the red colour persisted for ½ hour. As to 13.0 ml corresponds an equiv. wt. of 201, the mol. wt. of the lactones, this result may be explained by the assumption that the γ-modification is a mixture of 65—70 % β-lactone and 35—30 % α-lactone. We prepared a series of mixtures of β- and α-lactone with different content of the two components and determined their melting points. Table 1 shows that a mixture with 65—70 β-lactone and only such a mixture shows an approximately sharp m. p., concordant with the m. p. indicated for the γ-modification. This corroborates the impression gained by the titration.

Table 1.

α-β-Mixture	M. p.	M. p. after solidification
5 mg α— + 1.5 mg β—	112—125°	113—137°
5 α— + 2.0 β—	112—130°	112—120°
5 α— + 2.5 β—	112—113°	112—117°
5 α— + 3.0 β—	112—114°	110—113°
5 α— + 3.5 β—	112—125°	—
»γ-Modification«	109—110°	110—111°

Michaelis [7] indicates that the γ-modification by prolonged boiling with water with continuous renewal of the water evaporated is transformed to the α-lactone. We are now able to give another explanation of the phenomenon menticned by Michaelis. Incidentally we observed that the β-modification is somewhat volatile with water vapour. The prolonged boiling, which actually is a distillation with steam, thus eliminates the β-modification, and only the α-modification which is not volatile remains and may be isolated.

Usually the β-lactone is not observed, even if the distillate is collected. This is due to the fact that the lactone-ring is opened by boiling with water, and the 1-(2'-carboxyphenyl)-3-methyl-pyrazolone-5 (IV, R = CH_3) thus formed is more soluble in water than either of the lactone-modifications. The following experiment demonstrates clearly the opening of the lactone-ring during the boiling with water.

1-(2'-Carboxyphenyl)-3-methyl-pyrazolone-5
$C_{11}H_{10}O_3N_2 = 218.2$ (IV, R = CH_3)

0.2 g of the β-lactone were dissolved by refluxing the lactone for 1 ½ hour with 60 ml of water. The clear solution was left over night at room temperature. 0.01 g had separated out and were filtered off. The filtrate was concentrated to a small volume. From the distillate 0.01 g crystallised. M. p. of both crops of crystals was 134—135°, *i. e.* they consist of unaltered β-lactone.

The residue from the distillation was cooled in ice. 0.13 g crystals were filtered off. M. p. 189—191°. Michaelis [7] indicates m. p. 191° for the substance IV. As control we prepared IV from both the α- and the β-modification by dissolving the lactone in con-

centrated sodium hydroxide followed by acidification with hydrochloric acid (Michaelis, *l. c.*). The crystals melted about 191—193°, recrystallised from 30 % ethanol at 200°, somewhat higher than indicated by Michaelis.

Both the product obtained by boiling the β-lactone with water and the products obtained from the α- and β-modifications after solution in sodium hydroxide assumed a red colour during the melting process which was accompanied by an evolution of gas (vapour). Aqueous solutions of all 3 preparations gave a red colour reaction with ferric chloride.

The titration of an ethanolic solution of the pyrazolone with $Ba(OH)_2$ (indicator phenolphthalein) gave an equivalent weight of 110.2. (0.0476 g, 3.50 ml 0.1234 *N* Ba $(OH)_2$). This means that the pyrazolone is titrated as a dibasic acid whereas the neutralisation of the lactones claims only one equivalent of base. The transformation of the α-modification into the β-modification under the influence of barium hydroxide cannot, then, pass through the pyrazolone-carbonic acid IV as intermediate.

Bromination of the lactones

Michaelis indicates that all 3 modifications of the lactone may be brominated and that 3 different monobromolactones were isolated by him. As the γ-modification has been proved to be a mixture of the α- and the β-lactones we thought it necessary to investigate the bromination products too.

Bromination of the β-modification. The bromination was carried out as a titration with bromine as indicated by Meyer [8]. 0.1669 g claimed 18.5 ml 0.0864 *N* bromine solution. The equiv. wt. is 96, *i. e.* a double bond or an easily substituted hydrogen atom is found in 192 g lactone. In another experiment the equiv. wt. 101 was found. As the mol. wt. of the lactone is 200 it may be concluded that 1 mol. of β-lactone reacts with 1 mol. of bromine at room temperature. The bromination product was isolated. The m. p. was 152—153°, in accordance with the indication of Michaelis, 151°.

The α-lactone was brominated very slowly at room temperature so that a titration could not be carried out. To a sample of α-lactone the amount calculated (1 mol. bromine pr. mol. lactone) of a bromine solution was added and the mixture heated on steam bath. The colour of bromine disappeared very fast and by evaporation the bromination product was isolated. It showed m. p. 190—193° whereas Michaelis indicates m. p. 187° for the bromination product of the α-lactone.

The »γ-modification» was brominated according to Michaelis (*l. c.*) with bromine in glacial acetic acid. The bromination product started to cristallise in the acetic acid solution and was precipitated completely by addition of water. It melted unsharply at 118—125°, whereas Michaelis for the brominated γ-modification indicates m. p. 135—137°. By repeated recrystallisations, first from ethanol, then from acetone-water mixtures, we succeeded in separating the product into two fractions, one melting sharply at 151—152°, identical with the bromination product of the β-lactone, the other, more soluble, melting very unsharply, starting at 134° but completely melted only at 175°. We were not able to isolate the pure brominated α-lactone with m. p. 190—193°, but it is likely that the more soluble fraction contains this substance as main product.

1-(2′-Carboxyphenyl)-3-methyl-pyrazolone-5-hydrochloride

$C_{11}H_{11}O_3N_2Cl = 254.7$

Michaelis [7] indicates that the β-lactone when boiled with concentrated hydrochloric acid for 5 hours in an open vessel forms a chlorhydrate with m. p. 220°.

We boiled 1 g β-lactone with 100 ml conc. hydrochloric acid. After 3 hours so much water had disappeared that further boiling was impossible. The solution was cooled and a salt separated out in rather great crystals. The crystals were filtered off, washed with diluted hydrochloric acid and with alcohol. Yield 0.70 g with m. p. 218—221°. A determination of chlorine after Volhard showed $M = 260$. (0.1097 g, 4.22 ml 0.1000 N $AgNO_3$).

The chlorhydrate was recrystallised from ethanol and titrated in ethanolic solution with barium hydroxide (indicator phenolphthalein). 0.1848 g claim 17.7 ml 0.1234 N $Ba(OH)_2$. Equiv. wt. = 84.5 or 1/3 of that found by the chlorine-determination.

For the chlorhydrate of the lactone is calculated $M = 236.7$, for the chlorhydrate of the pyrazolone-carbonic acid IV (R = CH_3) $M = 254.7$. Evidently the chlorhydrate is titrated as a tribasic acid, whereas a chlorhydrate of the lactone could use only 2 equivalents of base.

The solution of the chlorhydrate remained colourless during the titration. An aqueous solution gave a red colour reaction with ferric chloride. This too is to be expected if it is the chlorhydrate of the open acid, but not if it is the chlorhydrate of the lactone.

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

SUMMARY

The anhydrides of 1-(2′-carboxyphenyl)-3-methyl-pyrazolone-5 previously examined by Michaelis and collaborators were reexamined. Michaelis claims that 3 modifications of the anhydrides may be isolated. We have been able to show that only 2 modifications exist, one of Michaelis' modifications being a mixture of the two others.

Structural formulas for the remaining two modifications have not been proposed. One, the β-modification, may be titrated directly as a monobasic acid with standard base, the other, the α-modification, only after rearrangement to the β-modification, this rearrangement taking place during the titration.

1-(2′-carboxyphenyl)-3-methyl-pyrazolone-5 is titrated as a dibasic acid.

Michaelis claims that the anhydride forms a chlorhydrate by treatment with hydrochloric acid. We have been able to show that the chlorhydrate is formed not by the anhydride but by the acid 1-(2′-carboxyphenyl)-3-methyl-pyrazolone-5.

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