Tetrahedron, 1957, Vol. 1, pp. 201–213. Pergamon Press Ltd., London

THE PREPARATION AND PROPERTIES OF SUBSTITUTED BENZO[*c*]PYRAZOLO[1:2-*a*]PYRAZOL-1:9-DIONES (MICHAELIS' BENZO-BIS-PYRAZOLONES)

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(*Received* 14 *May* 1957)

Abstract—A series of substituted benzo[*c*]pyrazolo[1:2-*a*]pyrazol-1:9-diones has been prepared by condensing β-ketoesters with β-acetyl-(2-carboxyphenyl-) hydrazine, using phosphorus trichloride as condensing agent.

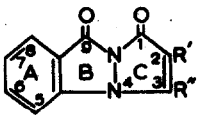
These substances are converted by (i) aqueous sodium hydroxide into substituted 1-(*o*-carboxyphenyl) pyrazol-3-ones, (ii) alcoholic solutions of sodium hydroxide into substituted 1-(*o*-alkoxycarbonylphenyl) pyrazol-3-ones, and (iii) a methanolic solution of piperidine into a mixture of 1-(*o*-methoxycarbonyl-phenylpyrazol-3-ones and the corresponding piperidide.

The titration curves of the acids in ethanolic solution with sodium hydroxide and of the bases in glacial acetic acid with perchloric acid have been recorded. From the latter the pK_B-values of the acids and esters have been estimated.

The u.v.-absorption curves of the substances prepared have been recorded.

The preparation of β,β-diacetyl-(*o*-carboxyphenyl)-hydrazine and of 1-acetylbenzopyrazol-3-one is mentioned.

MICHAELIS[1] investigated the reaction between *o*-carboxyphenylhydrazine and ethyl acetoacetate and found that in addition to pyrazol-5-one formation (which in this instance was accompanied by a further dehydration) an anhydride of the isomeric pyrazol-3-one was formed at a higher temperature during the reaction. Michaelis assigned the name benzo-5-methyl-bis-pyrazolone to the anhydride and later[2] proved its structure by an independent synthesis. In accordance with present nomenclature this is now named 3-methyl-benzo[*c*]pyrazolo[1:2-*a*]pyrazol-1:9-dione I.



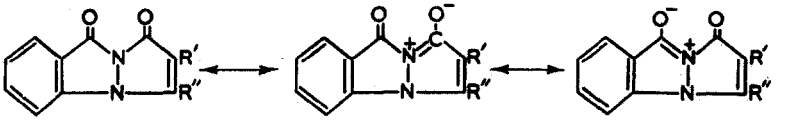
I; R'=H, R''=Me
II; R'=Et, R''=Me
III; R'=H, R''=Ph

Syntheses of I, II and III have now been achieved by condensation of β-acetyl-*o*-carboxyphenylhydrazine with ethyl acetoacetate, ethyl α-ethylacetoacetate and ethyl benzoylacetate respectively in phosphorus trichloride. All three substances form yellow crystals and their solutions in glacial acetic acid or ethanol show a very brilliant blue fluorescence.

Veibel *et al.*[3,4] have shown that 3-pyrazolones may be titrated in ethanolic solution with sodium hydroxide and in glacial acetic acid solution with perchloric acid. The substances investigated here, however, can be titrated neither as acids nor as bases.

[1] A. Michaelis *Liebigs Ann.* **373**, 148 (1910).
[2] A. Michaelis *Liebigs Ann.* **373**, 202 (1910).
[3] S. Veibel, J. Kjær, and E. Plejl *Acta Chem. Scand.* **5**, 1283 (1951).
[4] S. Veibel, K. Eggersen, and S. Linholt *Acta Chem. Scand.* **6**, 1066 (1952).

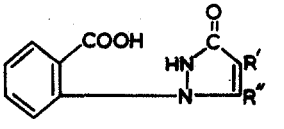
Their shortcomings as acids are easily understood, remembering that it is the enolised form of the pyrazolone which is titrated and realising that the lactimisation of the primarily formed *o*-carboxyphenyl pyrazol-3-one prohibits the enolisation. The pyrazolones may be titrated as bases when they are able to acquire a pyrazole structure or a 3-antipyrine structure IV or V. The participation of the structure I in the resonance hybride may perhaps reduce its reactivity in this titration. The resonance



between IV and V may be responsible for the fluorescence of the substances.

I may be regarded as having a 3-antipyrine structure, but only such antipyrines which have a hydrogen atom or an alkyl group on N^2 can be titrated, and here the hydrogen atom at N^2 is substituted by a benzoyl group which will certainly decrease the ability of N^2 to capture a proton so that the substance becomes almost non-basic.

Treated with aqueous sodium hydroxide the substances I–III, as indicated for I by Michaelis,[2] are converted into salts of 5-mono- or 4:5-disubstituted 1-(*o*-carboxyphenyl)pyrazol-3-ones from which the free acids VI–VIII may be liberated by addition



VI; $R' = H$, $R'' = CH_3$
VII; $R' = C_2H_5$, $R'' = CH_3$
VIII; $R' = H$, $R'' = C_6H_5$

of hydrochloric acid. The fluorescence vanishes during the opening of ring B. The acids VI–VIII on heating above their melting points lose water with ring closure to give I–III.

When titrated in ethanolic solution with sodium hydroxide VI–VIII behave as dibasic acids. When the titration is carried out electrometrically it is seen that the first jump of potential is similar to the jump generally found for carboxyphenylhydrazones,[5] the second jump is similar to the jump found for pyrazol-3-ones.[3] This is a difference from 1-(*p*-carboxyphenyl)-3-methylpyrazol-5-one which is titrated as a dibasic acid, the first jump of potential being only a hardly observable inflexion point on the titration curve.[6] The titration curves are seen in Fig. 1.

Glacial acetic acid solutions of VI–VIII may be titrated with perchloric acid in the same solvent. Fig. 2 shows the titration curves from which is estimated[4] that pK_B of the three substances are 12·2, 12·2 and 12·5 respectively, as compared with the pK_B values 12·2, 12·3 and 12·4 respectively for the corresponding 1-phenylsubstituted pyrazol-3-ones.[7] The introduction of a carboxyl group in place of a hydrogen atom in the phenyl-nucleus has evidently no significant effect on the basic properties of the pyrazolones.

When dilute sodium hydroxide is added slowly to ethanolic solutions or suspensions of I–III it is seen that the fluorescence vanishes when one equivalent of sodium hydroxide has been added. By addition of one equivalent of acid and evaporation of the solution *in vacuo* three substances may be isolated which are not the acids VI–VIII

[5] S. Veibel and H. W. Schmidt *Acta Chem. Scand.* **2**, 545 (1948).
[6] S. Veibel *Acta Chem. Scand.* **1**, 54 (1947).
[7] S. Veibel, K. Eggersen, and S. Linholt *Acta Chem. Scand.* **8**, 768 (1954).

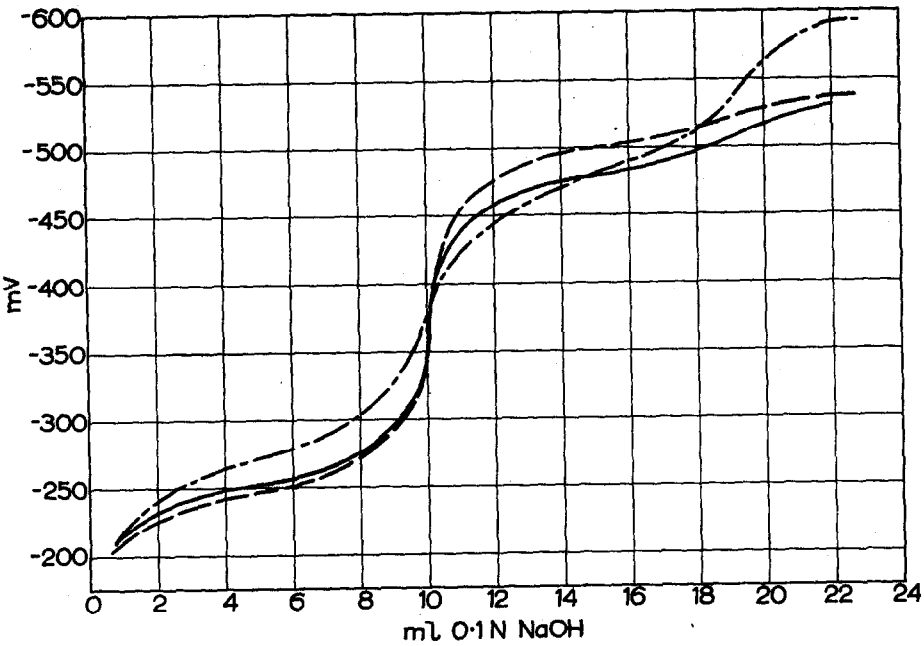


FIG. 1. Titration of 1-(*o*-carboxyphenyl)-pyrazol-3-ones with sodium hydroxide.
VI: ————
VII: — — — —
VIII: —.—.—.

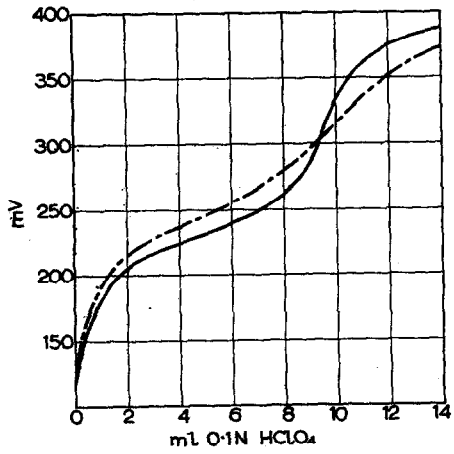


FIG. 2. Titration of 1-(*o*-carboxyphenyl)-pyrazol-3-ones with perchloric acid in glacial acetic acid.
VI and VII: ————
VIII: —.—.—

but their ethyl esters. In methanolic solution the corresponding methyl esters are formed. When the sodium hydroxide added is too strong (N instead of 0·1 N) a mixture of the free acid and the ester is formed. The formation of the ester may be compared with the formation of acid esters by addition of sodium hydroxide to ethanolic solutions of acid anhydrides.[8] We examined the effect of bases other than the hydroxide or alkoxide ion and found that trimethylamine did not catalyse the ester formation and had no effect on the ethanolic solution of I. On the other hand piperidine did catalyse a reaction, but slower than that catalysed by hydroxyl ions, which led to a mixture of ester and piperidide of VI.

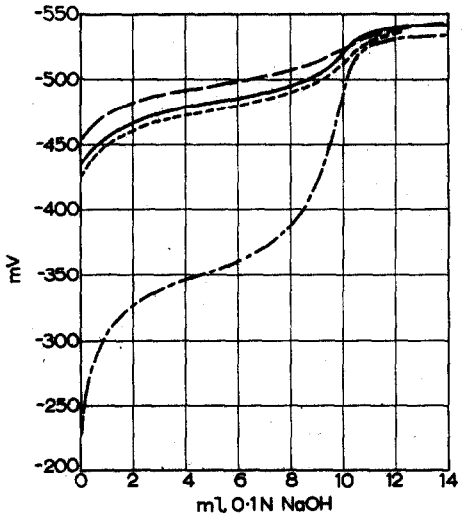


FIG. 3. Titration of 1-(*o*-ethoxycarbonylphenyl)-pyrazol-3-ones and the piperidide of 1-(*o*-carboxyphenyl)-5-methyl-pyrazol-3-one with sodium hydroxide.
Ethyl ester of VI: ———— Ethyl ester of VIII: —·—·—·
Ethyl ester of VII: — — — — Piperidide of VI: - - - - - -

The esters may be titrated both as acids with sodium hydroxide (ethanolic solution) and as bases with perchloric acid (glacial acetic acid solution). In both instances the absorption of the solution is shifted towards the longer wavelengths during the titration, and most pronounced by titration with sodium hydroxide. Absorption spectra are given below. From Fig. 3 it is seen that the titration curves with sodium hydroxide are typical curves of pyrazol-3-ones, showing no sign of the rather strong acid group which is responsible for the first jump of potential seen on Fig. 1.

From the titration curves with perchloric acid (Fig. 4) it is estimated that pK_B of the three esters are 12·3, 12·4 and 12·4 respectively, i.e. practically the same values as found for the corresponding 1-phenylpyrazol-3-ones and for the open acids. For the methyl ester of VI the pK_B-value is 12·3 as for the ethyl ester.

The piperidide of VI was titrated with sodium hydroxide and with perchloric acid. The pK_B-value was estimated to be 12·4, i.e. neither the carboxyl group nor the ester- or amide-group are modifying the basic properties of the pyrazolone.

[8] S. Veibel and C. Pedersen *Acta Chem. Scand.* 9, 1674 (1955).

In order to obtain some evidence with regard to structural changes in connection with the opening of one pyrazolone nucleus, with ester formation of the carboxyphenylpyrazolones and with the salt formation of the esters with sodium hydroxide

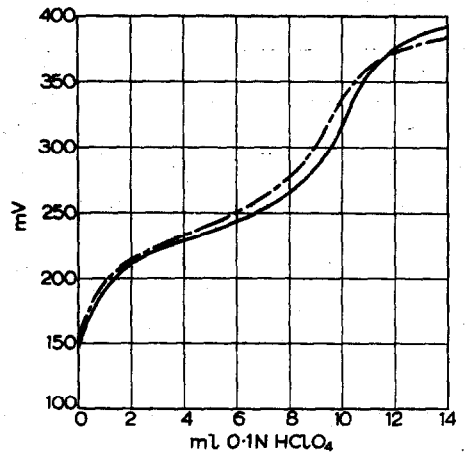


FIG. 4. Titration of 1-(*o*-ethoxycarbonylphenyl)-pyrazol-3-ones with perchloric acid in glacial acetic acid.
Ethyl esters of VI and VII: ———— Ethyl ester of VIII: —.—.—.

or perchloric acid the ultra-violet absorption of these substances was determined. The Figs. 5–10 show that:

(1) The benzo[*c*]pyrazolo[1:2-*a*]pyrazol-1:9-diones have 3 maxima of absorption, at 2000–2300 Å, at 2900 Å and at 3900 Å.

(2) The intensity of absorption in the region 2000–2300 Å is somewhat reduced by the opening of one pyrazolone nucleus, the maximum at 2900 Å is reduced to an inflexion point and the absorption at 3900 Å has been completely abolished.

(3) No significant difference between the absorption spectra of the carboxyphenylpyrazolones and their methyl esters is observed.

(4) The effect of the formation of sodium salts of the methyl esters is the re-establishment of an absorption at 2900–3000 Å which in the sodium salts is broadened towards longer wavelengths, the absorption in the whole region 2900–3900 Å being much more pronounced than for the ester in neutral solution.

(5) Salt formation with perchloric acid does not produce any significant difference in absorption.

EXPERIMENTAL

Preparation of β-acetyl o-carboxyphenylhydrazine, $HOOCC_6H_4NHNHCOCH_3$, *and β,β-diacetyl o-carboxyphenylhydrazine,* $HOOCC_6H_4NHN(COCH_3)_2$

The acetylation of *o*-carboxyphenylhydrazine was carried out according to standard procedures for the acetylation of arylhydrazines. *o*-Carboxyphenylhydrazine was liberated from an aqueous 5 per cent solution of its hydrochloride. The solution can be decolorised by shaking at room temperature with norite or charcoal. It was then filtered, cooled in ice water and cautiously neutralised with a little less than the calculated amount of 10 N sodium hydroxide, added dropwise to the mechanically stirred solution. The precipitate was filtered off and the filtrate tested for complete

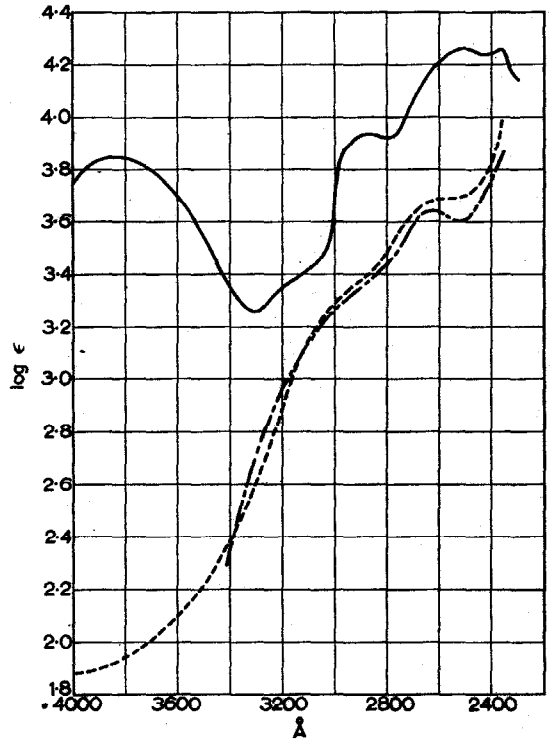


FIG. 5. Absorption of ultra-violet by 3-methyl-benzo[*c*]pyrazolo[1,2-*a*]pyrazol-1:9-dione, 1-(*o*-carboxyphenyl)-5-methyl-pyrazol-3-one and 1-(*o*-ethoxycarbonylphenyl)-5-methyl-pyrazol-3-one. Solvent: 96 per cent ethanol.
I: ———— VI: —·—·—· Ethyl ester of VI: - - - - - -

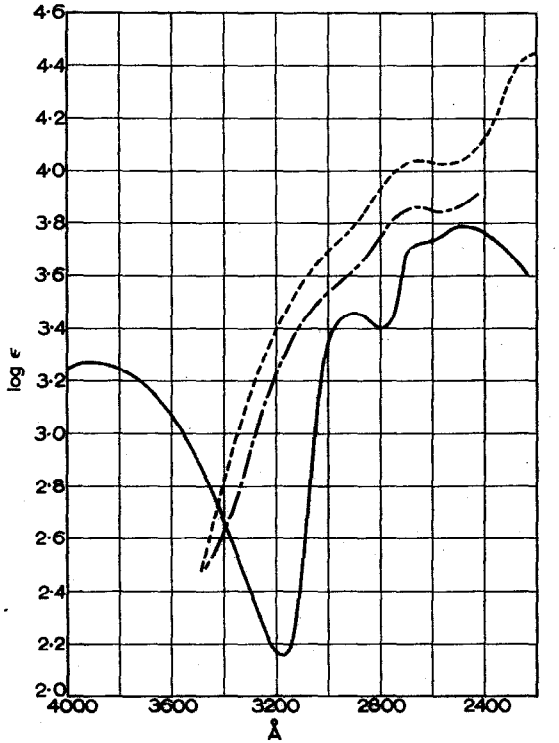


FIG. 6. Absorption of ultra-violet by 2-ethyl-3-methyl-benzo[*c*]pyrazolo [1,2-*a*]pyrazol-1:9-dione, 1-(*o*-carboxyphenyl)-4-ethyl-5-methyl-pyrazol-3-one and 1-(*o*-ethoxycarbonyl-phenyl)-4-ethyl-5-methylpyrazol-3-one. Solvent: 96 per cent ethanol.
II: ———— VII: —·—·—· Ethyl ester of VII: - - - - - -

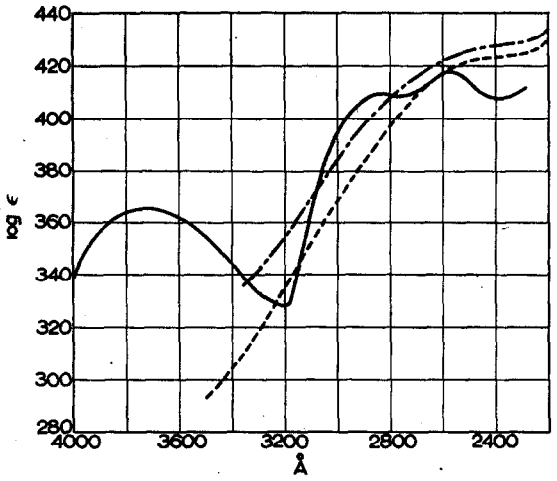


FIG. 7. Absorption of ultra-violet by 3-phenyl-benzo[*c*]pyrazolo[1,2-*a*]pyrazol-1:9-dione, 1-(*o*-carboxyphenyl)-5-phenyl-pyrazol-3-one and 1-(*o*-ethoxycarbonylphenyl)-5-phenyl-pyrazol-3-one. Solvent: 96 per cent ethanol.
III: ———— VIII: — · — · — · Ethyl ester of VIII: - - - - - -

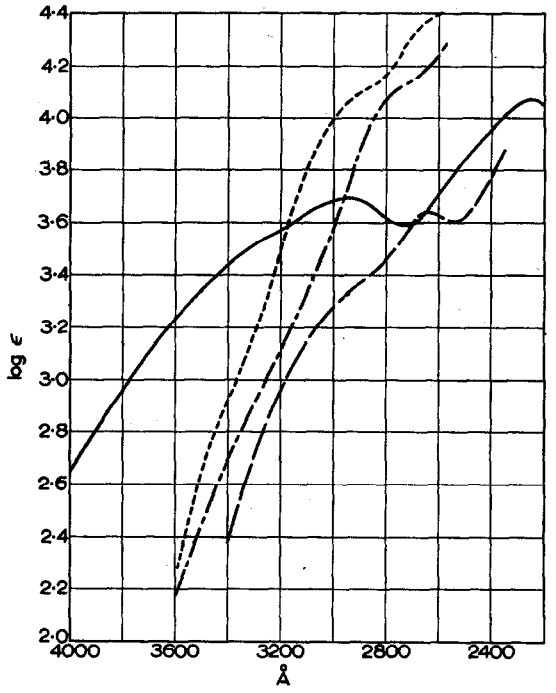


FIG. 8. Absorption of ultra-violet by 1-(*o*-methoxycarbonylphenyl) 5-methyl-pyrazol-3-one and its sodium salt, solvent 96 per cent ethanol, and of its perchlorate, solvent glacial acetic acid.
Methyl ester of VI: — — — —
Sodium salt of the methyl ester: ————
Methyl ester of VI in glacial acetic acid: - - - - - -
Perchlorate of the methyl ester: — · — · — ·

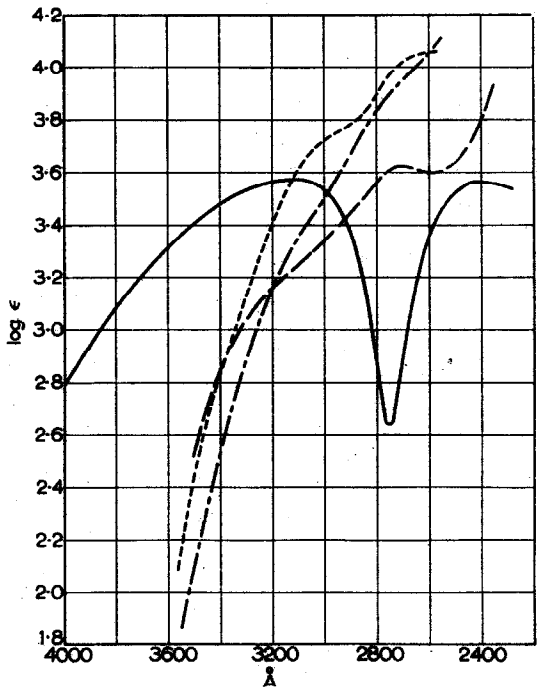


FIG. 9. Absorption of ultra-violet by 1-(*o*-methoxycarbonyl)-4-ethyl-5-methyl pyrazol 3-one and its sodium salt, solvent 96 per cent ethanol, and of its perchlorate, solvent glacial acetic acid.

Methyl ester of VII: — — — —
Sodium salt of the methyl ester: ————
Methyl ester of VII in glacial acetic ester: - - - - - -
Perchlorate of the methyl ester: —·—·—·

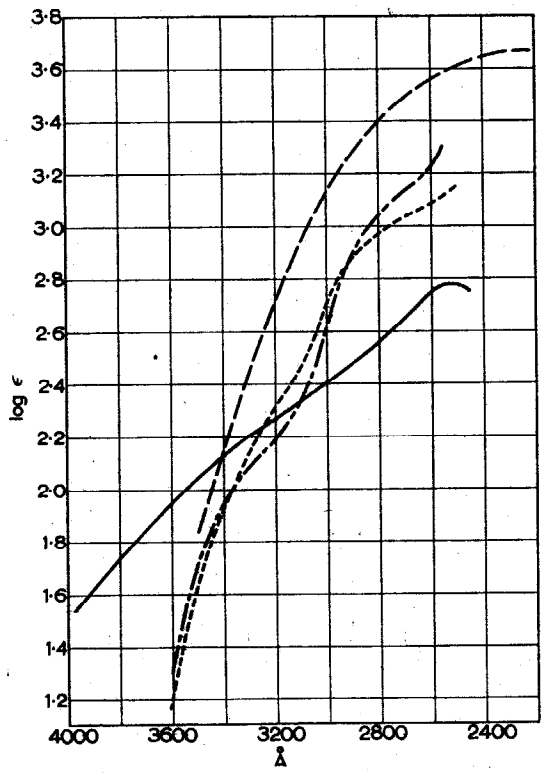


FIG. 10. Absorption of ultra-violet by 1-(*o*-methoxycarbonyl)-5-phenyl-pyrazol-3-one and its sodium salt, solvent 96 per cent ethanol, and of its perchlorate, solvent glacial acetic acid.

Methyl ester of VIII: — — — —
Sodium salt of the methyl ester: ————
Methyl ester of VIII in glacial acetic acid: - - - - - -
Perchlorate of the methyl ester: —·—·—·

neutralisation by addition of further 1-2 ml of 10 N sodium hydroxide. All precipitates were collected on the same filter, washed with water, ethanol and ether and finally air-dried.

The temperature was kept low at all stages of the reaction in order to avoid formation of benzopyrazolone by ring closure.

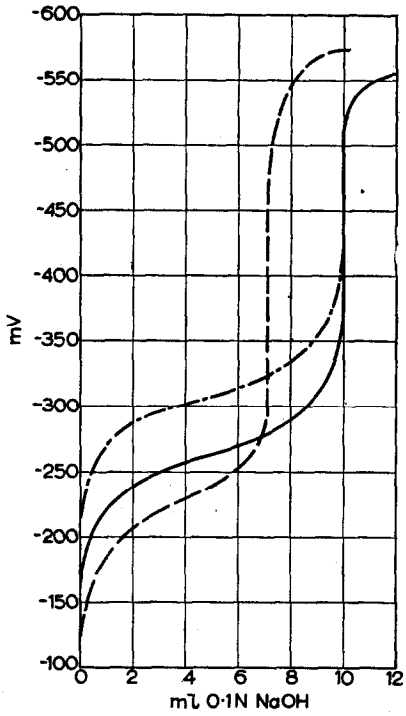


FIG. 11. Titration of β-acetyl *o*-carboxyphenylhydrazine, β,β-diacetyl-*o*-carboxyphenylhydrazine and 1-acetyl benzopyrazol-3-one.
β-Acetyl *o*-carboxyphenylhydrazine: ————
β,β-Diacetyl *o*-carboxyphenylhydrazine: — — — —
1-Acetyl benzopyrazol-3-one: —.—.—.

The free *o*-carboxyphenylhydrazine was refluxed for 2 hr with 8–10 parts (by weight) of glacial acetic acid. A quarter of the solvent was then removed *in vacuo* (bath temperature 50–60°C). The residue was cooled in water and filtered through a sintered-glass filter, washed with water and air-dried. A further crop was gained by diluting the filtrate with 2–3 volumes of water. Total yield was 68 per cent and the m.p. 243–245°C, indicating that the substance during the heating was converted into benzopyrazolone, m.p. 244°C.[9]

We tried to improve the yield by addition of 10 per cent acetic anhydride to the refluxing mixture. The result was, however, that the yield of β-acetyl *o*-carboxyphenylhydrazine was reduced and another substance with m.p. 200°C was formed in a yield of 20–30 per cent. This substance showed by electrometric titration with 0·1 N sodium hydroxide (solvent : ethanol) mol. wt. = 237·9 against 194·2 calculated for β-acetyl *o*-carboxyphenylhydrazine. The two titration curves are shown in Fig. 11. The new substance gave the following results on analysis (Found: C, 55·70; H, 5·00;

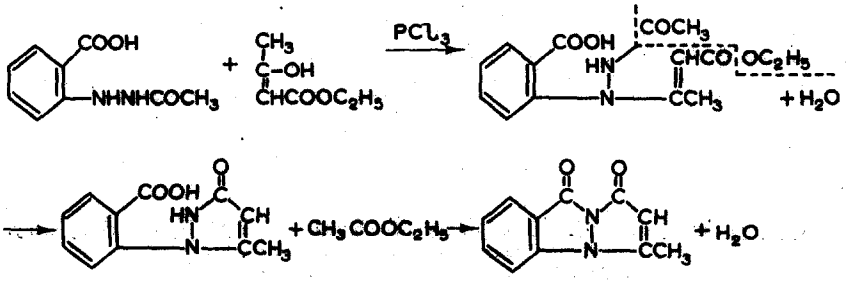
N, 11·92. mol. wt. = 237·9. $C_{11}H_{12}O_4N_2$ requires C, 55·92; H, 5·10; N, 11·86 per cent. mol. wt. = 236·2*).

This corresponds to a diacetyl derivative of *o*-carboxyphenylhydrazine. As the substance is not converted into a benzopyrazolone derivative on heating the structure β,β-diacetyl *o*-carboxyphenylhydrazine is more probable than the structure α,β-diacetyl *o*-carboxyphenylhydrazine.

3-*Methyl-benzo*[*c*]*pyrazolo*[1:2-*a*]*pyrazol*-1:9-*dione* (I)

In a 100–150 ml flask connected by a ground-glass joint to a reflux condenser 19·4 g (0·1 mole) of β-acetyl *o*-carboxyphenylhydrazine was thoroughly mixed with 26 g (0·2 mole) of ethyl acetoacetate. Eighteen ml (0·2 mole) of phosphorus trichloride were added dropwise through the reflux condenser, starting a reaction accompanied by evolution of hydrogen chloride. The vigorous reaction was controlled by cooling the flask in iced water. When all the phosphorus trichloride had been added the flask was left at room temperature for 2 hr with frequent shaking and then heated for some hours on the steam-bath till the evolution of hydrogen chloride had ceased. It was then left overnight at room temperature, whereupon 50 ml of water were added in small quantities, precipitating yellow crystals which were filtered through a sintered-glass filter and purified by recrystallisation from 10 parts (by weight) of glacial acetic acid or 20 parts (by weight) of 96 per cent ethanol.

The reactions are as follows:



Yield 12–14 g (60–70 per cent) with m.p. 268–270°C, Michaelis[2] gave m.p. 265°C (Found: C, 66·22; H, 3·92; N, 14·05 per cent. Calc. for $C_{11}H_8O_2N_2$: C, 66·00; H, 4·03; N, 14·00 per cent. mol. wt. = 200·2).

A diluted solution of the substance in glacial acetic acid shows a very brilliant blue fluorescence. Ethanolic solutions, too, are fluorescent, but not so brilliantly as are the acetic acid solutions.

2-*Ethyl*-3-*methyl-benzo*[*c*]*pyrazolo*[1:2-*a*]*pyrazol*-1:9-*dione* (II)

In a flask equipped as above 19·4 g (0·1 mole) of β-acetyl *o*-carboxyphenylhydrazine were thoroughly mixed with 24 g (0·15 mole) of ethyl α-ethylacetoacetate. Eighteen ml (0·2 mole) of phosphorus trichloride were added and the flask was heated slightly in order to start the reaction which was then continued, allowing the flask to stand for 2 hr at room temperature and then for 4 hr on the steam-bath and again at

* All microanalyses were done by Mr. Preben Hansen, Universitetets kemiske Laboratorium.

[2] E. Fischer *Ber. Dtsch. Chem. Ges.* 13, 680 (1880).

room temperature overnight. The following day the reaction was continued by heating once more on the steam-bath to ascertain that the evolution of hydrogen chloride had ceased. It was then cooled and 50 ml of iced water or, preferably, 100 ml of 96 per cent ethanol were added, hydrolysing the excess of phosphorus trichloride and leaving a resinous precipitate which crystallised when left overnight covered with ethanol. The crystals were isolated by filtration and recrystallised from 20–40 parts (by weight) of 96 per cent ethanol or 10 parts (by weight) of glacial acetic acid. Yield 6–7 g (25–28 per cent), m.p. 185°C (Found: C, 68·36; H, 5·31; N, 12·26. $C_{13}H_{12}O_2N_2$ requires C, 68·41; H, 5·30; N, 12·28 per cent. mol. wt. = 228·2).

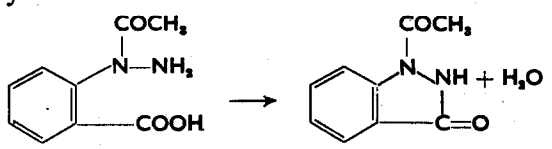
3-*Phenyl-benzo*[*c*]*pyrazolo*[1:2-*a*]*pyrazol*-1:9-*dione* (III)

The preparation of this compound was more difficult than that of the two first mentioned substances. It is recommended not to work with more than 0·05 mole (10 g) of *β*-acetyl *o*-carboxyphenylhydrazine and 0·075 mole (15 g) of ethyl benzoylacetate in each charge. The components were intimately mixed. Nine ml (0·2 mole) of phosphorus trichloride were added and the mixture was left at room temperature for some hours and then cautiously heated to 50–80°C for several hours. When the evolution of hydrogen chloride had ceased the flask was cooled and 50 ml of 96 per cent ethanol added, keeping the mixture cold by placing the flask in an iced bath. A resinous mass was formed which when left at room temperature covered with ethanol for a couple of days eventually crystallised. The crystals were isolated by filtration and recrystallised from 10–20 parts (by weight) of 96 per cent ethanol. Yield 4–4·5 g (30·35 per cent), m.p. 197–300°C (Found: C, 73·10; H, 3·85; N, 10·52. $C_{16}H_{10}O_2N_2$ requires C, 73·27; H, 3·84; N, 10·68 per cent. mol. wt. = 262·3).

Isolation of 1-*acetyl benzopyrazol*-3-*one*

Accompanying the formation of the substituted benzo [*c*] pyrazolo [1:2-*a*] pyrazol-1:9-diones a ring closure of the acetylated *o*-carboxyphenylhydrazine to benzopyrazol-3-one or an acetylated benzopyrazol-3-one may take place. From *β*-acetyl *o*-carboxyphenyl-hydrazine the unsubstituted benzopyrazol-3-one is easily prepared on heating. It has, as mentioned above, m.p. 244°C. From the reaction mixtures mentioned above we were able sometimes to isolate colourless crystals with m.p. 214–215°C which on analysis showed the composition $C_9H_8O_2N_2$, corresponding to an acetyl derivative of benzopyrazol-3-one (Found: C, 61·10; H, 4·96; N, 16·22. $C_9H_8O_2N_2$ requires C, 61·34; H, 4·57; N, 15·90 per cent. mol. wt. = 176·2).

As this substance can be titrated with sodium hydroxide (Fig. 11) and not with perchloric acid we consider it as 1-acetyl benzopyrazol-3-one, formed from *α*-acetyl *o*-carboxyphenyl-hydrazine present as an impurity in the preparations of *β*-acetyl *o*-carboxyphenyl-hydrazine used:



Opening of the ring B by addition of water or sodium hydroxide

Compounds I–III suspended in water and treated with 2 equivalents of sodium hydroxide were converted into the disodium salts of the corresponding substituted

1-*o*-carboxyphenylpyrazol-3-ones VI–VIII. Heating is unnecessary and should be avoided. Upon addition in the cold of 2 equivalents of dilute hydrochloric acid the free acids VI–VIII were precipitated. VI. m.p. 232–234°C, Michaelis[8] gave m.p. 221° (Found: C, 60·25; H, 4·53; N, 12·71. Calc. for $C_{11}H_{10}O_3N_2$: C, 60·51; H, 4·62; N, 12·844 per cent. mol. wt. = 218·2). VII. m.p. 215°C (Found: C, 63·13; H, 5·63; N, 11·55. $C_{18}H_{14}O_3N_2$ requires C, 63·38; H, 5·73; N, 11·38 per cent. mol. wt. = 246·3). VIII. m.p. 273–275°C (Found: C, 68·50; H, 4·46; N, 10·16°C. $C_{16}H_{12}O_3N_2$ requires C, 68·54; H, 4·33; N, 10·00 per cent. mol. wt. = 280·3). As indicated above these acids behave as dibasic acids when titrated in ethanolic solution with 0·1 N sodium hydroxide and as monoacid bases when titrated in glacial acetic acid solution with perchloric acid. Titration curves are seen in Figs. 1–2. Heated above the m.p. the acids lose water with closure of ring B.

Opening of the ring B by addition of sodium methoxide or sodium ethoxide

To a solution or suspension of 0·01 mole of the substances I–III in 200–300 ml of methanol or ethanol (96 per cent or absolute) 100 ml of 0·1 N sodium hydroxide (aqueous, methanolic or ethanolic) were added with mechanical stirring during 1/2–1 hr. The strong fluorescence of the solution vanishes during the addition. The solution was filtered in order to remove any undissolved particles, and the filtrate acidified with 0·01 mole of hydrochloric acid. The neutralised solution was evaporated to dryness *in vacuo* (bath temperature 30–40°C). The residue was extracted with 10–20 ml of hot methanol or ethanol, according to the solvent originally used. On cooling, the filtrate deposits crystals of the methyl- or ethyl ester of VI–VIII. Yield 70–80 per cent.

Methyl ester of VI, m.p. 163–164°C (Found: C, 62·07; H, 5·06; N, 12·09. $C_{12}H_{12}O_3N_2$ requires C, 62·07; H, 5·21; N, 12·07 per cent. (mol. wt. = 232·2).

Ethyl ester of VI, m.p. 160–161°C (Found: C, 63·28; H, 5·50; N, 11·42. $C_{13}H_{14}O_3N_2$ requires C, 63·38; H, 5·73; N, 11·38 per cent. mol. wt. = 246·3).

Methyl ester of VII, m.p. 168–169°C (Found: C, 64·51; H, 6·34; N, 10·52. $C_{14}H_{16}O_3N_2$ requires C, 64·58; H, 6·20; N, 10·76 per cent. mol. wt. = 260·3).

Ethyl ester of VII, m.p. 150–151°C (Found: C, 65·60; H, 6·77; N, 10·21. $C_{15}H_{18}O_3N_2$ requires C, 65·69; H, 6·57; N, 10·22 per cent. mol. wt. = 274·3).

Methyl ester of VIII, m.p. 135–136°C (Found: C, 69·47; H, 4·97; N, 9·49. $C_{17}H_{14}O_3N_2$ requires C, 69·38; H, 4:79; N, 9·52 per cent. mol. wt. = 294·3).

Ethyl ester of VIII, m.p. 129–130°C (Found: C, 70·18; H, 5·00; N, 9·08. $C_{18}H_{16}O_3N_2$ requires C, 70·13; H, 5·23; N, 9·09 per cent. mol. wt. = 308·3).

To catalyse the ring-opening with bases other than the hydroxyl ion or the alkoxide ion we added trimethylamine to a suspension of I in methanol. No effect was observed. Using piperidine instead of trimethylamine the substance dissolved after prolonged stirring of the suspension, and by the usual procedure a mixture of crystals was obtained from which the methyl ester and another substance was isolated. The latter had m.p. 168–169°C and gave, on titration with perchloric acid, the molecular weight 288, calculated for the piperidide of VI 285·3, for the methyl ester 232·2. The yield was, however, poor and further experiments were not made (Found: C, 67·35; H, 6·50; N, 14·88. $C_{16}H_{19}O_2N_3$ requires C, 67·36; H, 6·71; N, 14·73 per cent.

The esters were all titratable with perchloric acid, The titration curves are given in Figs. 3–4. In all titrations exactly 0·1 millimole of the ester was dissolved in 50 ml of

glacial acetic acid and titrated with a 0·1 N solution of perchloric acid in glacial acetic acid.

The piperidide, too, was titratable with perchloric acid as a monoacid base. Hardly any difference between the piperidide and the methyl ester was observed when 0·1 millimole in 50 ml was titrated.

Absorption of ultra-violet by the substances investigated

The absorption of the ultra-violet by ethanolic or glacial acetic acid solutions was determined with a Beckman DU-spectrophotometer by measuring 1:2000 or 1:5000 solutions of the substances against the solvent (ethanol, ethanol with addition of 1 equivalent of sodium hydroxide, glacial acetic acid or glacial acetic acid with addition of 1 equivalent of perchloric acid).

The absorption curves are given in Figs. 5–10.

Financial support from the Carlsberg Foundation is gratefully acknowledged.