Studies on Pyrazolones

IX. Reactions between Pyrazole Blue and Ethyl Cyanoacetate
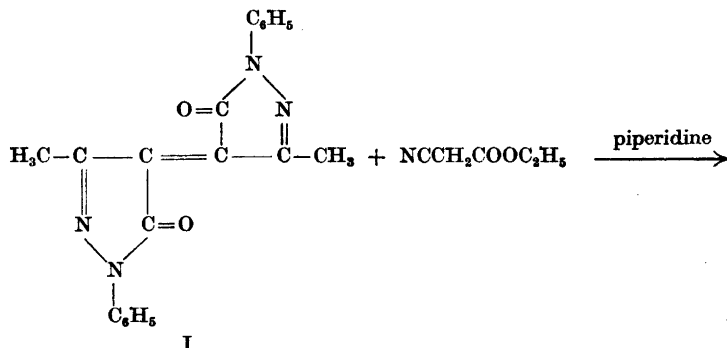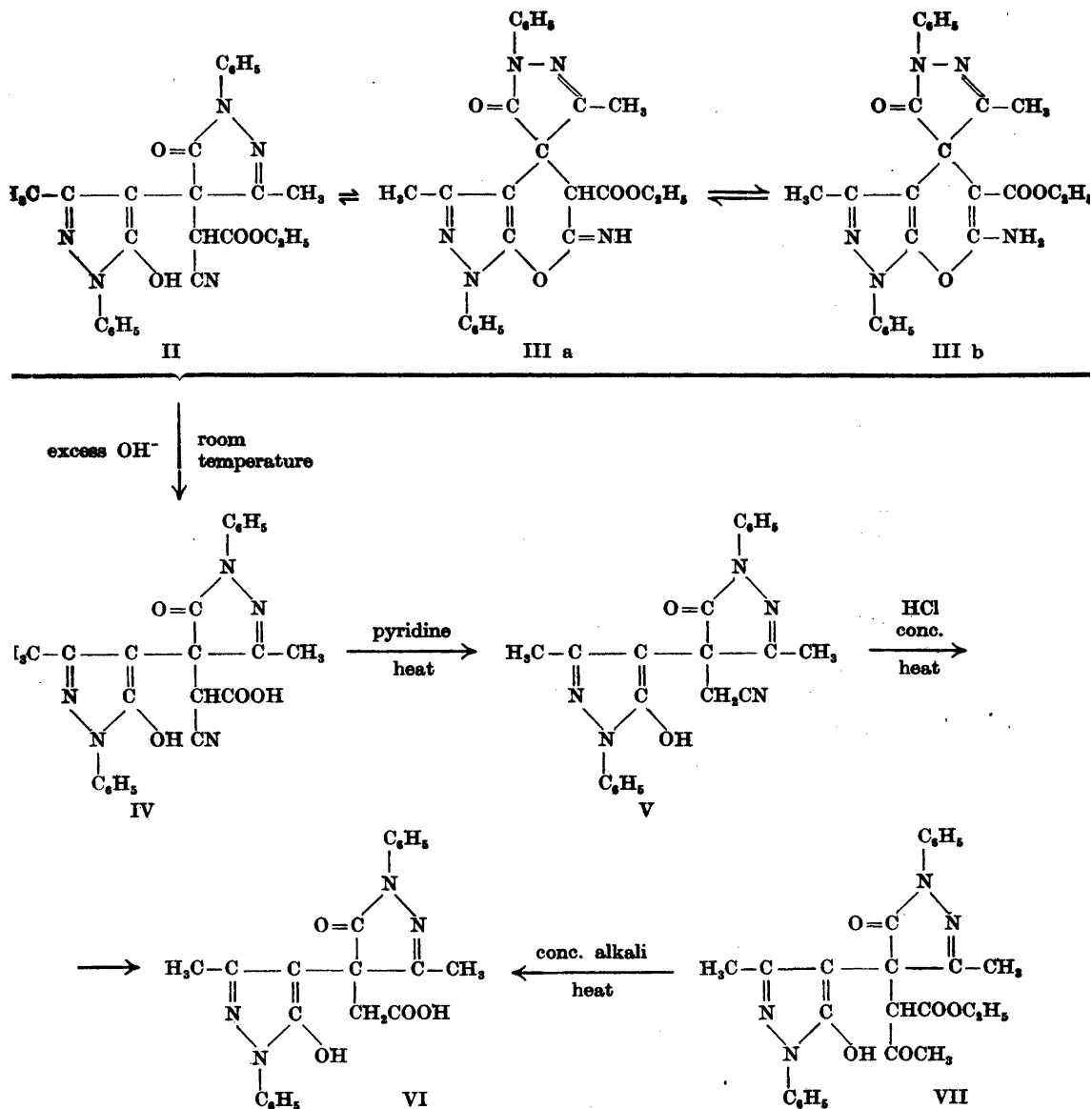
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The addition compounds II and III have been prepared from pyrazole blue (I) and ethyl cyanoacetate. By degradation of the adducts some 4-substituted 1,1'-diphenyl-3,3'-dimethyl-[4,4'-bi-2-pyrazoline]-5,5'-diones have been synthesized, *viz.* bispyrazolonyl-cyanoacetic acid (IV), 4-cyanomethylbispyrazolone (V) and bispyrazolonylacetic acid (VI).

In the presence of a small amount of piperidine, a chloroform solution of pyrazole blue (I) was rapidly decolorized when boiled with an equimolar amount of cyanoacetic ester. The reaction product obtained was a neutral addition compound, $C_{25}H_{23}N_5O_4$. On treatment with excess of alkali at room temperature it yielded an acid, $C_{23}H_{19}N_5O_4$, for which structure IV is suggested on the basis of the following facts. It is a dibasic acid. On decarboxylation it gave a cyanomethylated bispyrazolone (V), which could be hydrolysed to the acid VI, identical with the product obtained by acid cleavage of the adduct, VII, from pyrazole blue and ethyl acetoacetate.

These degradation reactions show that both the bispyrazolonyl group and the cyanoacetic acid skeleton are present in $C_{25}H_{23}N_5O_4$. These facts together with the neutral reaction of the compound indicate that III (a, b or — presumably — an equilibrium of both) is the correct structure for this adduct.

I

II   III a   III b

excess OH⁻ | room temperature

IV   pyridine heat → V   HCl conc. heat →

VI   ← conc. alkali heat   VII

The first step in the formation of III is considered to be a normal Michael addition of ethyl cyanoacetate to pyrazole blue giving the bispyrazolonylcyano-acetate, II. It is a well-known fact that both Michael condensations [1] and the reversible addition of alcohols to nitriles with formation of iminoethers are catalysed by basic compounds (Nef [2], Marshall and Acree [3]). In spite of the fact that the hydroxyl group of II has acidic properties, it is reasonable to
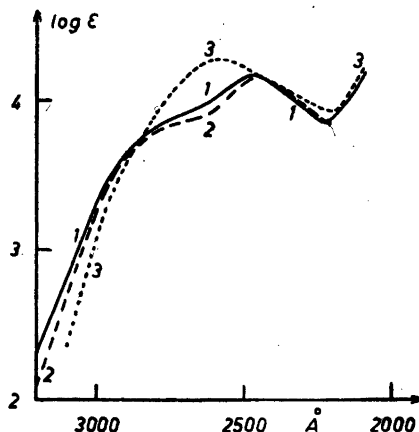
Fig. 1. UV absorption curves of the compounds II (1), III (3) and IV (2) in ethanol solution.

suppose that it adds to the cyano group of II in a way analogous to an alcoholic hydroxyl, i. e. that II is isomerized to III a (III a ⇌ III b). The ring closure ought to be facilitated since a six-membered ring is formed and since the structure III b is stabilized by resonance.

In order to check the proposed mechanism it was of interest to prepare and examine compound II. By performing the addition of ethyl cyanoacetate to pyrazole blue at room temperature, a mixture of the neutral compound, III, and the isomeric, acidic product, II, could be obtained. The components were separated by virtue of their different solubilities. The UV absorption curves of the two products were distinctly different. The curve of the acidic compound was very similar to the corresponding curve of IV (Fig. 1). Excess of dilute alkali at room temperature hydrolysed both products with formation of IV.

An ethanol solution of II was slowly isomerized to III even at room temperature. This isomerization was catalysed by a small amount of piperidine. In boiling chloroform containing a trace of piperidine (the same conditions as prevailed when III was prepared directly from pyrazole blue and ethyl cyanoacetate), the ring closure of II to form III was rapid. Dry hydrogen chloride (cf. Pinner [4]) in ethanol solution or heating of the solid compound also caused isomerization of II. All these facts are in favour of the proposed reaction sequence I→II→III. — The easy ring closure observed with II did not take place with the acids IV or V.

o-Hydroxy-α-phenylcinnamic nitrile [5] (VIII) has been found to isomerize in a similar manner to compound II but with greater ease. In ethanol solution it was completely transformed into the iminolactone, 2-imino-3-phenylcoumarine (IX) in a few hours. The solid nitrile slowly changed into the coumarine derivative even at room temperature.

VIII   IX
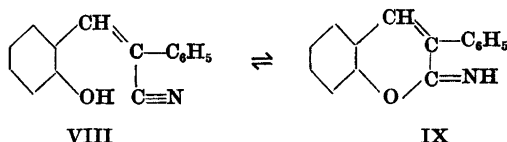
The isomerization of II to form III is reversible, for brief treatment of III with an equivalent amount of alkali yielded compound II, in addition to compound IV. Long treatment with excess of alkali gave only IV.

Houben and Pfankuch [6] made the similar observation that the iminolactone ring of 2-imino-3-phenylcoumarine is split by alkali to form o-hydroxy-α-phenylcinnamic nitrile (cf. Schlesinger [7]).

The acidic properties of compound II are of interest. The introduction of the electron attracting bispyrazolonyl group into the ethyl cyanoacetate molecule increases the acidity of the active hydrogen atom in the α-position of the cyano group with the result that, though ethyl cyanoacetate is only slightly acidic towards alizarine yellow in ethanol-water solution, its bispyrazolonyl derivative could be titrated as a dibasic acid using the same indicator, though with a poor end point. In IV (and of course in III and V) the cyanoacetate hydrogen is not acidic towards alizarine yellow.

The IR spectra[9] of the two addition compounds of pyrazole blue and ethyl cyanoacetate have been studied. The acid II had a distinct, though not very strong nitrile band at $2\ 240 \pm 15$ cm^{-1}, whereas the neutral compound exhibited no $C \equiv N$ absorption. This provides further support for III as the structure of the neutral adduct. However, great caution is necessary when drawing conclusions from the IR spectra of the nitriles. Thus a study of the absorption of IV, which compound certainly contains a cyano group, showed that the existence of a $C \equiv N$ band in the spectrum of the free acid was doubtful, whereas the potassium salt of IV had a strong $C \equiv N$ absorption band at $2\ 240 \pm 15$ cm^{-1}. Compound V (prepared from IV by decarboxylation) had a distinct but not very intense nitrile band at $2\ 240 \pm 15$ cm^{-1} (cf. Kitson and Griffith [8]).

EXPERIMENTAL

Preparation of compound III from pyrazole blue and ethyl cyanoacetate. Pyrazole blue (13.5 g), ethyl cyanoacetate (7 ml), chloroform (50 ml) and a few drops of piperidine were boiled until decolorization was complete (about 5 minutes). On standing a colourless product separated from the cooled solution. It was collected by filtration and washed with ethanol and ether. Impurities were removed by extraction with boiling ethanol. The product was dried *in vacuo* at 100°. Yield 17.4 g (97 %); m. p. about 245° with decomposition. The compound was only slightly soluble in most solvents. (Found: C 65.1; H 5.1; N 15.2. $C_{25}H_{23}N_5O_4$ requires C 65.6; H 5.1; N 15.3.) For UV absorption curve see Fig. 1.

Alkaline hydrolysis of compound III with the formation of IV. A suspension of III (7.6 g) in a solution of potassium hydroxide (8 g) in methanol (75 ml) and water (5 ml) was shaken for half an hour and then left overnight. The hydrolysate was precipitated with water and dilute sulphuric acid and the precipitate filtered, washed with water and air-dried. The crude product was dissolved in ethyl acetate at room temperature. From the solution the pure acid soon separated as colourless crystals. Yield 5.9 g of purified product, m. p. about 160° (decomp.) (Found: C 64.1; H 4.5; N 16.2; equiv. wt. 215. $C_{23}H_{19}N_5O_4$ requires C 64.3; H 4.5; N 16.3; equiv. wt. 215.) UV absorption see Fig. 1.

Decarboxylation of IV with formation of 1,1'-diphenyl-3,3'-dimethyl-4-cyanomethyl-[4,4'-bi-2-pyrazoline]-5,5'-dione (V). The bispyrazolonylcyanoacetic acid (IV) (5.8 g), ethyl alcohol (50 ml) and pyridine (0.75 ml) were boiled on a water bath for ten minutes. The decarboxylated product was precipitated with water and dilute hydrochloric acid. The precipitate was collected by filtration, washed with water and air-dried. After crystallization from ethyl acetate and ethanol, 2.9 g (56 %) of the colourless 1,1'-diphenyl-3,3'-dimethyl-4-cyanomethyl-[4,4'-bi-2-pyrazoline]-5,5'-dione (V) was obtained. It was

dried at 0.1 mm Hg, 100°. M. p. 160°. (Found: C 68.6; H 5.1; N 18.1; equiv. wt. 385 on titration using thymolphthalein indicator, 391 determined by means of the cyano group. $C_{22}H_{19}N_5O_2$ requires C 68.6; H 5.0; N 18.2; equiv. wt. 385.) The product was soluble in ethanol, chloroform and acetone, but only slightly soluble in ether and benzene.

Hydrolysis of 1,1'-diphenyl-3,3'-dimethyl-4-cyanomethyl-[4,4'-bi-2-pyrazoline]-5,5'-dione. The decarboxylated product (V) (0.2494 g) was boiled with a few ml of concentrated hydrochloric acid for one hour. The hydrolysate was precipitated with water, filtered, washed with water and air-dried. Impurities were removed by boiling the product once with ethyl acetate. The substance was then dissolved in ethyl alcohol and the solution evaporated to dryness, when an unstable modification was obtained, which was soluble in ethyl acetate. On scratching colourless crystals separated from the solution, m. p. 213° (decomp.) (Found: C 65.4; H 5.2; N 13.7; equiv. wt. 202. $C_{22}H_{20}N_4O_4$ requires C 65.3; H 5.0; N 13.9; equiv. wt. 202.)

To the mother liquor from the hydrolysis a large excess of sodium hydroxide was added, and the ammonia formed was distilled into 0.1050 N hydrochloric acid (10.00 ml). After distillation, 4.26 ml of 0.0966 N barium hydroxide solution was needed for neutralization. Hence the equiv. wt. of the cyano compound was 391 (calc. for the cyanomethylated bispyrazolone (V) 385).

Addition of ethyl acetoacetate to pyrazole blue with the formation of VII. Pyrazole blue (5.0 g), ethyl acetoacetate (2.4 g), ethyl alcohol (25 ml) and piperidine (0.5 ml) were mixed together. A rapid decolorization took place at room temperature. The colourless addition product separated immediately, but was dissolved by boiling the mixture briefly to ensure complete reaction. After cooling, the precipitation was completed by addition of water and dilute hydrochloric acid. The product was filtered off and washed with water and ethanol. Yield 6.7 g. Impurities were removed by extraction with ether and by crystallization from ethanol. The product was dried *in vacuo* (0.1 mm Hg) at 80°. It was difficult to obtain a solvent free product without decomposition taking place. M. p. 106°. (Found: C 64.8; H 6.0; N 11.6; equiv. wt. 475. $C_{26}H_{26}N_4O_5$ requires C 65.8; H 5.5; N 11.8; equiv. wt. 475.)

Acid cleavage of compound VII. The preceding product (VII) was heated on a boiling-water bath with ethanol and excess of concentrated potassium hydroxide solution for 5 minutes. On acidification the cleavage product separated. It was filtered off, washed with water and air-dried. Impurities were removed as previously described. M. p. 214° (decomp.) (Found: C 65.1; H 4.9; N 13.9; equiv. wt. 203. Calc. for $C_{22}H_{20}N_4O_4$: C 65.3; H 5.0; N 13.9; equiv. wt. 202.) The light absorption of this compound was identical with the absorption of the product obtained by hydrolysis of V.

Preparation of compound II from pyrazole blue and ethyl cyanoacetate. A mixture of pyrazole blue (1.35 g), ethyl cyanoacetate (0.7 ml), chloroform (5 ml) and a trace of piperidine was shaken at room temperature until decolorization took place. On addition of ethanol and scratching, crystals of III (0.25 g) separated.

The chloroform was rapidly removed from the filtrate *in vacuo* at room temperature, and the ethanol solution was immediately poured into N hydrochloric acid. The acid II, which precipitated, was collected by filtration, washed with water and dried *in vacuo*. The product could be purified by solution in cold benzene and precipitation with light petroleum. Benzene insoluble crystals (1.7 g) were obtained. The last trace of benzene was removed *in vacuo*. The product, which was hygroscopic, melted at 116—120°. When the heating was continued, the melt solidified, owing to ring closure with formation of III. At 240—245° it melted again with decomposition. (Found: C 65.2; H 5.0; N 15.3; equiv. wts 454 (potentiometric titration) and 230 (titration with sodium methoxide [10]). Calc. for $C_{25}H_{23}N_5O_4$: C 65.6; H 5.1; N 15.3; equiv. wts 457 and 229.) For UV absorption curve see Fig. 1.

The acid was isomerized to the neutral compound III, a) when heated in solid form or in solution, b) when kept in ethanol solution for several days (with piperidine as catalyst one day was sufficient), c) when its ethanol solution was treated with dry hydrogen chloride. The isomer III formed was in all cases identified by its melting point, neutral reaction, slight solubility in most solvents and UV absorption curve.

At room temperature alkali hydrolysed the ester but not the cyano group of II, compound IV being formed.

Partial hydrolysis of III. Product III (1.45 g) was shaken with 5 ml of 1.3 N methanolic potassium hydroxide solution for ten minutes. Undissolved material was removed by

filtration, and the filtrate was poured into N hydrochloric acid. The precipitate formed was washed with water and air-dried. The colourless product melted partly at 120°, solidified again and was decomposed at 160°. These facts as well as the equivalent weights of the product and the UV absorption (maximum at 250 mμ) indicate that a mixture of II and IV was formed.

o-Hydroxy-a-phenylcinnamic nitrile (VIII) and 2-imino-3-phenylcoumarine (IX). o-Hydroxy-a-phenylcinnamic nitrile (VIII) was prepared according to Borsche and Streitberger[5] and treated with alkali to transform any 2-imino-3-phenylcoumarine present into the hydroxynitrile. (Found: C 80.3; H 5.0; N 6.1. Calc. for $C_{15}H_{11}NO$: C 81.4; H 5.0; N 6.3.) 2-Imino-3-phenylcoumarine (IX) was prepared according to Houben and Pfankuch[6].

Treatment of an ethanolic solution of VIII with a small amount of piperidine for three hours and subsequent acidification with acetic acid yielded product IX. When a solution of VIII in ethanol was kept overnight without any catalyst, the same isomerization took place. The products were identified by their light absorption and different solubilities in concentrated hydrochloric acid (*cf.* Houben and Pfankuch[6]).

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