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Studies on Pyrazolones

VIII. 1,1′-Diphenyl-3,3′-dimethyl-4-cyano-[4,4′-bi-2-pyrazoline]-5,5′-dione and its Conversion to 1-Phenyl-3-methyl-4-(1-phenyl-3-methyl-5-amino-4-pyrazolyl)-5-pyrazolone

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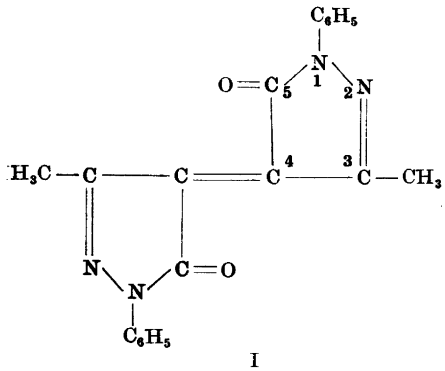
Addition of hydrocyanic acid to pyrazole blue (I) gives 1,1′-diphenyl-3,3′-dimethyl-4-cyano-[4,4′-bi-2-pyrazoline]-5,5′-dione (II), which on acid hydrolysis furnishes 1,1′-diphenyl-3,3′-dimethyl-[4,4′-bi-2-pyrazoline]-5,5′-dione (III). With alkali, however, 1-phenyl-3-methyl-4-(1-phenyl-3-methyl-5-amino-4-pyrazolyl)-5-pyrazolone (V) is formed. The mechanism of this rather unexpected reaction is discussed.

Sodium cyanide easily reacts with pyrazole blue (I) at room temperature with the formation of the sodium salt of 1,1′-diphenyl-3,3′-dimethyl-4-cyano-[4,4′-bi-2-pyrazoline]-5,5′-dione (II). When the cyano compound is treated with concentrated sulphuric acid, carbon dioxide is evolved and 1,1′-diphenyl-3,3′-dimethyl-[4,4′-bi-2-pyrazoline]-5,5′-dione (III) is formed. These reactions can be interpreted in the following way:

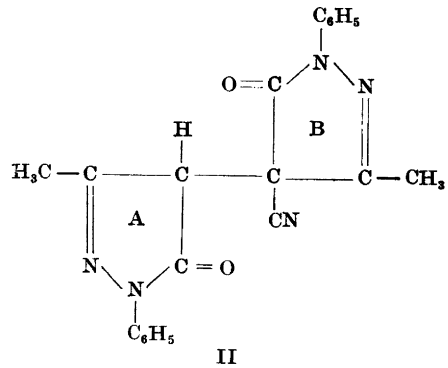
Py = Py → PyHPyCN → PyHPyCOOH → PyHPyH(Py = IV or tautomeric forms).

Treatment of II with alkali and subsequent acidification does not, however, give the expected dibasic acid, III. The product formed is a monobasic acid which similar to III is stable towards boiling, dilute alkali and acids. It has the composition $C_{20}H_{19}N_5O$ and like III forms a salt with two moles of hydrogen chloride. The free compound is obviously 1-phenyl-3-methyl-4-(1-phenyl-3-methyl-5-amino-4-pyrazolyl)-5-pyrazolone (V). This structure is supported by the fact that in neutral and acid solutions the differences between the light absorption curves of 1,1′-diphenyl-3,3′-dimethyl-[4,4′-bi-2-pyrazoline]-5,5′-dione and V are similar to the differences between the curves of 1-phenyl-3-methyl-5-pyrazolone and 1-phenyl-3-methyl-5-aminopyrazole (Figs. 1 and 2).

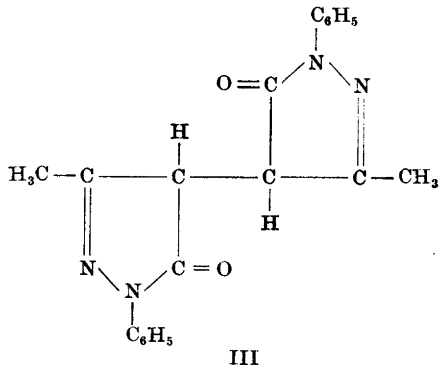
The reactions involved in the transformation of II into V are not immediately obvious. However, the electron attracting C≡N group in the four position of product II is likely to weaken the C_5—N bond of ring B of II, and hence



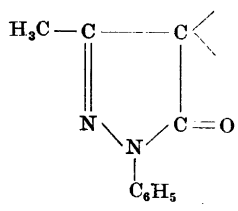
I



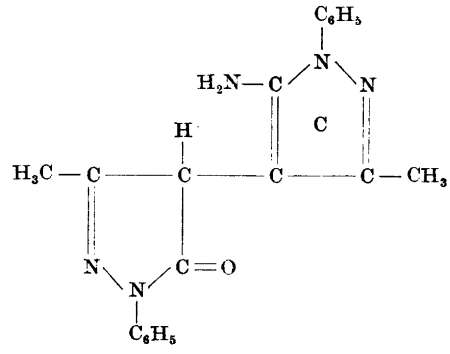
II



III



IV



V

an attractive mechanism is hydrolytic fission, followed by decarboxylation and the formation of a new fivemembered ring (C of V) containing the carbon atom of the C≡N group.

In order to test this hypothesis, 1,1′-diphenyl-3,3′-dimethyl-4-[^{14}C]cyano-[4,4′-bi-2-pyrazoline]-5,5′-dione (II) was prepared by addition of ^{14}C-labelled sodium cyanide to pyrazole blue. When the labelled cyano compound was treated with dilute, carbonate-free sodium hydroxide solution, unlabelled

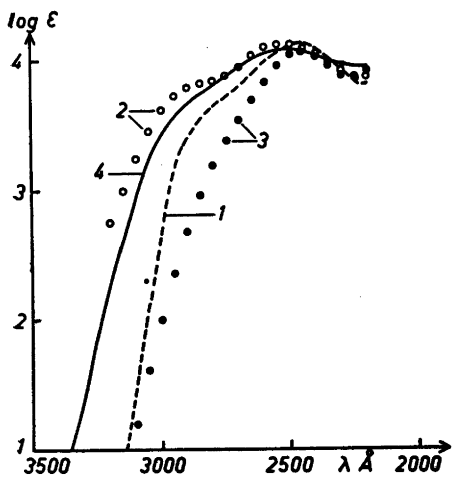


Fig. 1. Light absorption curves of 1-phenyl-3-methyl-5-pyrazolone (1), 1,1'-diphenyl-3,3'-dimethyl-[4,4'-bi-2-pyrazoline]-5,5'-dione (2), 1-phenyl-3-methyl-5-aminopyrazole (3) and 1-phenyl-3-methyl-4-(1-phenyl-3-methyl-5-amino-4-pyrazolyl)-5-pyrazolone (4) in ethanol.

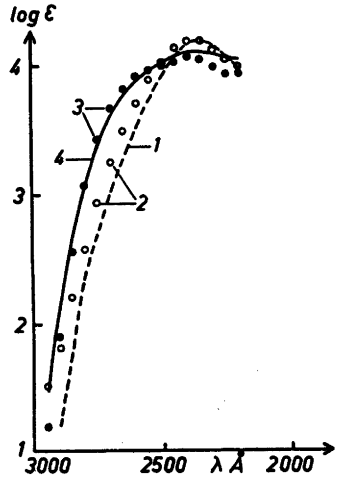


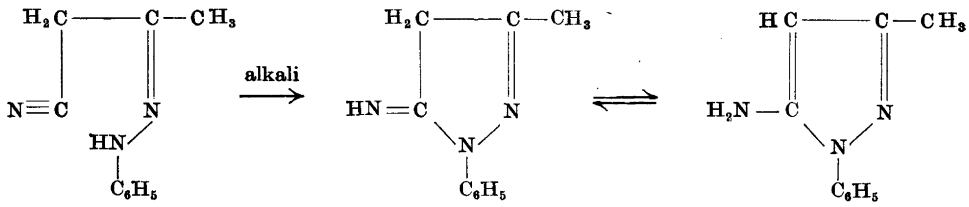
Fig. 2. Light absorption curves of 1-phenyl-3-methyl-5-pyrazolone (1), 1,1'-diphenyl-3,3'-dimethyl-[4,4'-bi-2-pyrazoline]-5,5'-dione (2), 1-phenyl-3-methyl-5-aminopyrazole (3) and 1-phenyl-3-methyl-4-(1-phenyl-3-methyl-5-amino-4-pyrazolyl)-5-pyrazolone (4) in ethanol with 150 ml of concentrated sulphuric acid per liter.

barium carbonate could be precipitated from the alkaline solution. Precipitation of V with acid yielded a product which contained the same amount of ^{14}C as the cyano compound. Consequently the eliminated carbon atom does not come from the nitrile group, but from a ring. Thus ring B of compound II has been split by alkaline hydrolysis with formation of VIII, and the product VIII has been decarboxylated to form IX in good agreement with the hypothesis.

Cleavage of a pyrazolone ring by alkali was observed by Knorr [1] as early as 1887. He obtained the phenylhydrazone of acetylglyoxylic acid by boiling rubazonic acid with alkali, probably *via* the intermediate 1-phenyl-3-methyl-4,5-pyrazoledione.

The facile decarboxylation in alkaline solution met with above is to be expected, as there are in VIII three multiple linkages in β-γ-position of the carboxyl group (*cf.* the esters of methanetetracarboxylic acid [2] with three double bonds in β-γ-positions and of 1-propene-1,3,3-tricarboxylic acid [3] with two).

Ring-closure of IX to form X probably takes place in the alkaline solution, for after storage overnight a solution of II in *N* methanolic potassium hydroxide has the same UV absorption as a solution of V in the same solvent ($\lambda_{max} = 255$ mμ), whereas neutral solutions of II and V have different absorption curves ($\lambda_{max\ II} = 245$ mμ; $\lambda_{max\ V} = 252$ mμ). Moreover, the phenylhydrazone of cyanoacetone (VI) can be isomerized to 1-phenyl-3-methyl-5-aminopyrazole (VII) by dilute alkali at room temperature.



VI VII

Mohr [4] has shown that the isomerization VI → VII is brought about by warm, dilute acids, and Bell [5] that concentrated hydrochloric acid has the same effect. In the preparation of V only cold, very dilute acid is used for a short time at the final stage, and hence the acid is not likely to cause the ring-closure.

Consequently the formation of 1-phenyl-3-methyl-4-(1-phenyl-3-methyl-5-amino-4-pyrazolyl)-5-pyrazolone from 1,1′-diphenyl-3,3′-dimethyl-4-cyano-[4,4′-bi-2-pyrazoline]-5,5′-dione can be formulated as shown on p. 801.

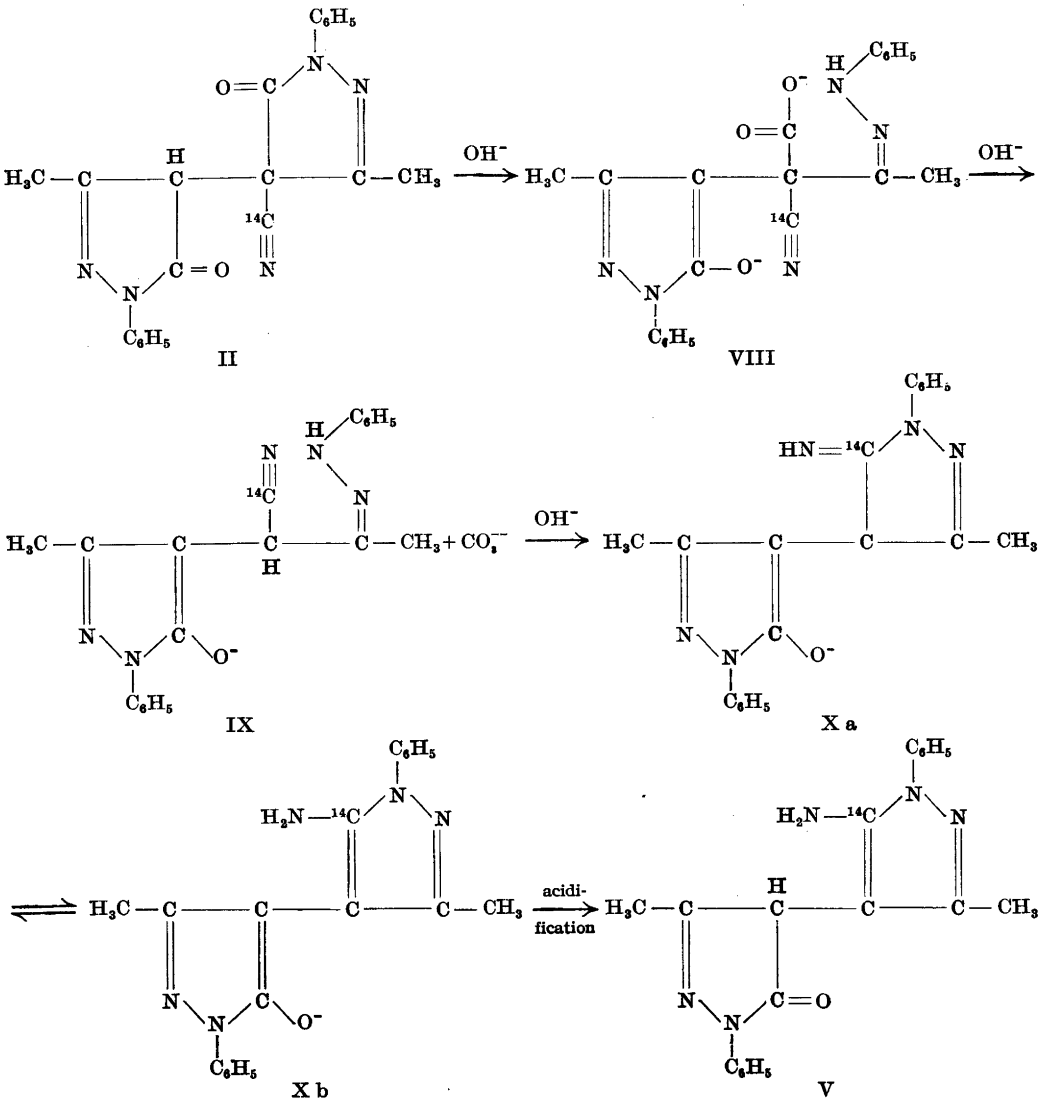
EXPERIMENTAL

1,1′-Diphenyl-3,3′-dimethyl-4-cyano-[4,4′-bi-2-pyrazoline]-5,5′-dione (II). Sodium cyanide (1.65 g) in water (5 ml) was added to a suspension of pyrazole blue (7.8 g) in ethanol (10 ml). The mixture was stirred until all the pyrazole blue had reacted (2—3 minutes), when water (250 ml) was added to the red solution. The PyHPyCN formed was precipitated by the addition of acid (10 ml of 4 *N* hydrochloric acid), filtered, washed with water and air-dried.

The product was purified by dissolving in boiling benzene and precipitating with petroleum ether. A small part of the precipitate was transformed into a benzene-insoluble form by heating at 90°—100° C. The rest was dissolved in benzene and seeded with the heated portion. Colourless crystals, soluble in ethanol and acetone, insoluble in benzene, separated. Yield of pure product: 7.5 g (89 %), m. p. 198° (with decomposition). (Found: C 67.8; H 4.8; N 19.0; equiv. wt. 371. Calc. for $C_{21}H_{17}N_5O_2$: C 67.9; H 4.6; N 18.9; equiv. wt. 371.) PyHPy^{14}CN was prepared analogously on a small scale.

Acid hydrolysis of 1,1′-diphenyl-3,3′-dimethyl-4-cyano-[4,4′-bi-2-pyrazoline]-5,5′-dione. PyHPyCN (II) (0.79 g) was heated for a few minutes with sulphuric acid monohydrate (5 ml). Carbon dioxide was evolved. The reaction product was precipitated with ice-water, filtered, washed with water and air-dried. The 1,1′-diphenyl-3,3′-dimethyl-[4,4′-bi-2-pyrazoline]-5,5′-dione (0.68 g) formed was purified by extraction of the byproducts with boiling ethanol. It was identified by the equiv. wt., 173, and the formation of pyrazole blue with nitrous acid. PyHPyH was also obtained when the cyano compound was dissolved in concentrated sulphuric acid at room temperature and the solution left overnight.

1-Phenyl-3-methyl-4-(1-phenyl-3-methyl-5-amino-4-pyrazolyl) - 5 - pyrazolone (V) by alkaline hydrolysis of 1,1′-diphenyl-3,3′-dimethyl-4-cyano-[4,4′-bi-2-pyrazoline]-5,5′-dione (II). PyHPyCN (2.1 g) was dissolved in 2.5 *N* sodium hydroxide solution (30 ml) and left overnight. Dilute hydrochloric acid was then added. It caused precipitation of the reaction product and impurities. Further addition of acid dissolved the main product but left impurities undissolved. They were removed by filtration, and 0.5 *N* sodium hydroxide was added to the filtrate until precipitation was complete. The precipitate was filtered, washed with water and air-dried. The product was sometimes readily soluble in acetone, sometimes insoluble. In the former case it was purified by solution in acetone, from which crystals soon separated. In the second case purification was simply achieved by extraction with small quantities of acetone. The product can also be purified *via* its hydrochloride. Yield: 1.6 g, m.p. 230—235° with decomposition. (Found: C 69.4; H 5.6;



N 20.1; O 4.70; equiv. wt. 345. $C_{20}H_{19}N_5O$ requires C 69.5; H 5.5; N 20.3; O 4.63; equiv. wt. 345.) 1-Phenyl-3-methyl-4-(1-phenyl-3-methyl-5-amino-4-[5-^{14}C]pyrazolyl)-5-pyrazolone was prepared in the same way.

The hydrochloride was obtained by boiling the substance with concentrated hydrochloric acid. White crystals formed. When heated, hydrogen chloride was liberated, and the substance finally melted at the same temperature as the free aminopyrazolone, about 235°. (Found: C 57.3; H 5.2; N 16.7; equiv. wt. 139.0. $C_{20}H_{19}N_5O$, 2HCl requires C 57.4; H 5.1; N 16.7; equiv. wt. 139.4.)

Measurement of radioactivity. The isotope contents of the ^{14}C-labelled pyrazolones were determined with thin endwindow Geiger-Müller tubes on samples containing less

than 0.1 mg/cm². The samples were prepared by evaporation of ethanol solutions of the products on aluminium planchets. The activity of PyHPy^{14}CN (II) was 7.9×10^9 counts/min./mole, the activity of compound V also 7.9×10^9 counts/min./mole. The ^{14}C-content of barium carbonate, prepared from the carbonate formed during the reaction II → V, was determined on an infinitely thick sample. The activity was negligible.

Isomerisation of cyanoacetone phenylhydrazone with alkali. Cyanoacetone phenylhydrazone was dissolved in ethanol, and 2.5 *N* sodium hydroxide solution was added. The solution was kept overnight, and the product formed was precipitated with water and purified by one crystallization from toluene. It had the same melting point, 115°, and light absorption as an authentic 1-phenyl-3-methyl-5-aminopyrazole. The mixed melting point was unchanged.

Light absorption measurements. In the expression $\log \varepsilon = \log \log \frac{I_0}{I} - \log c \times 1$, used in the diagrams, c is expressed in pyrazole units per liter.

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