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Studies on Pyrazolones

I. Light Absorption and Constitution of Certain 4-Halo-5-pyrazolones

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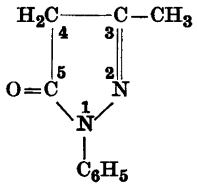
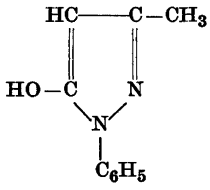
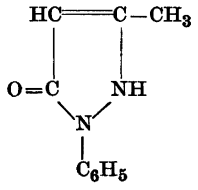
By studying the light absorption of 1-phenyl-3-methyl-5-pyrazolone and its N- and C-alkyl derivatives, Biquard and Grammaticakis[1] showed in 1941 that 1-phenyl-3-methyl-5-pyrazolone exists in three forms (I—III) in a state



I

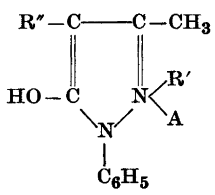


II

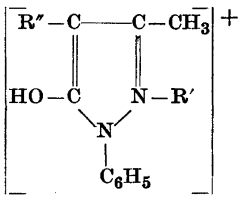


III

of equilibrium. These forms had already been proposed by Knorr [2] in 1896. In 1940 and 1941, Valyashko and Bliznyukov [3] published investigations on the light absorption of various pyrazolones and pyrazoles, and, on the basis of the absorption curves, deduced the structures of the substances. They confirm the salt formula (IV) proposed by Knorr [2] (the formula is written in a modern



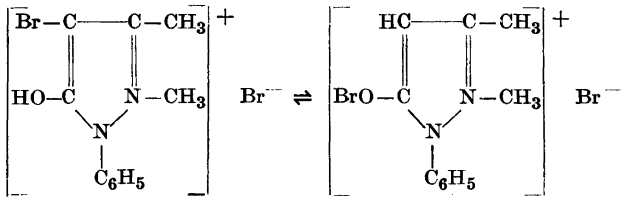
IV



V

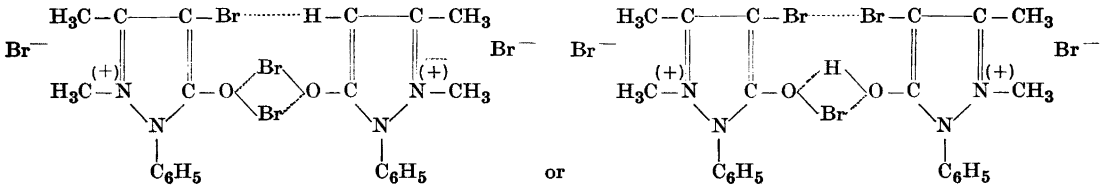
a) R′ = H R″=CH_3
b) R′ = H R″=Br
c) R′ = CH_3 R″=Br
d) R′ = H or CH_3
R″ = H

way in V). For monobromoantipyrine hydrobromide, Kitamura and Sunagawa[4]



VI VII

suggest oscillation between the two forms VI and VII, and also analogous



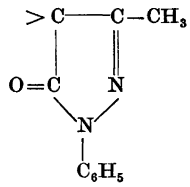
VIII

formulas for antipyrine perbromide (VIII). In the present paper the light absorption curves of some 4-halo-5-pyrazolones * and 5-pyrazolone salts under various conditions are reported and the structures of the substances are discussed.

The stimulus to this investigation were some observations made during the preparation of halopyrazolones. When 1-phenyl-3,4-dimethyl-5-pyrazolone **, $PyHCH_3$, is dissolved in glacial acetic acid and an equimolar amount of bromine in the same solvent is added, the solution turns red. This is because with concentrated solutions in such anhydrous solvents as glacial acetic acid and chloroform (but not ethanol) only half of the pyrazolone is brominated in accordance with the formula

$$2\ PyHCH_3 + Br_2 \rightarrow Py(CH_3)Br + PyHCH_3 \cdot HBr$$

* The iodo-compounds were so sensitive to light that their absorptions could not be measured.

** Throughout this paper Py will be used as a substitute for the radical 

In dilute solutions the greater dissociation of the salt into acid and pyrazolone allows the reaction to continue further than halfway. In the salt Py*H*$CH_3 \cdot HBr$, however, the italicized hydrogen atom, which is easily substituted in the corresponding free pyrazolone, does not react with bromine. If water is added, the salt is decomposed and the remaining bromine is rapidly absorbed.

$$PyHCH_3 \cdot HBr \xrightarrow{H_2O} PyHCH_3 + HBr; \quad PyHCH_3 + Br_2 \rightarrow PyBrCH_3 + HBr$$

The same effect is observed in the preparation of 1-phenyl-3-methyl-4,4-dibromo-5-pyrazolone. The reaction in concentrated glacial acetic acid solution between one mole of 1-phenyl-3-methyl-5-pyrazolone and two moles of bromine stops when half the bromine has reacted.

$$PyH_2 + Br_2 \rightarrow PyHBr \cdot HBr$$

When water is added, a second bromine atom is introduced.

$$PyHBr \cdot HBr \xrightarrow{H_2O} PyHBr + HBr; \quad PyHBr + Br_2 \rightarrow PyBr_2 + HBr.$$

These facts show that whereas PyHCH$_3$ and PyHBr possess a hydrogen atom easily substituted by bromine, the corresponding HBr-salts do not.

On the other hand, repeated attempts to synthesize 1,3-diphenyl-4-bromo-5-pyrazolone hydrobromide from equimolar amounts of bromine and pyrazolone in glacial acetic acid have failed. Part of the diphenyl-compound combined with two bromine molecules, forming the yellow 1,3-diphenyl-4,4-dibromo-5-pyrazolone, even when a large excess of the pyrazolone was present. The different behaviour towards bromine of 1,3-diphenyl-4-bromo-5-pyrazolone hydrobromide and the hydrobromides of $PyHCH_3$ and PyHBr is certainly not caused by different structures, but is a consequence of the weaker basic strength of the diphenyl-compound, which allows dissociation of the salt into free base and acid even when the acid is present in moderate excess.

When antipyrine reacts with bromine in chloroform or glacial acetic acid, 4-bromoantipyrine hydrobromide (1-phenyl-2,3-dimethyl-4-bromo-5-pyrazolone hydrobromide) is formed [4]. (This compound was first prepared by Knorr [5], who regarded it as 3,4-dibromoantipyrine.) If bromine is added in excess, antipyrine perbromide [4, 6] is obtained. The affinity of the bromoantipyrine salt for the halogen can not be caused by dissociation in this case, as 4-bromoantipyrine has no reactive hydrogen. *Thus the existence of a reactive hydrogen atom in 4-bromoantipyrine hydrobromide is certain.* Consequently a difference in structure between this salt and the hydrobromides of PyHBr and $PyHCH_3$ is very likely. This opinion is supported by the different colours of

the salts. The hydrobromide of 4-bromoantipyrine is distinctly yellow. Other pyrazolone salts are colourless unless the anions are coloured. Kitamura and Sunagawa [4] attribute the colour to a perbromide impurity. However, the substance still retains its colour after purification by precipitation from absolute alcohol solution by the addition of dry ether. But if it is dissolved in 95 per cent alcohol and precipitated with ether, a colourless product having the composition 1-phenyl-2,3-dimethyl-4-bromo-5-pyrazolone hydrobromide monohydrate is obtained. Here no perbromide can be present, for this compound is precipitated by ether in orange-yellow crystals from 95 per cent as well as from absolute alcohol. The monohydrate turns yellow when it is dried under a pressure of 0.1 mm Hg at room temperature over phosphorus pentoxide. Moreover, it the hydrate is dissolved in glacial acetic acid, a yellow solution is obtained that is decolorized by the addition of water. From the yellow solution the yellow, anhydrous 4-bromoantipyrine hydrobromide may be precipitated by dry ether. The same colour-changes as described above are found if 4-bromoantipyrine hydrobromide is prepared from pure 4-bromoantipyrine and bromine-free hydrobromic acid. Thus the yellow colour is not caused by an impurity but is characteristic of 4-bromoantipyrine hydrobromide.

As the difference in reactivity of the pyrazolone salts is accompanied by a difference in light absorption, it was of interest to characterize the compounds by absorption curves. The salts are insoluble in hydrocarbons but readily soluble in alcohol, where, however, they suffer extensive dissociation into pyrazolone and acid. Hence the absorption was measured in ethanol containing sulphuric acid.

Diagram 1 shows the light absorption of $PyHCH_3$, PyHBr and monobromoantipyrine in ethanolic solution with varying amounts of acid, a considerable excess of which is necessary to suppress the free base. The absorption curves of the salts differ distinctly from those of the free pyrazolones and are in accordance with the structure V. This is evident from a comparison with the light absorption curves of 1-phenyl-3-methyl-5-chloropyrazole and 1-phenyl-3-methyl-5-methoxypyrazole, investigated by Valyashko and Bliznyukov [3]. Thus in ethanol solution, salts of $PyHCH_3$ are represented by V a, of PyHBr by V b and of 4-bromoantipyrine by V c, no difference in structure existing between the various salts.

The light absorptions of PyH_2 and antipyrine in neutral and hydrochloric acid alcohol solutions measured by Valyashko and Bliznyukov [3] show essentially the same variations as the above. On account of the similarity between the light absorption curves of PyH_2 and antipyrine in concentrated, alcoholic hydrogen chloride and the corresponding curves of 1-phenyl-3-methyl-5-

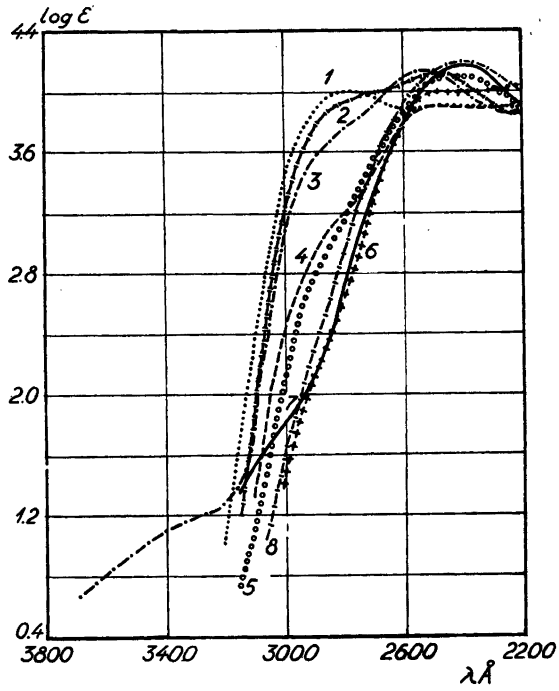
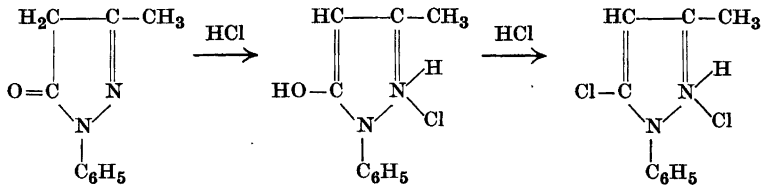
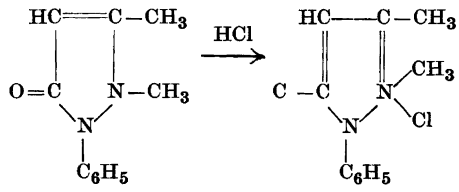


Diagram 1. 1) 4-Bromoantipyrine in ethanol ($3.6 \cdot 10^{-3}$, $3.6 \cdot 10^{-4}$ and $3.6 \cdot 10^{-5}$ M solutions) 2) 1-Phenyl-3,4-dimethyl-5-pyrazolone in ethanol ($4.5 \cdot 10^{-3}$, $4.5 \cdot 10^{-4}$ and $4.5 \cdot 10^{-5}$ M solutions) 3) 1-Phenyl-3-methyl-4-bromo-5-pyrazolone in ethanol (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions) 4) 4-Bromoantipyrine in ethanol with 50 ml of concentrated sulphuric acid per liter (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions) 5) 1-Phenyl-3-methyl-4-bromo-5-pyrazolone in ethanol with 50 ml of concentrated sulphuric acid per liter (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions) 6) 4-Bromoantipyrine in ethanol with 150 ml of concentrated sulphuric acid per liter (4.10^{-3} 4.10^{-4} and 4.10^{-5} M solutions) 7) 1-Phenyl-3,4-dimethyl-5-pyrazolone in ethanol with 150 ml of concentrated sulphuric acid per liter (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions) 8) 1-Phenyl-3-methyl-4-bromo-5-pyrazolone in ethanol with 150 ml of concentrated sulphuric acid per liter (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions).

chloropyrazole and 1-phenyl-3-methyl-5-chloropyrazole-2-chloromethylate, the Russian authors conclude that PyH_2 has changed into 1-phenyl-3-methyl-5-chloropyrazole (IX) and antipyrine into 1-phenyl-3-methyl-5-chloropyrazole-2-chloromethylate (X) via the salts. It seems preferable to ascribe the great similarity of the curves solely to the stable pyrazole structure of both the salts (V d) and the 5-chloro-pyrazole (XI a). This is not only because sulphuric acid has the same effect on the pyrazolone spectra as hydrogen chloride, but also because a hydroxyl group attached to a pyrazole nucleus should not be substi-

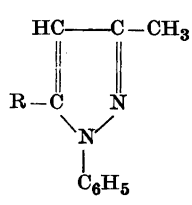


IX



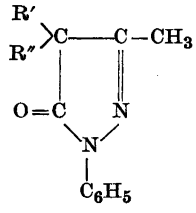
X

tuted by halogen on mere treatment with hydrogen halide, and because dilution alone suffices to regain the unchanged pyrazolone from the solution in strong hydrochloric acid (*cf.* Michaelis and Pasternack [7]).



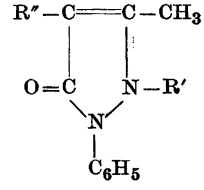
XI

a) R=Cl



XII

a) R′=CH_3 R″=Br
b) R′=H R″=Br



XIII

a) R′=CH_3 R″=Br

In contrast to $PyHCH_3$ and PyH_2, PyHBr exhibits quite different light absorption curves in neutral alcohol and in solvents with smaller dielectric constants, *e.g.* chloroform (Diagram 2). This indicates that different molecular structures are present in alcohol and chloroform solution. 1-Phenyl-3,4-dimethyl-4-bromo-5-pyrazolone, $Py(CH_3)Br$, which can only exist in one form (XII a), is characterized by the same light absorption curve in ethanol, strongly acidified ethanol and chloroform (Diagram 2). This curve resembles the curve of PyHBr in chloroform very much, which shows that PyHBr has chiefly the structure XII b in that solvent. The absorption, especially above 3 200 Å, proves that in alcoholic solution PyHBr is present in the form XII b only

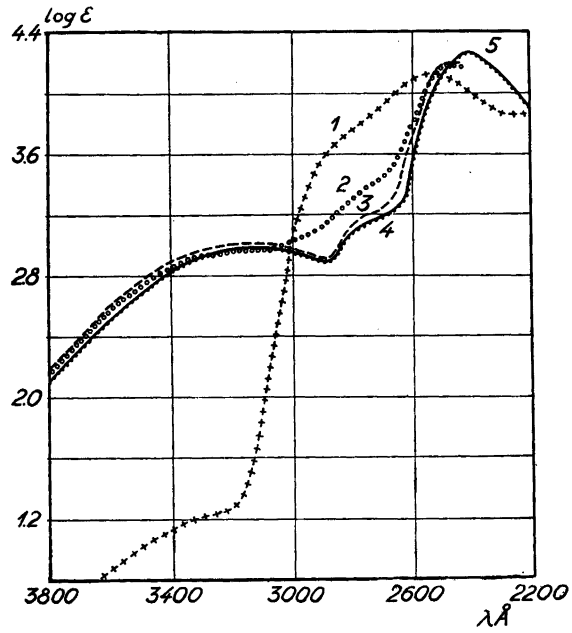


Diagram 2. 1) 1-Phenyl-3-methyl-4-bromo-5-pyrazolone in ethanol (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions) 2) Ditto in chloroform (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions) 3) 1-Phenyl-3,4-dimethyl-4-bromo-5-pyrazolone in chloroform (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions) 4) Ditto in ethanol (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions) 5) Ditto in ethanol with 150 ml of concentrated sulphuric acid per liter (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions).

to a very small extent. If Beer's law is valid, not more than 2 % of the substance possesses that structure.

It is interesting to compare the light absorption curves of $Py(CH_3)Br$, $Py(CH_3)Cl$, $Py(CH_3)OH$* and $Py(CH_3) \cdot PyCH_3$ (Diagram 3). They are all derivatives of the structure I of 1-phenyl-3-methyl-5-pyrazolone. The introduction of halogen or hydroxyl into the 4-position markedly increases the light absorption at wave-lengths longer than 2 900 Å. From the curves is evident that the greater absorption in the visible range is caused by a long-wave displacement and broadening of an already existing band, the maximum extinction coefficient of which is, however, decreased. The halogens and the hydroxyl group thus lower the difference in energy between the excited and ground states of the molecule. (Red shifts caused by halogens have been described before, *e.g.* by Mohler and Polya [8]). A similar displacement on intro-

* The compound $Py(CH_3)OH$ was prepared in cooperation with Prof. S. Veibel and will be described in another paper.

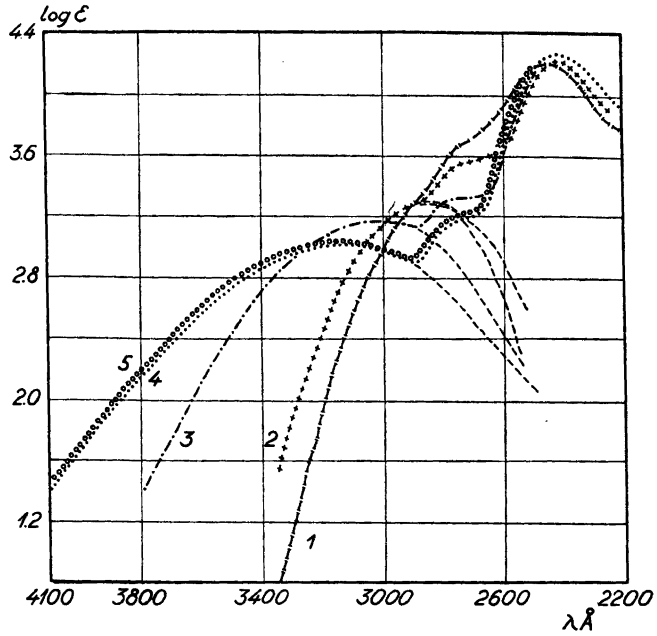


Diagram 3. 1) 1,1-Diphenyl-3,3',4,4'-tetramethyl-[4,4'-bi-2-pyrazoline]-5,5'-dione in ethanol ($5.0 \cdot 10^{-3}$, $5.0 \cdot 10^{-4}$ and $5.0 \cdot 10^{-5}$ M solutions). 2) 1-Phenyl-3,4-dimethyl-4-hydroxy-5-pyrazolone in ethanol ($5.8 \cdot 10^{-3}$, $5.8 \cdot 10^{-4}$ and $5.8 \cdot 10^{-5}$ M solutions) 3) 1-Phenyl-3,4-dimethyl-4-chloro-5-pyrazolone in chloroform ($4.3 \cdot 10^{-3}$, $4.3 \cdot 10^{-4}$ and $4.3 \cdot 10^{-5}$ M solutions) 4) 1-Phenyl-3,4-dimethyl-4-bromo-5-pyrazolone in ethanol (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions) 5) Ditto in chloroform (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions).

duction of halogen into the 4-position of 1-phenyl-3-methyl-5-pyrazolone or 1,3-diphenyl-5-pyrazolone is shown in Diagram 4.

Substances with antipyrine or pyrazole structures like XIII, V and XI do not give rise to the above band, as is evident from the absorption curves of monobromoantipyrine (XIII a), the acid sulphate of PyHBr (V b) (Diagram 1) and of 1-phenyl-3-methyl-5-chloropyrazole [3] (XI a). This band is thus associated with the structure XII and its two chromophores C = O and C = N. In the halogen-compounds, the polarizable halogen atoms, linked with the same C-atom (4) as the chromophores, evidently furnish electrons capable of interaction with the π-electrons of the double bonds and thus cause the red shift. This involvement of electrons from the C-Hal-group in the pyrazolone nucleus must diminish the electron density around this group, which explains the electrophilic reactions of the halogen atoms of $Py(CH_3)Hal$, PyHHal and $PyHal_2$. All these compounds, with the exception of PyHCl, oxidize hydrogen

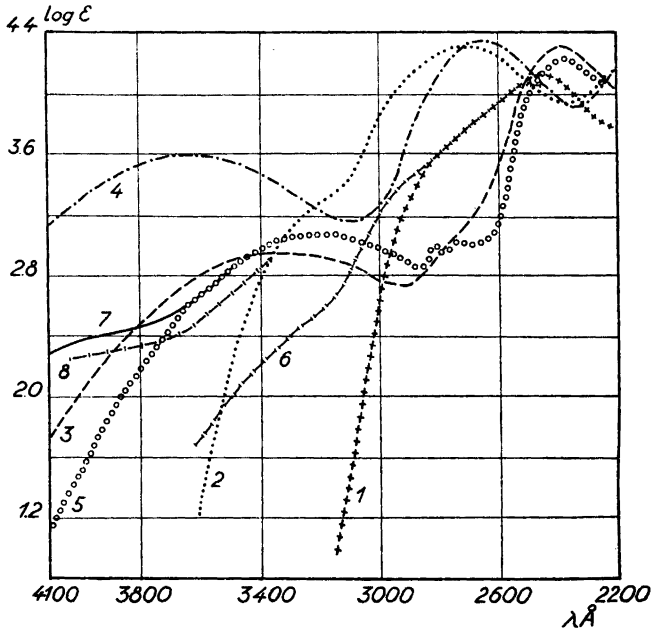


Diagram 4. 1) 1-Phenyl-3-methyl-5-pyrazolone in ethanol ($7.3 \cdot 10^{-3}$, $7.3 \cdot 10^{-4}$ and $7.3 \cdot 10^{-5}$ M solutions) 2) 1.3-Diphenyl-5-pyrazolone in ethanol ($4.8 \cdot 10^{-3}$, $4.8 \cdot 10^{-4}$ and $4.8 \cdot 10^{-5}$ M solutions) 3) 1-Phenyl-3-methyl-4,4-dibromo-5-pyrazolone in ethanol (4.10^{-3}, 4.10^{-4} and 4.10^{-5} M solutions) 4) 1,3-Diphenyl-4,4-dibromo-5-pyrazolone in ethanol ($3.3 \cdot 10^{-3}$, $3.3 \cdot 10^{-4}$ and $3.3 \cdot 10^{-5}$ M solutions) 5) 1-Phenyl-3-methyl-4,4-dichloro-5-pyrazolone in ethanol ($6.7 \cdot 10^{-3}$, $6.7 \cdot 10^{-4}$ and $6.5 \cdot 10^{-5}$ M solutions) 6) 1-Phenyl-3-methyl-4-chloro-5-pyrazolone in chloroform ($6.2 \cdot 10^{-3}$, $6.2 \cdot 10^{-4}$ and $6.2 \cdot 10^{-5}$ M solutions) 7) Antipyrine perbromide in chloroform ($2.8 \cdot 10^{-3}$ M solution) 8) Ditto ($1.6 \cdot 10^{-3}$ M solution).

iodide to iodine in alcoholic solution at room temperature (*e.g.* $PyCl_2 + 2\ HI \rightarrow PyHCl + I_2 + HCl$ or $PyHI + HI \rightarrow PyH_2 + I_2$), the reaction velocity increasing from the chloro to the iodo compounds. Furthermore they can attack an inert metal such as mercury at room temperature.

The investigation of the light absorption of the salts in chloroform and acetic acid must be done with rather dilute solutions, where the dissociation is consequently important. The higher the concentration, the more is the equilibrium of the dissociation reaction, salt $\rightleftharpoons$ pyrazolone + acid, displaced towards the left, and the more should the light absorption curve be displaced towards the curve of the undissociated salt. If the structure of the salts is the same in chloroform and acetic acid as in ethanol, the absorption at longer wave-lengths should be suppressed. Diagrams 5 and 6 show that this is the

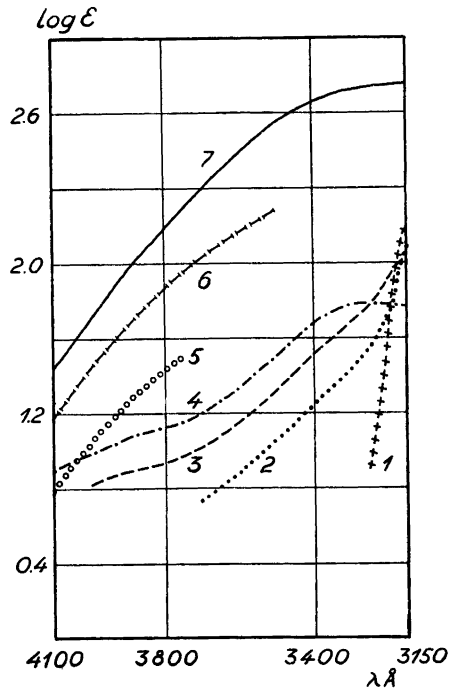


Diagram 5. 1) Monobromoantipyrine in chloroform (10^{-2} M solution) 2) Monobromoantipyrine hydrobromide in chloroform (10^{-2} M solution) 3) Ditto ($1.7 \cdot 10^{-2}$ M solution) 4) Ditto ($3.4 \cdot 10^{-2}$ M solution) 5) 1-Phenyl-3-methyl-4-bromo-5-pyrazolone hydrobromide in chloroform ($6.7 \cdot 10^{-2}$ M solution) 6) Ditto (10^{-2} M solution) 7) 1-Phenyl-3-methyl-4-bromo-5-pyrazolone in chloroform ($4 \cdot 10^{-3}$ M solution) (Log ε decreases only slightly when the concentration of PyHBr is increased).

case with solutions of PyHBr · HBr. Thus, the salts of PyHBr have the same constitution in chloroform and glacial acetic acid as in ethanol (V b) and, consequently, a hydrogen atom attached to the oxygen in position 5 of the pyrazolone molecule V is not substituted by bromine at room temperature (pp. 1500—1501).

The light absorption of the hydrobromide of monobromoantipyrine in chloroform and acetic acid solutions above 3 300 Å (Diagrams 5 and 6), however, increases with the concentration quite differently. It follows that the hydrobromide of monobromoantipyrine possesses not only the constitution V c. There must be an equilibrium between at least two forms. The alternative VII proposed by Kitamura and Sunagawa [4], which well explains the ability of the substance to act as a brominating agent, assumes that the bromine atom can easily shift from position 4 to the oxygen atom in position 5 and back

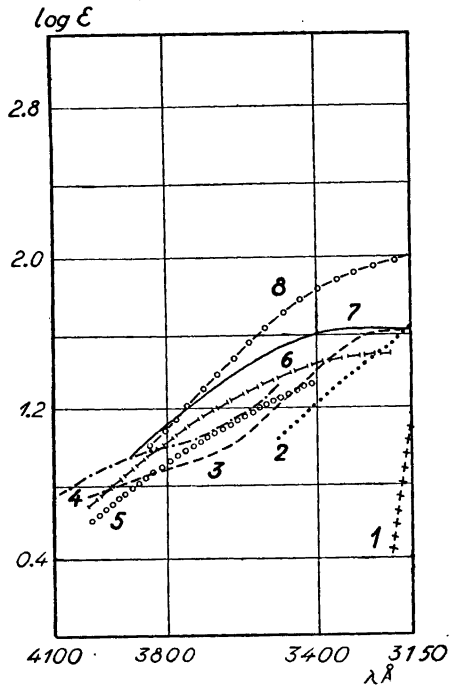
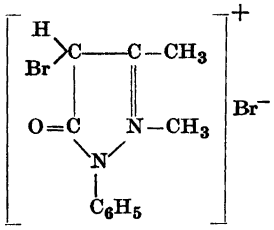


Diagram 6. 1) Monobromoantipyrine in glacial acetic acid (10^{-2} M solution) 2) Monobromoantipyrine hydrobromide in glacial acetic acid (10^{-2} M solution) 3) Ditto ($5 \cdot 10^{-2}$ M solution) 4) Ditto (10^{-1} M solution) 5) 1-Phenyl-3-methyl-4-bromo-5-pyrazolone hydrobromide in glacial acetic acid (10^{-1} M solution) 6) Ditto ($5 \cdot 10^{-2}$ M solution) 7) Ditto (10^{-2} M solution) 8) 1-Phenyl-3-methyl-4-bromo-5-pyrazolone in glacial acetic acid (10^{-2} M solution).

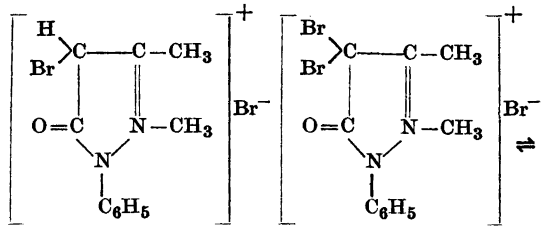
again. There is little precedence for such shifts. Moreover, it was shown above that the hydrogen of the 5-hydroxy-group of the closely related PyHBr · HBr is not easily substituted by bromine. Accordingly, an equilibrium between the forms V c and XIV seems preferable.

A substance with the structure XIV is likely to absorb light in the visible range like compounds of the structure XII (R″ = halogen) (Diagram 2). This explains the colour of monobromoantipyrine hydrobromide and the light absorption curves in Diagrams 5 and 6.

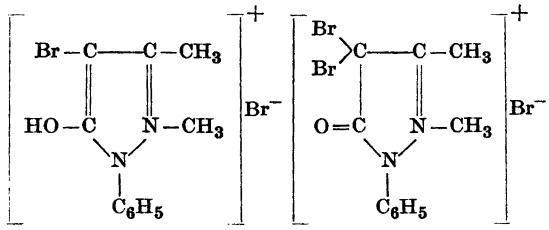
In a subsequent paper, "Studies on Pyrazolones VII", it will be shown that $PyBr_2$ and $Py(CH_3)Br$ can act as brominating agents. Accordingly the formation of bromoacetone from acetone and monobromoantipyrine hydrobromide [4] is no argument against the formula XIV.



XIV



XV



XV

The structure XIV is also in accordance with the existence of an antipyrine perbromide (Kitamura and Sunagawa [4]), for the hydrogen atom in the 4 position of XIV ought to be easily substituted by bromine. The double salt formula XV, which is consistent both with the light absorption (strongly dependent on the concentration) of the substance (Diagram 4) and with its brominating and oxidizing properties, seems a resonable formula for the perbromide.

EXPERIMENTAL

I. 1-Phenyl-3,4-dimethyl-4-halo-5-pyrazolones

1-Phenyl-3,4-dimethyl-4-chloro-5-pyrazolone. 1-Phenyl-3,4-dimethyl-5-pyrazolone (5 g) was dissolved in glacial acetic acid (40 ml), and water (300 ml) was added. Chlorine was introduced with vigorous stirring of the solution. The colourless reaction product was collected by filtration and washed with water. The yield of crude chloropyrazolone was 98%. It was purified by recrystallization from ethanol (cooling in a freezing mixture). M.p .68° C. (Found: C 59.2; H 5.1; Cl 15.97; N 12.67. Calc. for $C_{11}H_{11}ClON_2$ (222.7): C 59.3; H 5.0; Cl 15.92; N 12.58.) When the reaction: $PyHCH_3 + Cl_2 \rightarrow Py(CH_3)Cl + HCl$ takes place in dilute acetic acid, $Py(CH_3)Cl$ precipitates as soon as formed and is thus prevented from being further attacked by the chlorine.

1-Phenyl-3,4-dimethyl-4-bromo-5-pyrazolone. $PyHCH_3$ (20 g) and bromine (17 g) were dissolved separately in glacial acetic acid. A few pieces of ice were placed in the pyrazolone solution and the bromine solution was poured into it with stirring. The bromine combined rapidly and completely with the pyrazolone. First ice and then water were added in portions with stirring to precipitate the yellow $Py(CH_3)Br$. The yield was

quantitative. M.p. 83° C. (Found: C 49.5; H 4.1; Br 29.88; N 10.46. $C_{11}H_{11}BrON_2$ (267.3) requires C 49.4; H 4.1; Br 29.92; N 10.49.)

The bromination of $PyHCH_3$ in glacial acetic acid was studies in the following way. When one mole of bromine was added per mole of $PyHCH_3$, a solution strongly coloured by bromine was obtained. The colour appeared when slightly more than half of the bromine had been added. The acetic acid and the bromine that had not reacted were removed by evaporation under reduced pressure. Colourless crystals and a yellow solution were obtained by extraction of the residue with dry ethyl ether. $Py(CH_3)Br$ crystallized from the ether solution on evaporation. The yield was somewhat more than half a mole of $Py(CH_3)Br$ per mole of $PyHCH_3$ added. The colourless product, which was insoluble in ether, contained 0.371 equivalents of bromide ions per 100 grams, the same amount of strong acid (HBr) and twice as much total acid, all determined by potentiometric titrations. In a buffered alcoholic solution half of the hydrogen atoms react with the bromine atoms in $Py(CH_3)Br$ with formation of HBr (the rest of the molecules gives $Py(CH_3) \cdot PyCH_3$) in quite the same way as $PyHCH_3$ (*cf.* Smith [9]). These facts show that the salt $PyHCH_3 \cdot HBr$ has been formed. The substance may be purified by dissolving it in anhydrous alcohol and precipitating it with anhydrous ether, or alternatively by dissolving it in 95 per cent alcohol and precipitating it with ether. In the latter case the molecule takes up two molecules of water and is transformed into $PyHCH_3 \cdot HBr \cdot 2H_2O$, identical with the salt that is obtained on treating $PyHCH_3$ with concentrated hydrobromic acid. (Found: C 43.2; H 5.6; Br 26.13. Calc. for $C_{11}H_{12}ON_2 \cdot HBr \cdot 2H_2O$ (305.4): C 43.3; H 5.6; Br 26.09.)

1-Phenyl-3,4-dimethyl-4-iodo-5-pyrazolone. An equivalent amount of dilute sodium hydroxide was added to a saturated solution of 1-phenyl-3,4-dimethyl-5-pyrazolone in ethanol. Much crushed ice and ice water were added, followed by the addition (with efficient stirring) of an equivalent amount of iodine in aqueous potassium iodide. Yellow crystals of 1-phenyl-3,4-dimethyl-4-iodo-5-pyrazolone separated immediately. The yield of crude product was 98%. For purification the iodopyrazolone was dissolved in glacial acetic acid at room temperature, cooled in an ice-bath, and precipitated with a small amount of crushed ice. M.p. 70° C. (Found: C 42.0; H 3.5; I 40.4; N 8.92. $C_{11}H_{11}ION_2$ (314.1) requires C 42.1; H 3.5; I 40.4; N 8.92.)

$PyCH_3I$ is sensitive to light and heat. On heating, the reaction: $2\ Py(CH_3)I \rightarrow Py(CH_3)PyCH_3 + I_2$ takes place.

All the 1-phenyl-3,4-dimethyl-4-halo-5-pyrazolones are readily soluble in alcohol, ether, chloroform, ethyl acetate and glacial acetic acid, but are insoluble in water. Alkali splits off the halogen atoms quantitatively as ions, and the reaction is suitable for analytical purposes (*cf.* p. 1514). There is no simple exchange of halogen by hydroxyl, but the rest of the pyrazolone is attacked too.

Examples. $Py(CH_3)Br$ (0.3777 g) was dissolved in ethanol (30 ml), and 2.5 *N* sodium hydroxide solution (15 ml) was added. The solution became orange-red. After one hour it was acidified with 5 *N* sulphuric acid (yellow colour) and titrated potentiometrically with 0.1006 *N* $AgNO_3$-solution. 14.05 ml were consumed, which is equivalent to 29.88% of bromine (calc. 29.92). In the case of $Py(CH_3)Cl$, more concentrated alkali, 25 ml of 2.5 *N* sodium hydroxide to 25 ml of ethanol, and a longer time of reaction, two hours, were used.

Neither Volhard titration nor weighing of the silver halide is suitable because the product of hydrolysis has strong reducing properties and transforms the excess of silver nitrate to metallic silver. Therefore potentiometric titration is necessary.

II. 1-Phenyl-3-methyl-4,4-dihalo-5-pyrazolones

1-Phenyl-3-methyl-4,4-dichloro-5-pyrazolone. This compound has been prepared by Knorr [5] by treating 1-phenyl-3-methyl-5-pyrazolone either with chlorine or with phosphorus pentachloride. The former method gives a poor yield and the latter is somewhat laborious. The compound is prepared more simply in the following way.

PyH_2 was dissolved in about six parts of glacial acetic acid and chlorine was introduced with stirring. An excess must be avoided because $PyCl_2$ reacts with chlorine. The solution was cooled, and $PyCl_2$ was precipitated with crushed ice and ice-cold water. Alternatively, water may be added before the introduction of the halogen. The advantage of this variation was that $PyCl_2$ precipitated as soon as formed and so was protected from oxidation by the chlorine. In this case the product was green, but it was easily purified by crystallization from ethanol. In either case the yield was 95—98%. M.p. 65° C. (Found: C 49.5; H 3.3; Cl 29.15. Calc. for $C_{10}H_8Cl_2ON_2$ (243.1): C 49.4; H 3.3; Cl 29.17.)

1-Phenyl-3-methyl-4,4-dibromo-5-pyrazolone. The following procedure differs from the methods described by Knorr [5] and Smith [9] mainly in avoiding both heating and long reaction time. — PyH_2 (10 g) and bromine (18.4 g) were dissolved separately in glacial acetic acid. A few pieces of ice (about 10 g) were added to the pyrazolone solution and the bromine was introduced with stirring. The solution acquired a clear yellow colour. Crushed ice was added with stirring, causing yellow crystals of $PyBr_2$ precipitate. The precipitation was completed by addition of water. The yield was quantitative.

As in the preparation of 1-phenyl-3,4-dimethyl-4-bromo-5-pyrazolone, the bromination in concentrated glacial acetic acid solution stops when half the bromine has reacted (p. 1501). Addition of water makes the reaction continue. The intermediate product, PyHBr · HBr, can be precipitated by addition of anhydrous ether to the glacial acetic acid solution. It may be purified by dissolution in a small amount of anhydrous ethyl alcohol and precipitation with anhydrous ether. That the precipitated substance is the salt PyHBr · HBr, may be inferred from the following data:

1. $C_{10}H_9BrON_2 \cdot HBr$ (334.1) requires C 35.9; H 3.0. Found: C 35.7; H 3.05.
2. Each molecule contains one ionizable and one non-ionizable bromine atom. On potentiometric titration with silver nitrate solution 0.304 equivalents of bromide per 100 g of substance were found (calc. for PyHBr · HBr: 0.299 equivalents per 100 g).
3. The product reacts in buffered alcoholic solution in the same way as PyHBr, *e. g.* formation of hydrogen bromide and pyrazole blue (*cf.* Knorr [2]): 2 PyHBr → 2 HBr + Py = Py.
4. On titration with barium hydroxide solution (phenolphthalein as indicator) the equivalent weight 165 was found. (Calc. for PyHBr · HBr 167.)

1-Phenyl-3-methyl-4,4-diiodo-5-pyrazolone. 1-Phenyl-3-methyl-5-pyrazolone (4 g) in ethyl alcohol (15 ml) was neutralized by 2.3 *N* sodium hydroxide (19.5 ml, equivalent to both hydrogen atoms in the pyrazolone). Ice-water (1.5 l) was added and then, with stirring, an equivalent amount of iodine (180 ml of a 0.5 *N* solution in aqueous potassium iodide). 1-Phenyl-3-methyl-4,4-diiodo-5-pyrazolone was obtained as a yellow precipitate. PyI_2 adsorbs sodium and potassium iodide and must be washed carefully with water. It is very unstable and sensitive to light and is difficult to purify by crystallization. (Found: C 28.3; H 1.9; N 6.50; 0.97 % sulphate ash. $C_{10}H_8I_2ON_2$ (426.0) requires C 28.2; H 1.9; N 6.58.)

The $PyHal_2$ compounds are easily reduced, PyI_2 even by cold methanol or ethanol. As has already been shown by Knorr in the case of $PyBr_2$ the dihalogenated pyrazolones are attacked by alkali, halide ions being split off. The reaction is not complete enough to be suitable for analysis. For analytical purposes one can use sodium to cleave off the halogen (Rauscher [10]).

III. 1-Phenyl-3-methyl-4-halo-5-pyrazolones

1-Phenyl-3-methyl-4-chloro-5-pyrazolone. This substance has been prepared by Alphen [11] from $C_6H_5N = NC(CH_3) = CHCOOC_2H_5$ and HCl. In the present investigation it has been obtained from 1-phenyl-3-methyl-5-pyrazolone and chlorine and also by reduction of 1-phenyl-3-methyl-4,4-dichloro-5-pyrazolone.

It was shown above (p. 1512) that bromine reacts with PyH_2 in glacial acetic acid according to the equation: $PyH_2 + Br_2 \rightarrow PyHBr \cdot HBr$, and that further bromination does not occur until the acetic acid has been diluted with water. On the other hand, when chlorine was used as halogenating agent, even with less than 1 mole of chlorine per mole of pyrazolone, $PyCl_2$ was formed to a certain extent according to the equation: $PyH_2 + 2Cl_2 \rightarrow PyCl_2 + 2HCl$. Thus some of the unsubstituted pyrazolone remained in the form of $PyH_2 \cdot HCl$, (this salt, which easily absorbed one mole of water, could be precipitated by ether. Found: C 52.5; H 5.86; Cl 15.45. The hydrate, $C_{10}H_{13}ClO_2N_2$, (228.7) requires C 52.5; H 5.73; Cl 15.50.) On addition of ice the dichloro-compound precipitated first. If the precipitate was removed by filtration and the mother liquor allowed to stand a few hours, PyHCl separated from the solution.

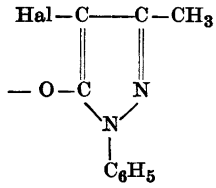
A better yield of PyHCl was obtained by reduction of $PyCl_2$ with hydrogen iodide at room temperature in the dark. $PyCl_2$ (15 g) was dissolved in ethyl alcohol (270 ml), and constant boiling hydroiodic acid (25 ml) was added. Then the reaction: $PyCl_2 + 2HI \rightarrow PyHCl + HCl + I_2$ took place. The liberated iodine was reduced as formed by adding a sodium thiosulphate solution dropwise (concentrated solution at the beginning in order not to precipitate $PyCl_2$ by the water!). After a short while PyHCl started to separate. When the reaction was finished as indicated by the iodine formation having ceased, the precipitation was completed by water. The yield of colourless product was 11.3 g (88 %). The small amounts of impurities present were removed by extraction with chloroform (boiling half a minute) or by recrystallization from ethanol. M.p. 153° C with decomposition. (Found: C 57.6; H 4.35; Cl 17.00; N 13.46; equ.wt 208.7 on titration with sodium hydroxide against phenolphthalein. Calc. for $C_{10}H_9ClON_2$ (208.7): C 57.5; H 4.35; Cl 16.99; N 13.43; equ.wt 208.7)

1-Phenyl-3-methyl-4-bromo-5-pyrazolone. This compound was prepared by a modification of the method of Knorr [5] (Compare Smith [9]). 1-Phenyl-3-methyl-5-pyrazolone was dissolved in glacial acetic acid, and an equivalent amount of bromine in the same solvent was added. After stirring a short while, the salt PyHBr · HBr usually separated. If seeding was necessary, crystals were prepared by adding ether to a small part of the solution. The colourless crystals were filtered by suction and washed successively with glacial acetic acid and ether. When impure PyH_2 was used, the salt was coloured yellow and was then purified by precipitation with dry ether from a solution in absolute alcohol. The pure salt was suspended in five parts of glacial acetic acid, and crushed ice was added with efficient stirring. The salt was decomposed by the water into hydrogen bromide and PyHBr, and at the same time it dissolved. When the acetic acid was sufficiently diluted, PyHBr separated as colourless crystals. The product was pure enough for most purposes,

but could be further purified by recrystallization from chloroform. Yield 95%. As PyHBr · HBr is more stable than PyHBr, the substance is best stored as the salt. (Found: Br 31.55; equ.wt 253.2 on titration with sodium hydroxide against phenolphthalein. Calc. for $C_{10}H_9BrON_2$ (253.2): Br 31.57; equ.wt 253.2.)

1-Phenyl-3-methyl-4-iodo-5-pyrazolone. 1-Phenyl-3-methyl-5-pyrazolone was dissolved in a little alcohol and an equimolecular quantity of sodium hydroxide solution was added. Much crushed ice and an equivalent quantity of iodine solution (in aqueous potassium iodide) were introduced with stirring. Yellow crystals of 1-phenyl-3-methyl-4-iodo-5-pyrazolone precipitated. (Found: C 40.2; H 3.0; I 42.3; N 9.39. Calc. for $C_{10}H_9ION_2$ (300.1): C 40.0; H 3.0; I 42.3; N 9.34.) PyHI is very sensitive to light and heat.

In contrast to the halogen atom of $Py(CH_3)Hal$ that of PyHHal cannot be hydrolyzed even by boiling with alkali hydroxide solutions. The diminished reactivity of the halogen atom in the alkali salts of PyHHal is to be expected, as it is attached to an unsaturated C-atom belonging to a stable pyrazole nucleus (XVI).



XVI

IV. *1-Phenyl-2,3-dimethyl-4-bromo-5-pyrazolone hydrobromide monohydrate.* Solutions of equimolar amounts of 1-phenyl-2,3-dimethyl-5-pyrazolone and bromine in glacial acetic acid were mixed, and the resulting 1-phenyl-2,3-dimethyl-4-bromo-5-pyrazolone hydrobromide was precipitated with dry ether. (Found: equ.wt 348 on potentiometric titration with silver nitrate. Calc. for $C_{11}H_{12}Br_2ON_2$ (348.1): equ.wt 348.1.) Solution of the yellow product in 95% alcohol and precipitation with ether gave colourless crystals of the monohydrate. (Found: C 36.2; H 3.85; equ.wt 366 on potentiometric titration with silver nitrate. $C_{11}H_{12}Br_2ON_2 \cdot H_2O$ (366.1) requires C 36.1; H 3.85; equ.wt 366.1.)

Antipyrine perbromide. Bromine (4.4 g) in acetic acid (15 ml) was mixed with a solution of antipyrine (2.3 g) in acetic acid (35 ml). On addition of ether antipyrine perbromide separated as orange-yellow crystals. Yield: 3.9 g. M.p. 171—172° C. (Found: C 33.9; H 3.0; Br 51.3. $C_{11}H_{11}Br_3ON_2$, $C_{11}H_{12}Br_2ON_2$ (775.2) requires C 34.1; H 3.0; Br 51.6.)

V. *Bromination of 1,3-diphenyl-5-pyrazolone.* A glacial acetic acid solution of bromine (7.0 g) was poured into a solution of 1,3-diphenyl-5-pyrazolone (10.3 g) in the same solvent. On precipitation with ether or toluene, only a sticky product was obtained. By means of ethyl acetate it was possible to isolate 1,3-diphenyl-5-pyrazolone hydrobromide (5.6 g) from the ether precipitate. (Found: equ.wt 159.2 on potentiometric titration with sodium hydroxide; *M* 318 on potentiometric titration with sodium hydroxide and silver nitrate. $C_{15}H_{13}BrON_2$ (317.3) requires equ.wt 158.6; *M* 317.3.) The ether-acetic acid solution contained 1,3-diphenyl-4,4-dibromo-5-pyrazolone, even when the amount of pyrazolone added was increased.

Light absorption measurements

All light absorption measurements were performed with a Beckmann spectrophotometer model DU in silica cells. Systems identical with the measured solutions except that they did not contain any pyrazolone were used as comparison solutions.

In the diagrams $\log \varepsilon = \log \log \frac{I_0}{I} - \log c \cdot l$ is plotted against the wave length λ (in Ångström units). I_0 and I are the intensities of the light before and after the passage of the cell, c is the concentration of the pyrazolone in moles per liter with one exeption, the bis-pyrazolone in Diagram 3, where c is expre sed in pyrazolone units per liter, and l is the length of the cell in cm.

SUMMARY

The 1-phenyl-3-methyl-4-halo-5-pyrazolones, 1-phenyl-3,4-dimethyl-4-halo-5-pyrazolones and 1-phenyl-3-methyl-4,4-dihalo-5-pyrazolones have been prepared, and the light absorption of these substances (except the iodo-compounds), of antipyrine perbromide, the acid sulphate of 1-phenyl-3,4-dimethyl-5-pyrazolone and the bromides and acid sulphates of 1-phenyl-3-methyl-4-bromo-5-pyrazolone and 1-phenyl-2,3-dimethyl-4-bromo-5-pyrazolone has been studied. The significance of the absorption curves with respect to the structures of the substances is discussed.

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