## **323.** *The Action of Chlorine upon the* 3-*Carbethoxy*-4-*hydroxy*-1-*nitrophenylpyrazoles.*

By F. D. Chattaway and D. R. Ashworth.

Chlorine, when passed into an acetic acid or chloroform solution of any one of the 3-carbethoxy-4-hydroxy-1-nitrophenylpyrazoles (I), converts it into the corresponding 5 : 5-*dichloro*-3-*carbethoxy*-1-*nitrophenyl*-4-*pyrazolone* (II). The reaction is a general one and takes place with all the 4-hydroxy-1-nitrophenyl- and the 4-hydroxy-1-monohalogenonitrophenyl-3-carbethoxypyrazoles.

It is probable that a 5-chloro-derivative (III) of the 4-hydroxy-pyrazole is first formed,

$$\underset{\text{(I.)}}{\begin{array}{l}\text{CO}_2\text{Et}\\ \text{C}{=\!=\!=}\text{N}\\ \text{C(OH)}\!:\!\text{CH}\end{array}\!>\!\text{NR}} \longrightarrow \left[\underset{\text{(III.)}}{\begin{array}{l}\text{CO}_2\text{Et}\\ \text{C}{=\!=\!=}\text{N}\\ \text{C(OH)}{=}\text{CCl}\end{array}\!>\!\text{NR}} \longrightarrow \begin{array}{l}\text{CO}_2\text{Et}\\ \text{C}{=\!=}\text{N}\\ \text{CO}\cdot\text{CHCl}\end{array}\!>\!\text{NR}\right] \longrightarrow \underset{\text{(II.)}}{\begin{array}{l}\text{CO}_2\text{Et}\\ \text{C}{=\!=}\text{N}\\ \text{CO}\cdot\text{CCl}_2\end{array}\!>\!\text{NR}}$$

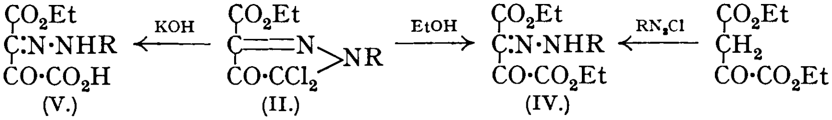
the equilibrium between the enolic and the keto-form of this being continually disturbed as the latter is further substituted.

Both the 5-bromo- and the 5-chloro-3-carbethoxy-4-hydroxy-1-nitrophenylpyrazoles similarly yield the corresponding 5 : 5-dichloropyrazolones, the bromine in the former being replaced by chlorine.

In the case of 3-carbethoxy-4-hydroxy-1-(2′ : 6′-dichloro-4′-nitrophenyl)pyrazole the action does not go beyond the first stage, *5-chloro-3-carbethoxy-4-hydroxy-1-(2′ : 6′-dichloro-4′-nitrophenyl)pyrazole* being the final product.

The 5 : 5-dichloro-3-carbethoxy-1-nitrophenyl-4-pyrazolones (II) are well-crystallised, comparatively stable compounds. They all react with hydriodic acid in acetic acid solution, iodine being liberated, and *5-chloro-3-carbethoxy-4-hydroxy-1-nitrophenylpyrazoles* (III), all of which yield well-crystallised *acetyl* derivatives, re-formed.

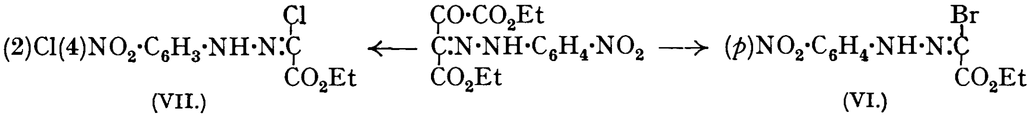
The pyrazole ring in the dichloro-compounds (II) readily opens when they are boiled with alcohol, or dissolved in cold dilute alkali: *e.g.*, the 1-*p*-nitrophenyl compound (II) in boiling alcohol gives *ethyl diketosuccinate*-p-*nitrophenylhydrazone* (IV), identical with the compound obtained by coupling *p*-nitrophenyldiazonium chloride with ethyl oxalacetate; while with cold dilute alkali and subsequent acidification *1-ethyl 2-hydrogen diketosuccinate-1*-p-*nitrophenylhydrazone* (V) is obtained, which is readily esterified by cold alcoholic hydrogen chloride to give the same well-crystallised stable diethyl ester (IV).



$$\underset{\text{(V.)}}{\begin{array}{l}CO_2Et\\ C{:}N{\cdot}NHR\\ CO{\cdot}CO_2H\end{array}} \xleftarrow{\text{KOH}} \underset{\text{(II.)}}{\begin{array}{l}CO_2Et\\ C{=\!=}N\\ CO{\cdot}CCl_2\end{array}}\!\!>\!NR \xrightarrow{\text{EtOH}} \underset{\text{(IV.)}}{\begin{array}{l}CO_2Et\\ C{:}N{\cdot}NHR\\ CO{\cdot}CO_2Et\end{array}} \xleftarrow{RN_2Cl} \begin{array}{l}CO_2Et\\ CH_2\\ CO{\cdot}CO_2Et\end{array}$$

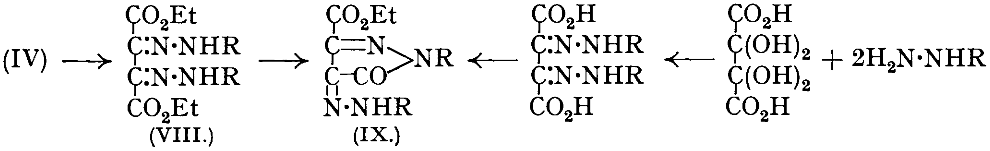
These two reactions are quite general; methyl, propyl, and benzyl alcohols react similarly and give mixed esters.

The dialkyl diketosuccinatemononitrophenylhydrazones (IV) react in an interesting way with halogens, the $CO{\cdot}CO_2Alk$ group being replaced by a halogen atom; *e.g.*, when bromine acts upon ethyl diketosuccinate-*p*-nitrophenylhydrazone in acetic acid containing sodium acetate, ethyl α-bromoglyoxylate-*p*-nitrophenylhydrazone (VI) is formed. The action of chlorine is similar but more vigorous, for besides replacing the $CO{\cdot}CO_2Et$ group, it enters the nucleus in an ortho-position, ethyl α-chloroglyoxylate-2-chloro-4-nitrophenylhydrazone (VII) being produced.



$$\underset{\text{(VII.)}}{(2)Cl(4)NO_2{\cdot}C_6H_3{\cdot}NH{\cdot}N{:}\begin{array}{l}Cl\\ C\\ CO_2Et\end{array}} \longleftarrow \begin{array}{l}CO{\cdot}CO_2Et\\ C{:}N{\cdot}NH{\cdot}C_6H_4{\cdot}NO_2\\ CO_2Et\end{array} \longrightarrow \underset{\text{(VI.)}}{(p)NO_2{\cdot}C_6H_4{\cdot}NH{\cdot}N{:}\begin{array}{r}Br\\ C\\ CO_2Et\end{array}}$$

The carbonyl group in the dialkyl diketosuccinatemononitrophenylhydrazones is very reactive and condenses readily with arylhydrazines and with hydroxylamine: *e.g.*, when ethyl diketosuccinate-*p*-nitrophenylhydrazone (IV) is treated with *p*-nitrophenylhydrazine, an *osazone* (VIII) is formed; this in boiling pyridine loses alcohol to form *ethyl 4 : 5-diketo-1-(4′-nitrophenyl)pyrazolone-3-carboxylate-4-(4″-nitrophenylhydrazone)* (IX), identical with that obtained from dihydroxytartaric acid and *p*-nitrophenylhydrazine, with subsequent ring closure and esterification (compare Chattaway and Humphrey, J., 1927, 2794):



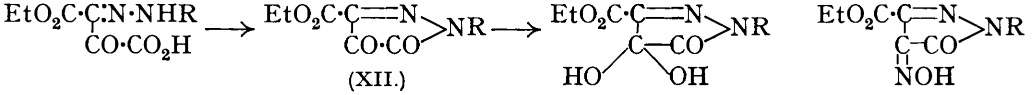
$$\text{(IV)} \longrightarrow \underset{\text{(VIII.)}}{\begin{array}{l}CO_2Et\\ C{:}N{\cdot}NHR\\ C{:}N{\cdot}NHR\\ CO_2Et\end{array}} \longrightarrow \underset{\text{(IX.)}}{\begin{array}{l}CO_2Et\\ C{=}N\\ C{-}CO\\ N{\cdot}NHR\end{array}}\!\!>\!NR \longleftarrow \begin{array}{l}CO_2H\\ C{:}N{\cdot}NHR\\ C{:}N{\cdot}NHR\\ CO_2H\end{array} \longleftarrow \begin{array}{l}CO_2H\\ C(OH)_2\\ C(OH)_2\\ CO_2H\end{array} + 2H_2N{\cdot}NHR$$

With hydroxylamine, *ethyl diketosuccinate-oximino*-p-*nitrophenylhydrazone* (X) is formed, which on heating with sodium acetate in acetic acid solution readily loses alcohol, ring closure takes place, and *3-carbethoxy-4-keto*iso*oxazolone-4*-p-*nitrophenylhydrazone* (XI) is formed:

$$\text{(IV)} \longrightarrow \begin{matrix}\text{EtO}_2\text{C·C:N·NHR}\\ \text{EtO}_2\text{C·C:NOH}\end{matrix} \longrightarrow \text{O}\!<\!\begin{matrix}\text{N=C·CO}_2\text{Et}\\ \text{CO–C:N·NHR}\end{matrix}$$

(X.) (XI.)

1-Ethyl 2-hydrogen diketosuccinate-1-*p*-nitrophenylhydrazone (V) is a well-crystalline stable substance. When heated with acetic anhydride, it loses water, and ring closure follows, with the formation of 3-carbethoxy-4 : 5-diketo-1-*p*-nitrophenylpyrazolone (XII), which on addition of water to the acetic acid solution separates as the colourless *monohydrate* (XIII) (compare Sachs and Borschall, *Ber.*, 1902, **35**, 1437) :



(XII.) (XIII.) (XIV.)

The molecule of water in this hydrate is firmly held, and is only removed very slowly in a vacuum over phosphoric oxide. The anhydrous form is a highly coloured, reddish solid, which cannot be crystallised in a pure state, even from an anhydrous solvent, owing to the ease with which it takes up water, from the air, to re-form the colourless hydrate.

The 4-keto-group in (XII) is very reactive and condenses readily with *p*-nitrophenylhydrazine, yielding ethyl 4 : 5-diketo-1-(4′-nitrophenyl)pyrazolone-3-carboxylate-4-(4″-nitrophenylhydrazone) (IX). It also condenses with hydroxylamine, yielding *4-oximino-3-carbethoxy-*1-p-*nitrophenyl-5-pyrazolone* (XIV).

When 3-carbethoxy-4 : 5-diketo-1-*p*-nitrophenylpyrazolone (XII) is heated with alcohol or water, ethyl diketosuccinate-*p*-nitrophenylhydrazone (IV) and 1-ethyl 2-hydrogen diketosuccinate-1-*p*-nitrophenylhydrazone (V) are respectively obtained. As these are the compounds produced when the ring in 5 : 5-dichloro-3-carbethoxy-1-*p*-nitrophenyl-4-pyrazolone is opened with alcohol and alkali respectively, it seems that in the latter reactions the replacement of the two chlorine atoms by oxygen precedes the opening of the ring.

## EXPERIMENTAL.

5 : *5-Dichloro-3-carbethoxy-*1-p-*nitrophenyl-4-pyrazolone* (II).—2 G. of 3-carbethoxy-4-hydroxy-1-*p*-nitrophenylpyrazole were suspended in 20 c.c. of chloroform, and chlorine rapidly passed in. Heat was given out and a clear red solution formed. After evaporation of the solvent, the *dichloro*-compound was crystallised from chloroform–light petroleum, forming orange, long, slender, four-sided prisms, m. p. 131° (Found : Cl, 20·6. $C_{12}H_9O_5N_3Cl_3$ requires Cl, 20·5%).

In a similar manner the following have been prepared and crystallised : 5 : *5-dichloro-3-carbethoxy-1-(2′-chloro-4′-nitrophenyl)-4-pyrazolone*, pale yellow, dense, rectangular prisms, m. p. 87° (Found : Cl, 28·0. $C_{12}H_8O_5N_3Cl_3$ requires Cl, 28·0%), and the corresponding 1-o-*nitrophenyl* compound, deep yellow, compact, irregular prisms, m. p. 98° (Found : Cl, 20·6%), and 1-m-*nitrophenyl* compound, yellow, long, slender, flattened, four-sided prisms, m. p. 135° (Found : Cl, 20·65%).

*5-Chloro-3-carbethoxy-4-hydroxy-*1-p-*nitrophenylpyrazole* (III).—A solution of 2 g. of 5 : 5-dichloro-3-carbethoxy-1-*p*-nitrophenyl-4-pyrazolone in 20 c.c. of warm acetic acid was added to one of 2 g. of potassium iodide in 10 c.c. of water and 10 c.c. of acetic acid. Iodine was set free at once, and after ¼ hour cautious addition of water precipitated *5-chloro-3-carbethoxy-4-hydroxy-*1-p-*nitrophenylpyrazole*, which crystallised from alcohol in colourless, long, compact, four-sided prisms, m. p. 146° (Found : Cl, 11·6. $C_{12}H_{10}O_5N_3Cl$ requires Cl, 11·3%). Its *acetyl* derivative, made by warming it with acetic anhydride containing a drop of sulphuric acid, crystallised from alcohol in colourless, long, slender prisms, m. p. 121·5° (Found : Cl, 10·2. $C_{14}H_{12}O_6N_3Cl$ requires Cl, 10·0%).

In a similar manner the following have been prepared : *5-chloro-3-carbethoxy-4-hydroxy-1-(2′-chloro-4′-nitrophenyl)pyrazole*, colourless, long, slender needles from alcohol, m. p. 191° (Found : Cl, 20·45. $C_{12}H_9O_6N_3Cl_2$ requires Cl, 20·5%), and the corresponding 1-o-*nitrophenyl* compound, colourless, long, slender, four-sided prisms from benzene, m. p. 142° (Found : Cl, 11·6%), and 1-m-*nitrophenyl* compound, colourless, irregular, compact prisms from alcohol, m. p. 109° (Found : Cl, 11·5%).

*Ethyl Diketosuccinate*-p-*nitrophenylhydrazone* (IV).—(I) 2 G. of 5 : 5-dichloro-3-carbethoxy-1-*p*-nitrophenyl-4-pyrazolone were heated for a few minutes with 15 c.c. of ethyl alcohol. Hydrogen chloride was evolved and *ethyl diketosuccinate*-p-*nitrophenylhydrazone* separated. It crystallised from alcohol in pale yellow, long, flattened, obliquely truncated, four-sided prisms, m. p. 125° (Found : C, 50·1; H, 4·2; N, 12·5. $C_{14}H_{15}O_7N_3$ requires C, 49·8; H, 4·4; N, 12·5%).

(II) 3 G. of *p*-nitroaniline (1 mol.) were diazotised with 1·5 g. of sodium nitrite (1 mol.) in 20 c.c. of concentrated hydrochloric acid, and the filtered solution slowly run into a well-stirred cooled mixture of 5 g. of ethyl oxalacetate (1 mol. + excess) and 30 g. of sodium acetate in 200 c.c. of water. The pasty yellow solid obtained, after crystallisation from alcohol, was identical with the above compound.

In a similar manner to (I) above the following have been prepared by using the appropriate alcohol and 5 : 5-dichloro-4-pyrazolone : 1-*ethyl* 2-*methyl diketosuccinate*-1-p-*nitrophenylhydrazone*, deep yellow, long, flattened prisms, with domed ends, from alcohol, m. p. 138° (Found : N, 12·9. $C_{13}H_{13}O_7N_3$ requires N, 13·0%); 1-*ethyl* 2-n-*propyl diketosuccinate*-1-p-*nitrophenylhydrazone*, pale yellow, long, slender, flattened prisms from alcohol–light petroleum, m. p. 92° (Found : N, 12·1. $C_{15}H_{17}O_7N_3$ requires N, 12·0%); 1-*ethyl* 2-*benzyl diketosuccinate*-1-p-*nitrophenylhydrazone*, pale yellow, long, slender prisms from alcohol, m. p. 147° (Found : N, 10·7. $C_{19}H_{17}O_7N_3$ requires N, 10·5%); 1-*ethyl* 2-*methyl diketosuccinate*-1-(2′-*chloro*-4′-*nitrophenylhydrazone*), yellow, flattened, irregular prisms from alcohol, m. p. 115° (Found : Cl, 9·9. $C_{13}H_{12}O_7N_3Cl$ requires Cl, 9·9%); 1-*ethyl* 2-*methyl diketosuccinate*-1-(2′-*bromo*-4′-*nitrophenylhydrazone*), yellow, very slender prisms from alcohol, m. p. 126° (Found : Br, 19·6. $C_{13}H_{12}O_7N_3Br$ requires Br, 19·9%); 1-*ethyl* 2-*methyl diketosuccinate*-1-o-*nitrophenylhydrazone*, yellow, long, somewhat flattened prisms from alcohol, m. p. 116° (Found : N, 13·1%); *ethyl diketosuccinate*-m-*nitrophenylhydrazone*, yellow, compact prisms from alcohol, m. p. 84° (Found : N, 12·4%); 1-*ethyl* 2-*methyl diketosuccinate*-1-m-*nitrophenylhydrazone*, pale yellow, long, slender, flattened, four-sided prisms from alcohol, m. p. 105° (Found : N, 13·1%).

*Action of Chlorine upon* 3-*Carbethoxy*-4-*hydroxy*-1-(2′ : 6′-*dichloro*-4′-*nitrophenyl*)*pyrazole*.—Chlorine was passed for 10 minutes through a solution of 1 g. of the pyrazole in 25 c.c. of chloroform. 5-*Chloro*-3-*carbethoxy*-4-*hydroxy*-1-(2′ : 6′-*dichloro*-4′-*nitrophenyl*)*pyrazole*, obtained by evaporating the solvent on a water-bath, crystallised from alcohol in colourless irregular plates, m. p. 200° (Found : Cl, 27·8. $C_{12}H_8O_5N_3Cl_3$ requires Cl, 28·0%).

*Ethyl Diketosuccinate*-p-*nitrophenylosazone* (VIII).—2 G. of ethyl diketosuccinate-*p*-nitrophenylhydrazone were dissolved in boiling alcohol, and 1 g. of *p*-nitrophenylhydrazine added. The *osazone*, which separated, crystallised from alcohol in clusters of yellow, hair-like needles, m. p. 190° (Found : N, 17·55. $C_{20}H_{20}O_8N_6$ requires N, 17·8%).

When the osazone (1 g.) was heated with 10 c.c. of pyridine, a clear solution was first formed. *Ethyl* 4 : 5-*diketo*-1-(4′-*nitrophenyl*)*pyrazolone*-3-*carboxylate*-4-(4″-*nitrophenylhydrazone*), which separated on further heating, crystallised from pyridine in clusters of deep yellow, hair-like needles, m. p. 257° (decomp.) (Found : N, 19·55. $C_{18}H_{14}O_7N_6$ requires N, 19·7%). This compound (1) separated gradually when 2·2 g. of sodium dihydroxytartrate (1 mol.) were added to 75 c.c. of alcohol saturated with hydrogen chloride and containing 2·4 g. of *p*-nitrophenylhydrazine (2 mols.) and the whole was heated in a sealed tube at 100° for 24 hours, (2) separated almost immediately when 1 g. of 1-ethyl 2-hydrogen diketosuccinate-*p*-nitrophenylhydrazone, dissolved in 10 c.c. of alcohol, was added to a boiling alcoholic solution of 0·5 g. of *p*-nitrophenylhydrazine containing 1 g. of anhydrous sodium acetate, and (3) separated at once when 0·25 g. of *p*-nitrophenylhydrazine and 0·5 g. of anhydrous sodium acetate were added to a boiling solution of 0·5 g. of 3-carbethoxy-4 : 5-diketo-1-*p*-nitrophenylpyrazolone hydrate in 10 c.c. of acetic acid.

*Ethyl Diketosuccinate-oximino*-p-*nitrophenylhydrazone* (X).—1 G. of ethyl diketosuccinate-*p*-nitrophenylhydrazone and 0·25 g. of hydroxylamine hydrochloride were heated together in 20 c.c. of alcohol for 5 minutes. The *oximino*-derivative, which separated over-night, crystallised from alcohol in pale yellow, slender prisms, m. p. 163° (decomp.) (Found : N, 16·0. $C_{14}H_{16}O_7N_4$ requires N, 15·9%).

When the oximino-derivative was treated with sodium acetate in acetic acid, 3-*carbethoxy*-4-*keto*iso*oxazolone*-4-p-*nitrophenylhydrazone* (XI) was formed. This compound was also obtained when 1 g. of ethyl diketosuccinate-*p*-nitrophenylhydrazone, 0·25 g. of hydroxylamine, and 1 g. of fused sodium acetate were heated to 100° in 25 c.c. of acetic acid, and water was added to the cooled product. It crystallised from alcohol in yellow, long, slender needles, m. p. 186° (decomp.) (Found : N, 18·3. $C_{12}H_{10}O_6N_4$ requires N, 18·3%).

*Action of Bromine and of Chlorine upon Ethyl Diketosuccinate*-p-*nitrophenylhydrazone.*—Bromine (0·2 c.c.) was added to a boiling solution of 1 g. of the hydrazone and 1 g. of fused sodium acetate in 20 c.c. of acetic acid. On addition of water, ethyl α-bromoglyoxylate-*p*-nitrophenylhydrazone separated; after crystallisation it was identical with an authentic specimen (see Chattaway and Ashworth, this vol., p. 475).

Ethyl α-chloroglyoxylate-2-chloro-4-nitrophenylhydrazone, similarly obtained after chlorine had been passed for 10 minutes through a solution of 1 g. of the hydrazone in 20 c.c. of acetic acid, was also identical with an authentic specimen (Chattaway and Ashworth, *loc. cit.*).

*Action of Dilute Alkali upon* 5 : 5-*Dichloro*-3-*carbethoxy*-1-p-*nitrophenyl*-4-*pyrazolone.*—2 G. of the finely powdered pyrazolone were shaken with 2 g. of sodium hydroxide in 500 c.c. of water and after ½ hour the resulting solution was acidified with dilute hydrochloric acid. 1-*Ethyl* 2-*hydrogen diketosuccinate*-p-*nitrophenylhydrazone*, which separated, crystallised from benzene in yellow, short, compact prisms, m. p. 141° (Found : N, 13·3. $C_{12}H_{11}O_7N_3$ requires N, 13·6%).

When the ethyl hydrogen or the diethyl ester (1 g.) was boiled for ¾ hour with 10 c.c. of alcohol and 20 c.c. of concentrated hydrochloric acid, *diketosuccinic anhydride* p-*nitrophenylhydrazone* separated as a spongy mass. It crystallised from acetic acid in orange hair-like needles, m. p. 243° (decomp.) (Found : N, 16·1. $C_{10}H_5O_6N_3$ requires N, 16·0%).

*Action of Acetic Anhydride upon* 1-*Ethyl* 2-*Hydrogen Diketosuccinate*-p-*nitrophenylhydrazone.*—A solution of 2 g. of the ethyl hydrogen ester in 15 c.c. of acetic anhydride was heated to boiling and cooled, and water cautiously added. 3-*Carbethoxy*-4 : 5-*diketo*-1-p-*nitrophenylpyrazolone hydrate* separated in colourless crystals. Recrystallised from chloroform–light petroleum, it formed long, slender, four-sided prisms, m. p. 95—105° (very indefinite) (Found : N, 13·3. $C_{12}H_9O_6N_3,H_2O$ requires N, 13·6%). The hydrate lost the molecule of water after being kept for a week in a vacuum over phosphoric oxide, and 3-carbethoxy-4 : 5-diketo-1-*p*-nitrophenylpyrazolone remained as a red microcrystalline powder, m. p. 152° (Found : loss, 6·4. Calc., 5·8%).

4-*Oximino*-3-*carbethoxy*-1-p-*nitrophenyl*-5-*pyrazolone* (XIV).—When 2 g. of 3-carbethoxy-4 : 5-diketo-1-*p*-nitrophenylpyrazolone hydrate and 0·6 g. of hydroxylamine hydrochloride were gently warmed together in 20 c.c. of acetic acid, the *oximino*-compound separated. It crystallised from acetic acid in yellow, small, irregular plates decomposing above 222° (Found : N, 18·2. $C_{12}H_{10}O_6N_4$ requires N, 18·3%)

This compound was also obtained by the action under similar conditions of excess of hydroxylamine hydrochloride upon 5 : 5-dichloro-3-carbethoxy-1-(*p*-nitrophenyl)-4-pyrazolone.

THE QUEEN'S COLLEGE LABORATORY, OXFORD. [*Received, August 5th,* 1933.]