T H E S I S

submitted to

THE UNIVERSITY OF GLASGOW

in fulfilment of the

requirements for the

DEGREE OF DOCTOR OF PHILOSOPHY

by

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STUDIES IN THE PYRAZOLIDINE FIELD

CONTENTS

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Errata

Page 26. In line 1, for "its" read 'it is'

Page 32 and pp.87, 89. Structures (LXXXll) and (LXXXlll) should be named as pyrazolo-pyrazines.

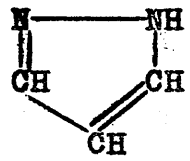
Page 40. In the reaction scheme, for " $\xrightarrow{H^+}$ " read ' $\xrightarrow{-H^+}$ '. In the last but one line for "and 280 mu " read 'to 280 mu '

Page 48. In line 15, for "carboxyl" read 'carbonyl'

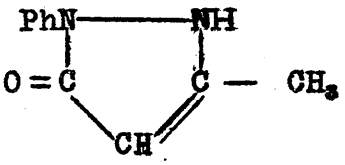
Page 49. In line 6 of text, for "siluble" read 'soluble'

INTRODUCTION

A compound containing the pyrazole ring system (I) was first synthesized by Knorr (1,2) by the reaction of ethyl acetoacetate and phenylhydrazine which gave 3-methyl-1-phenyl-5-pyrazolone (II). Since then the pyrazole group has been very considerably developed and



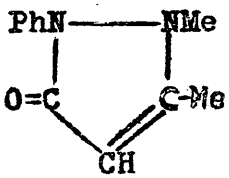
(I)



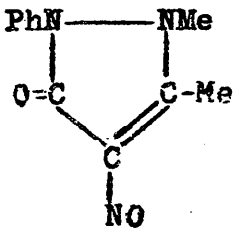
(II)

its members are obtained solely by synthesis; it is not known with certainty whether this ring system occurs in natural products.

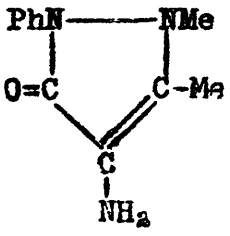
Certain keto-derivatives of pyrazoline, the pyrazolones, have been very extensively studied. The reason for this was the important discovery, made by Knorr (3), that 2,3-dimethyl-1-phenyl-5-pyrazolone (III), (antipyrine, phenazone) possessed interesting pharmacological properties. The group of compounds was therefore thoroughly investigated from this point of view by Knorr and his school, as well as by industry. Antipyrine (III) is



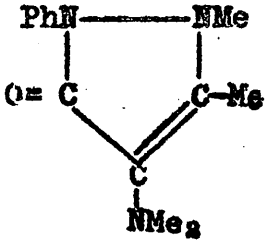
(III)



(IV)

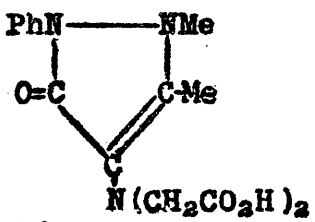


(V)

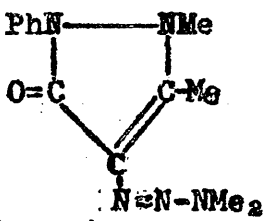


(VI)

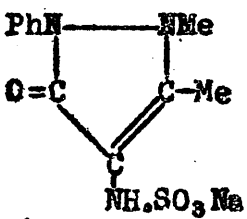
prepared by the methylation of (II) (4). Nitrous acid forms the 4-nitroso-derivative of antipyrine (IV). When (IV) is reduced using zinc dust and acetic acid to the amine (V) followed by methylation, pyramidon (VI)(5) is formed, which is appreciably more powerful than antipyrine. (VI) can also be prepared (6) by treating amino-antipyrine (V) with chloroacetic acid to form a dicarboxylic acid (VII) which when heated above its melting point loses carbon dioxide to give (VI). Another method of preparation (7) is by the diazotisation of (V) with nitroso-dimethylamine to give (VIII) which on the loss of nitrogen gives (VI).



(VII)



(VIII)

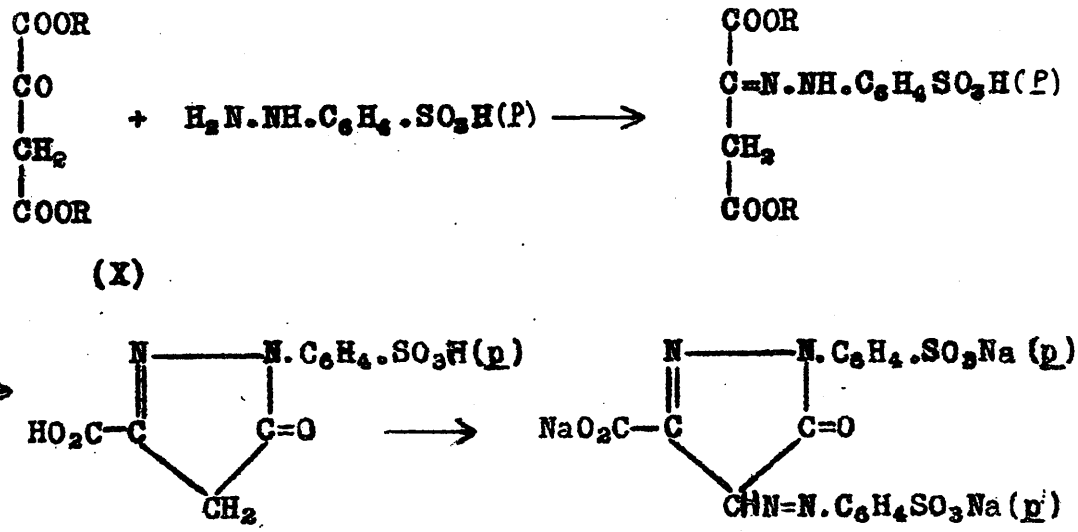


(IX)

The method (8) used for the commercial production of pyramidon consists in treating (IV) with excess sodium bisulphite to give 4-sulphamino-antipyrine (IX) which is then methylated with formaldehyde and formic acid to give (VI).

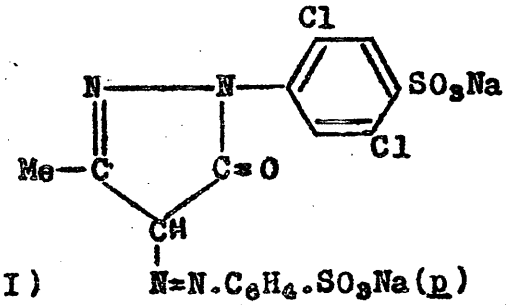
The two main systemic actions of antipyrine and pyramidon are analgesic and antipyresis. The pharmacology of antipyrine and related drugs has been reviewed (9,10,11). Both antipyrine and pyramidon are no longer in common use because the latter compound can cause severe and often fatal agranulocytic angina, and the former has lost favour as the salicylates have become more prominent.

The pyrazolones and their derivatives were also investigated because, besides their therapeutic value, they were found to be useful as dyes or in the synthesis of dyes. The pyrazole dyes include many important commercial examples, the chief being the bright greenish yellow dyes for wool. They are very fast to light and particularly valuable as the yellow components in two- and three- colour mixtures. Tartrazine (XII), the first known pyrazolone dye and still of considerable importance both as a yellow wool dye and as the most widely used of all synthetic dyes in the colouring of food, was discovered by Ziegler (1884) (12). It is now obtained technically by condensing oxalacetic ester (X) and phenylhydrazine sulphonic acid giving sulphophenylpyrazolone carboxylic acid (XI) and this is coupled with diazotised sulphanilic acid.



(X) (XI) (XII)

A more durable, though slightly more expensive, yellow dye is Xylene Light Yellow (XIII).



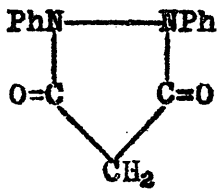
(XIII)

The synthesis and chemistry of the pyrazoles, the pyrazolines and the pyrazolone dyes have been fully described in Elderfield's "Heterocyclic Compounds" (13) and Rodd's "Chemistry of Carbon Compounds" (14).

During the last decade interest, also, in derivatives of pyrazolidine has been greatly stimulated by the introduction of phenylbutazone (4n-butyl-3,5-dioxo--1,2-diphenylpyrazolidine) (15), a drug of considerable

value in the treatment of rheumatoid arthritis and allied conditions (16). Little however, has been written about the 3,5-dioxopyrazolidines and it was felt that since these compounds are relevant to the work described later, a review of the chemistry of 3,5-dioxo-1,2-diphenyl-pyrazolidine (XIV) was expedient.

3,5-Dioxo-1,2-diphenylpyrazolidine (XIV) was first prepared by Tsumaki (17) who obtained it from the reaction of hydrazobenzene and malonyl chloride. Diphenyldioxo-pyrazolidine (XIV) was also prepared (18) by the base catalysed condensation of diethyl malonate and hydrazoben-zene. (XIV) can be prepared in 90% yield by bubbling gaseous carbon suboxide (C_3O_2) through a solution of

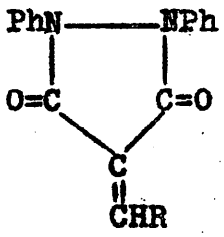


(XIV)

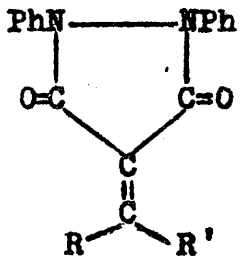
hydrazobenzene in ether (19).

(XIV) is readily soluble in alkali and a solution of (XIV) in ethanol gives a red colour with ferric chloride. The C_4 position of (XIV) behaves as an active methylene group condensing with aldehydes and ketones to give products with the general structure (XV) and (XVI) respectively. Tsumaki (17,20) prepared a large number

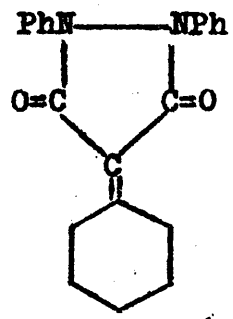
of these condensation products all of which are highly coloured. The cyclohexylidene (XVII), the cyclopentylidene (XVIII) and the benzylidene (XIX) derivatives have all been reduced by catalytic hydrogenation to the colourless dihydro-derivatives (15).



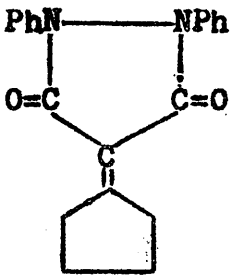
(XV)



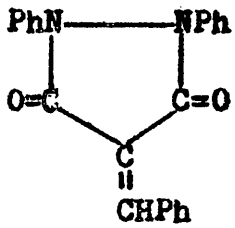
(XVI)



(XVII)

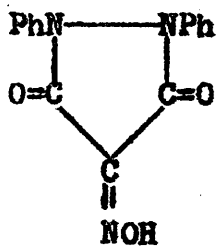


(XVIII)

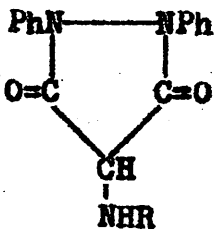


(XIX)

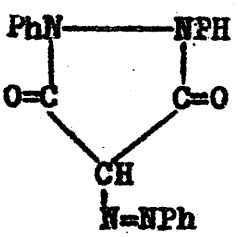
3,5-Dioxo-1,2-diphenylpyrazolidine (XIV) reacts with nitrous acid to give the red 4-isonitroso-derivative (XX) (17) which can be catalytically reduced to 4-amino--3,5-dioxo-1,2-diphenylpyrazolidine (XXI; R=H)(21). (XIV) coupled with benzenediazonium chloride, furnishes the 4-phenylazo-derivative (XXII) (22). This can be reduced catalytically with palladium-charcoal to (XXI; R = H) (22).



(XX)



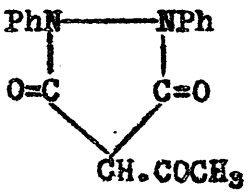
(XXI)



(XXII)

Reduction of (XX) using zinc in acetic acid–acetic anhydride gives 4–acetamido–3,5–dioxo–1,2–diphenyl–pyrazolidine (XXI; R = Ac) (22).

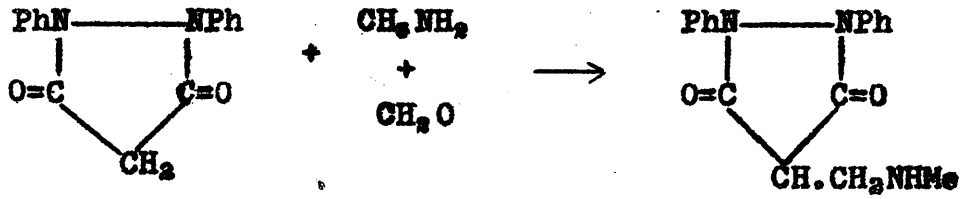
3,5–Dioxo–1,2–diphenylpyrazolidine (XIV) can be acetylated using acetic anhydride–pyridine (23), the alkali soluble 4–acetyl derivative (XXIII) being obtained.



(XXIII)

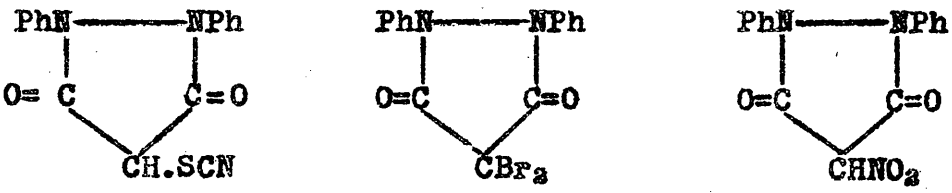
(XXIII) can also be prepared by the Friedel–Crafts reaction (24); (XIV) on treatment with acetyl chloride and using aluminium chloride as catalyst, gives (XXIII). This reaction is quite general for the preparation of 4–acyl derivatives of (XIV) and potassium carbonate or pyridine can be used as condensing agents in place of aluminium chloride.

3,5–Dioxo–1,2–diphenylpyrazolidine (XIV) also enters into the Mannich reaction (24) e.g.



(XIV) (XXIV)

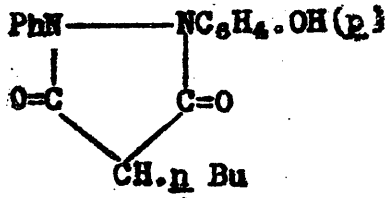
(XIV) also forms a 4-bromo-derivative (21,25) when treated with bromine in the presence of ultraviolet light, and a 4-chloro-derivative is also known (25). Treatment of (XIV) with ammonium thiocyanate affords a 4-thiocyanate--derivative (XXV). When a boiling chloroform solution



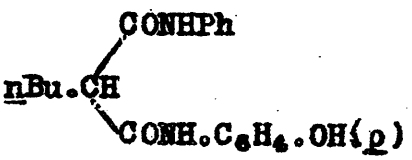
(XXV) (XXVI) (XXVII)

of (XIV) is treated with bromine a 4,4-dibromo-derivative (XXVI) (25) is produced, and (XIV), on reaction with mixed acids with cooling, yields a 4-nitro derivative (XXVII) (25).

When 3,5-dioxo-1,2-diphenylpyrazolidine (XIV) or a 4-substituted derivative is hydrogenated with Raney nickel at temperatures above room temperature, the pyrazolidine ring is cleaved (26), so that for example mono-p-hydroxy-phenylbutazone (XXVIII) yields mono-p--hydroxy-n-butylmalonyldianilide (XXIX).



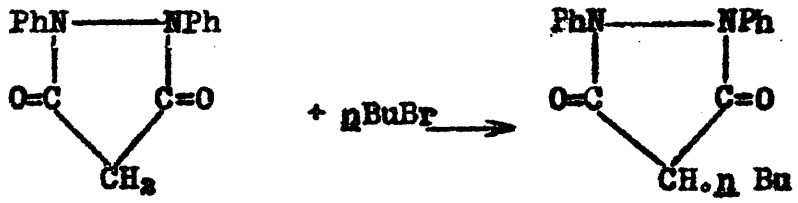
(XXVIII)



(XXIX)

Pharmacologically, the most important derivative of 3,5-dioxo-1,2-diphenylpyrazolidine (XIV) to be discovered is phenylbutazone (4n-butyl-3,5-dioxo-1,2-diphenylpyrazolidine) (XXX) (15). Phenylbutazone has been used to a considerable extent in the treatment of rheumatoid arthritis and allied conditions (16). Its similarity in action to cortisone was soon noticed, and being appreciably less expensive, it was rapidly accepted as a therapeutic substitute in certain conditions. However several indications of toxic effects associated with its use have been reported (27-32) the most serious being an agranulocytosis which may appear at any time after the administration of the drug has begun. This has led to the preparation of a large number of derivatives of 3,5--dioxo-1,2-diphenylpyrazolidine (XIV), substituted in the 4-position or in the phenyl rings or both, in an attempt to find less toxic congeners of phenylbutazone.

Phenylbutazone was first prepared by Geigy (33) who treated (XIV) with n-butyl bromide in the presence of sodium hydroxide. This method has been replaced, and

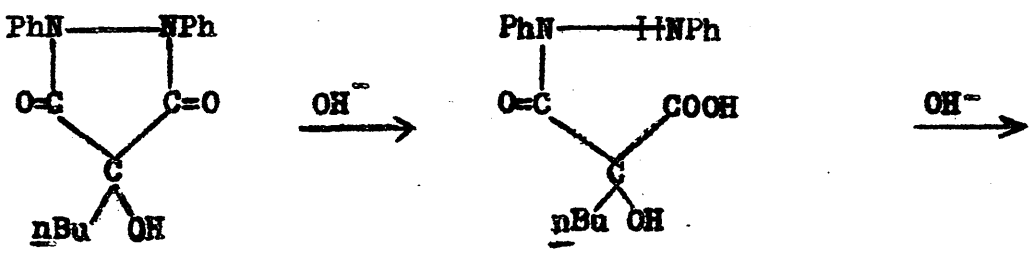


(XIV) (XXX)

the two methods most generally used now are firstly, the condensation of ethyl n-butylmalonate (XXXI; R = OEt) with hydrazobenzene in the presence of sodium ethoxide (15) and secondly the condensation of n-butylmalonyl chloride (XXXI; R = Cl) with hydrazobenzene in the presence of pyridine (34).

$$\underset{\text{(XXXI)}}{\text{n-BuCH(COR)}_2} + (\text{PhNH})_2 \longrightarrow \text{(XXX)}$$

In the first method a by-product is formed and it has recently been identified (35,15) as 4n-butyl-4-hydroxy-3,5-dioxo-1,2-diphenylpyrazolidine (XXXII). Structure (XXXII) was proved by alkaline hydrolysis and decarboxylation to give α-hydroxycaproic acid (XXXV) as shown (XXXII) — (XXXV).

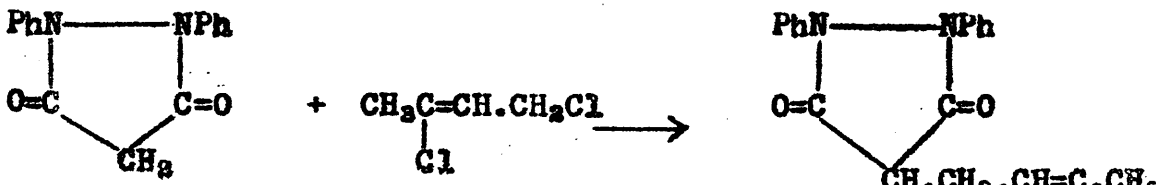


(XXXII) (XXXIII)

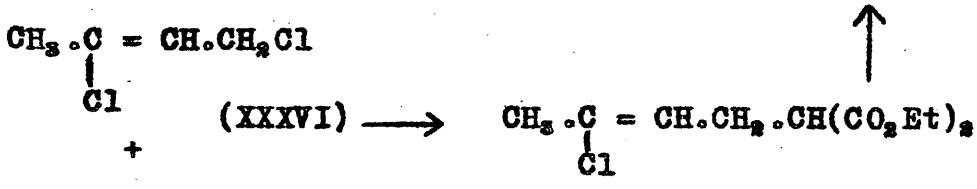
$$\underset{\text{OH}}{\text{nBuC.(COOH)}_2} \xrightarrow{-CO_2} \text{nBu.CH(OH)COOH}$$

(XXXIV) (XXXV)

Most of the other methods used for the preparation of phenylbutazone are usually modifications of the above two or methods which involve the alkylation of 3,5-dioxo--1,2-diphenylpyrazolidine (XIV) e.g.



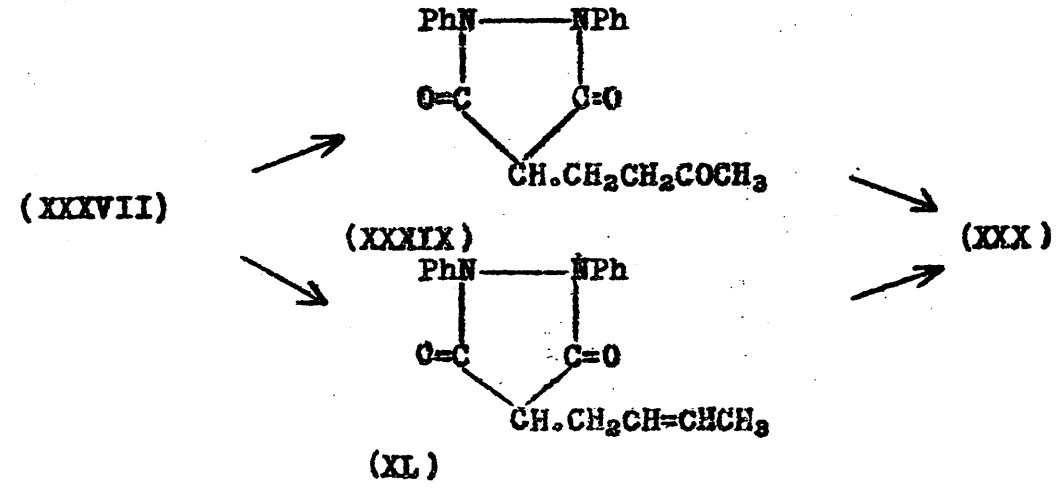
(XIV) (XXXVI) (XXXVII)



(XXXVI) (XXXVIII)

(XIV) is condensed with 1,3-dichloro-butene-2 (XXXVI) in the presence of one equivalent of sodium hydroxide to give 4-(3-chloro-2-butenyl)-3,5-dioxo-1,2-diphenylpyrazolidine (XXXVII) (36). (XXXVII) can also be prepared by condensing diethyl malonate with (XXXVI) to give ethyl 3-chloro-2-butenylmalonate (XXXVIII) which with hydrazobenzene gives the pyrazolidine (XXXVII) (36). (XXXVII) is converted to phenylbutazone (XXX) by hydrogenation using Raney nickel as catalyst. Phenylbutazone can also be obtained by conversion of (XXXVII) into 4-(3-oxobutyl)-3,5-dioxo-1,2--diphenylpyrazolidine (XXXIX) using concentrated sulphuric acid, followed by Huang-Minlon reduction, or by the

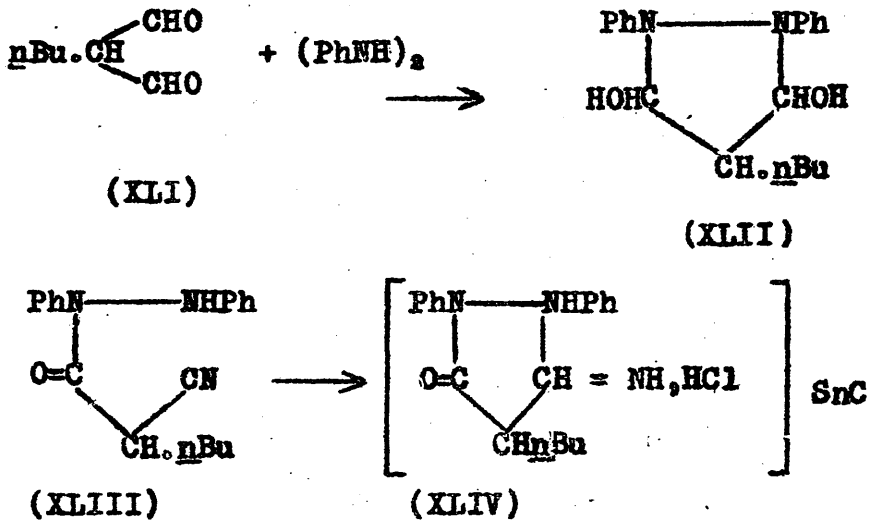
reduction of (XXXVII) to 4-(2-butenyl)-3,5-dioxo-1,2-diphenylpyrazolidine (XL) followed by catalytic hydrogenation (36).



(XL) can also be prepared by the condensation of hydrazobenzene and ethyl 2-butenylmalonate using sodium ethoxide as condensing agent (37).

Various other methods for preparing phenylbutazone (XXX) have also been patented. If n-butylmalonyldianilide is treated with dehydrogenating agents such as sulphur or aluminium chloride, cyclisation occurs with the formation of the pyrazolidine (XXX) (38). A modification of this method consists in treating n-butylmalonyldianilide with a hypochlorite or a chloramine followed by cyclisation of the resulting N,N'-dichloro-intermediate using Raney nickel (39). A final method (40) which might be mentioned involves the condensation of a monosubstituted malonic

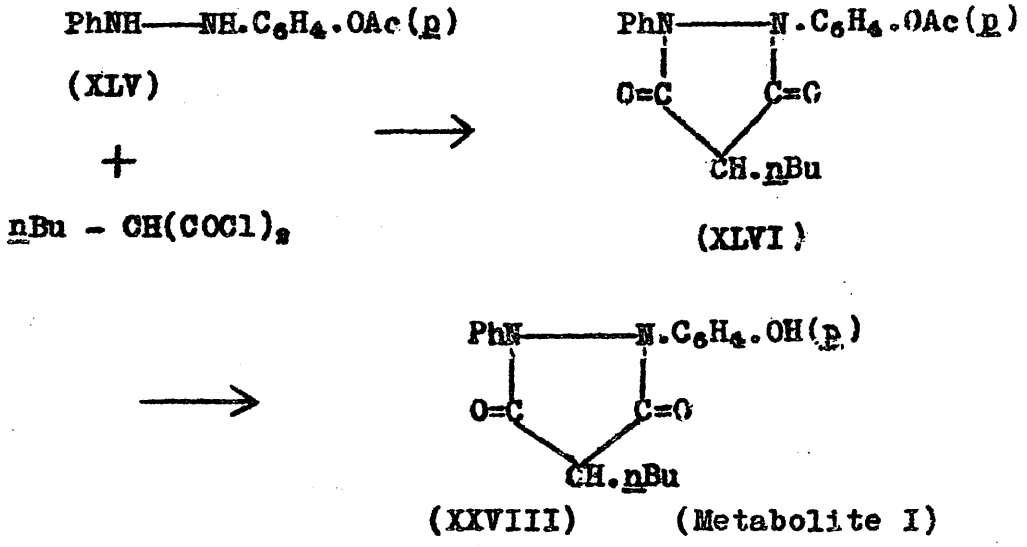
dialdehyde (XLI) and hydrazobenzene, and the resulting secondary alcohol (XLII) oxidised with a hydrogen acceptor such as acetone or cyclohexanone, in the presence of a catalyst like aluminium butoxide or aluminium iso-propoxide, to (XXX). Another method of obtaining (XLII) consists



in treating NC.CHR.COR'(R' = halogen, hydrogen or alkoxy radical) with hydrazobenzene to give (XLIII). This product is then agitated for a few minutes in anhydrous stannous chloride in ether saturated with gaseous hydrochloric acid; the product (XLIV) on refluxing with water gives phenylbutazone. This method is of little practical importance since no physical constants of the compounds prepared and only a few experimental details are given.

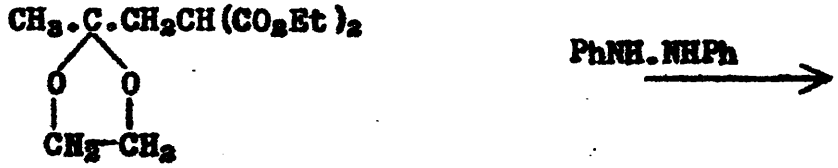
Two metabolic products of phenylbutazone in man have been isolated (41) both of which are mono-hydroxy

phenylbutazones; metabolite I (XXVIII) has one of the phenyl rings hydroxylated in the p-position and metabolite II (L) has a hydroxyl group in the γ-position of the butyl side chain. Von Pfister and Häfliger (42,43) have confirmed these two structures by the following syntheses. p-Acetoxyhydrazobenzene (XLV) was condensed with n-butylmalonyl chloride to give the pyrazolidine

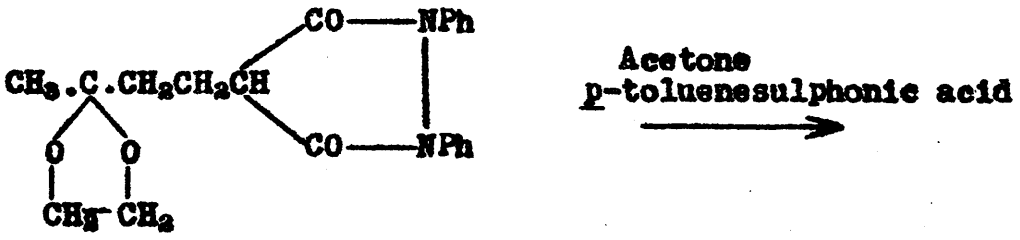


(XLVI) which on saponification yielded metabolite I (XXVIII). Metabolite II was synthesized in the following manner (44). The condensation of γ-(ethylenedioxy)-butylmalonic ester (XLVII) with hydrazobenzene gave γ-ethylenedioxy-phenylbutazone (XLVIII) which on treatment with p-toluenesulphonic acid in acetone gave the ketone (XLIX), the latter on reduction with sodium borohydride or with

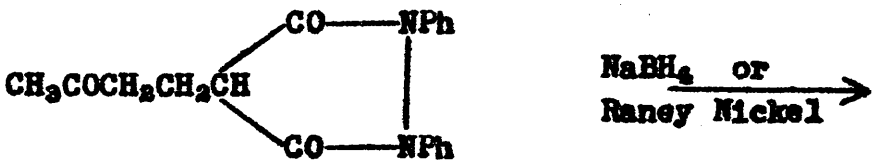
Raney nickel gave γ-hydroxy-phenylbutazone, metabolite II (L).



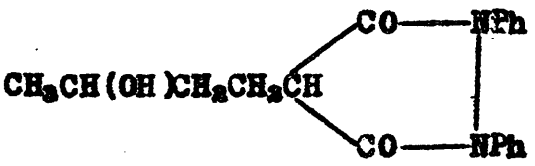
(XLVII)



(XLVIII)



(XLIX)



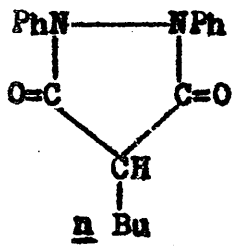
(L) Metabolite II

THEORETICAL

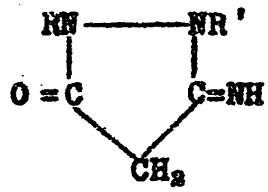
S E C T I O N I.

The Synthesis of 3-Imino-5-oxo-1,2-diphenylpyrazolidine and Derivatives.

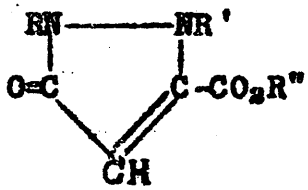
Although a large number of 3,5-dioxopyrazolidines, substituted either in the 4-position or in the phenyl rings or in both have been described as analogues of phenylbutazone (XXX) (15) [see introduction], no derivatives have been described in which one of the oxo groups in the 1,2-diaryl compounds was replaced by an imino group. Some 1-alkyl-2-aryl-3(5)-imino-5(3)-oxo-pyrazolidines



(XXX)



(LI)

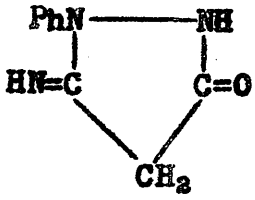


(LII)

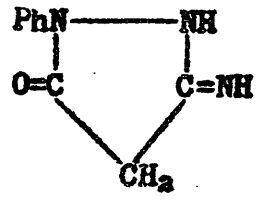
(LI; R = alkyl or aryl; R' = alkyl) are known (44,45) and they have an antipyretic effect. These compounds are usually prepared by the alkylation of 1-aryl-3(5)-imino--5(3)-oxo-pyrazolidines (LI; R = aryl; R' = H) e.g. methylation of 3-imino-5-oxo-1-phenylpyrazolidine (LI, R = Ph; R' = H) gives 2-methyl-3-imino-5-oxo-1-phenylpyrazolidine (LI; R = Ph; R' = Me) (46). The latter compound can be also prepared from 2-alkyl-1-aryl-5--pyrazolone-3-carboxylic acid (LII; R = aryl; R' = alkyl; R" = H) either by the Hofmann or Curtius methods (44,45).

There are a number of methods which can be used for the preparation of imino-oxo-pyrazolidines. If

phenylhydrazine is used as the hydrazine derivative, then the first method is by the condensation of phenylhydrazine and ethyl cyanoacetate using sodium alkoxide as the condensing agent. Using this method Conrad and Zart (47) obtained a compound which they assumed to be 5-imino-3-oxo--1-phenylpyrazolidine (LIII). This reaction was reinvestigated by Weissberger and Porter (48) who suggested that the

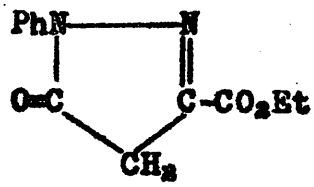


(LIII)

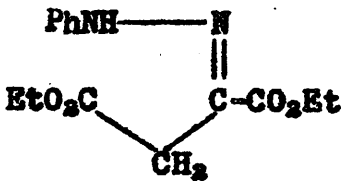


(LIV)

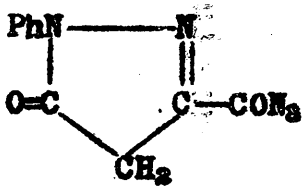
reaction could also lead to the isomeric 3-imino-5-oxo-1--phenylpyrazolidine (LIV). In order to establish whether the compound from the reaction had structure (LIII) or (LIV), they synthesized (LIV) in an unambiguous way starting with 1-phenyl-3-carbethoxy-5-pyrazolone (LV) (49). This latter compound can be prepared by ring closure of the well characterised ethyl oxalacetate phenylhydrazone (LVI) (49). (LV) was transformed to the hydrazide and then to the azide (LVII) using nitrous acid, and the latter subjected to a Curtius degradation. The compound obtained was identical with that prepared by Conrad and Zart. Thus the condensation of ethyl cyanoacetate with phenyl-



(LV)

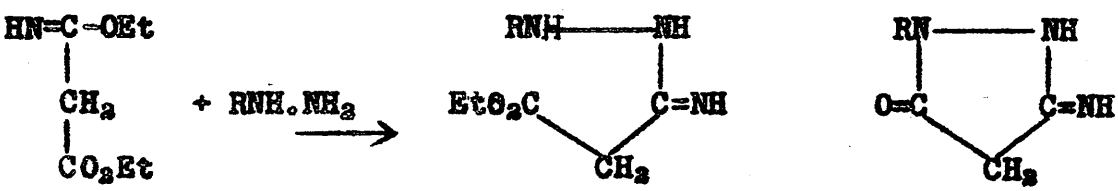


(LVI)



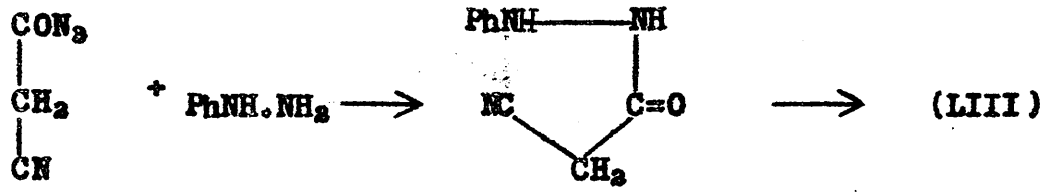
(LVII)

hydrazine in the presence of sodium alkoxide results in the formation of 3-imino-5-oxo-1-phenylpyrazolidine (LIV). This reaction, however, is not general because with other monosubstituted hydrazines, the corresponding 3-imino-5--oxopyrazolidine is not always isolated e.g. 2-pyridyl-hydrazine and 2-quinolylhydrazine yield the respective 5-imino-3-oxopyrazolidine (50). These hydrazines can however be converted to the 3-imino-5-oxopyrazolidines by another method (51). In this synthesis the hydrazine ($RNH.NH_2$) is condensed with ethyl malonate monoimidoester (LVIII) either directly to the respective 3-imino-5-oxo-pyrazolidine (LX) or with isolation of the intermediate ethyl β-(β-R-hydrazine)-β-iminopropionate (LIX). The latter on treatment with alkali ring closes to the pyrazolidine.



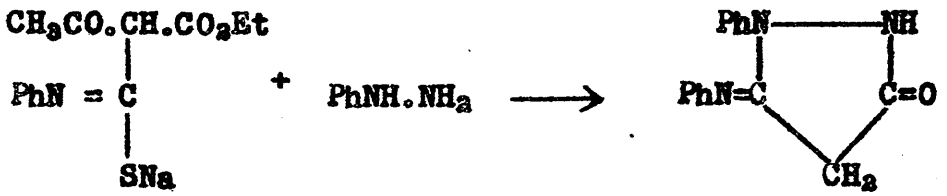
(LVIII) (LIX) (LX)

To prepare the isomeric series of compounds, i.e. 5-imino-3-oxo-1-arylpyrazolidines, a general synthesis is the condensation of cyanoacetyl chloride or azide (LXI) with a hydrazine (52) e.g. phenylhydrazine, as illustrated (LXI - LIII). To prepare derivatives of the latter type e.g. 5-anilino-3-oxo-1-phenylpyrazolidine (LXIV) (53)



(LXI) (LXII)

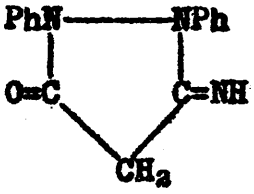
phenylhydrazine is condensed with the sodium salt of α-carbethoxyacetothioacetanilide (LXIII) (54).



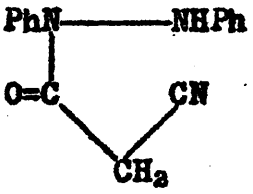
(LXIII) (LXIV)

The first objective in this work was the preparation of 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV). In this compound the 3- and the 5- positions are equivalent and no problem of isomerism will arise. Since N,N'-diaryl-hydrazines are less basic than the N-monosubstituted hydrazines, it was decided to use the more reactive

cyanoacetyl chloride in the initial synthesis of (LXV).



(LXV)



(LXVI)

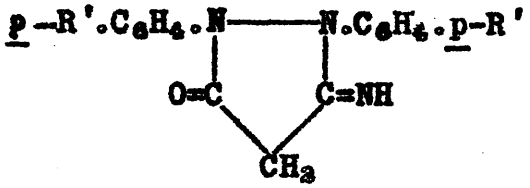
A potential intermediate for the synthesis of this compound, cyanoacetylhydrazobenzene (LXVI) had been previously described (55) as the product of reaction between hydrazobenzene, cyanoacetic acid and phosphorus oxychloride in the presence of pyridine. Lacking experimental details we were unable to reproduce it and the reaction of cyanoacetyl chloride with hydrazobenzene in the presence of pyridine was therefore examined. Using 1.5 mols. of cyanoacetyl chloride per mol. of hydrazobenzene, (LXVI) was only obtained in ca.15% yield, 30% of the hydrazobenzene being recovered. If 2-3 mols. of the acid chloride per mol. of hydrazobenzene was used then a 30% yield of (LXVI) was obtained. Cyanoacetylhydrazobenzene (LXVI) could then be cyclised to 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) by heating with either aqueous ethanolic sodium carbonate or less effectively with solutions of sodium methoxide or ethoxide in the corresponding alcohol. The oxo-imino compound was also isolated in 9% yield from the cyanoacetyl-

hydrazobenzene mother liquors of the acid chloride reaction. Also isolated from the condensation of cyanoacetyl chloride with hydrazobenzene was an acidic compound whose structure is discussed on page 45.

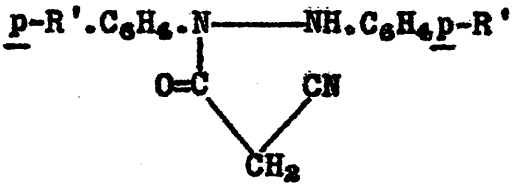
The purification of cyanoacetyl chloride by distillation even under reduced pressure sometimes resulted in pyrolysis and decomposition. For this reason it was decided to investigate the reaction of ethyl cyanoacetate and hydrazobenzene. However when the condensation was carried out in the presence of sodium ethoxide and in a nitrogen atmosphere, only an 8% yield of (LXV) was obtained, a considerable amount of hydrazobenzene being recovered along with some azobenzene. Several attempts to increase the yield of (LXV) from the above condensation were carried out. Solutions of ethyl cyanoacetate and hydrazobenzene in ethanolic sodium ethoxide, in pyridine and in N-methylmorpholine were left for two days at room temperature and in an atmosphere of nitrogen. In all three cases a 95% recovery of hydrazobenzene was obtained; no reaction appeared to have taken place.

pp'-Dimethylhydrazobenzene was converted into its cyanoacetyl derivative (LXVII; R' = Me) as described above and the latter compound was cyclised using sodium carbonate to 3-imino-5-oxo-1,2-di-p-tolylpyrazolidine (LXVIII; R' = Me)

which was also prepared in poor yield by base catalysed interaction between ethyl cyanoacetate and pp'-dimethylhydrazobenzene.

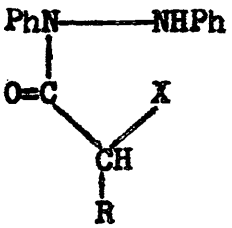


(LXVIII)

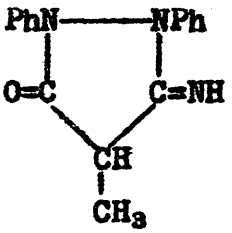


(LXVII)

Because of the low yield of (LXV) from the base catalysed ethyl cyanoacetate condensation with hydrazobenzene another synthesis had to be devised. It was found that the most convenient method for the preparation of 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) was the reaction of the known chloroacetylhydrazobenzene (LXIX; R = H; X = Cl) (56) with potassium cyanide in aqueous ethanol when a 57% yield was obtained, the intermediate (LXVI) being presumably cyclised as it was formed under the alkaline conditions, none being isolated. Similarly α-bromopropionylhydrazobenzene (LXIX;R=CH_3,X=Br), which had



(LXIX



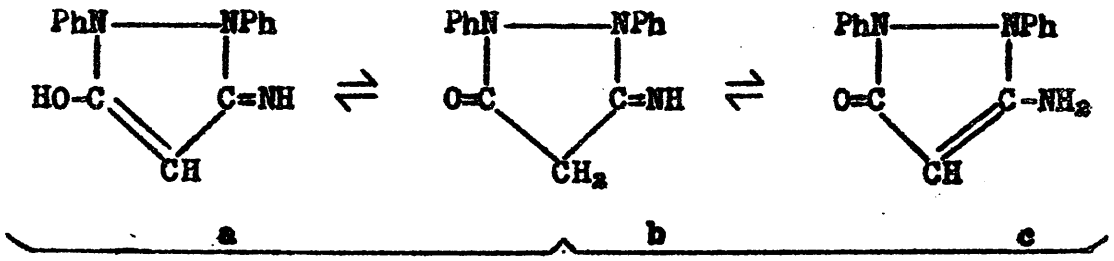
(LXX)

been prepared by Bischoff (57) could be cyclised (58) by refluxing with aqueous ethanolic potassium cyanide, to 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (LXX). Potassium cyanide treatment of α-chloropropionylhydrazobenzene (LXIX; R = CH_3, X = Cl), the product from the condensation of α-chloropropionyl chloride and hydrazobenzene, also gave (LXX).

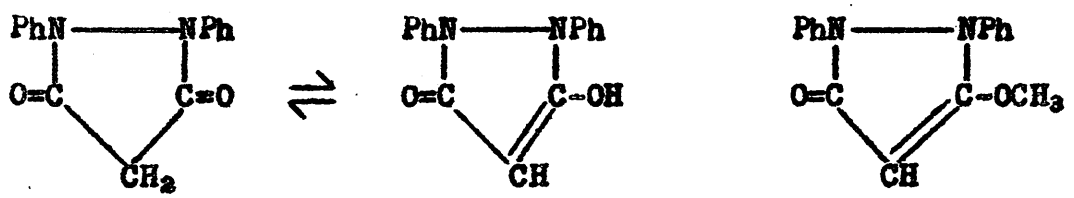
Using the above method of synthesizing imino-oxo pyrazolidines from the action of potassium cyanide on N-α-haloacyl derivatives of hydrazobenzene it should be possible to extend it to preparing other 4-alkyl and 4,4-dialkyl derivatives of (LXV). Due to lack of time this was unable to be carried out.

An attempt to prepare N-acetyl-N'-cyanoacetylhydrazobenzene by refluxing N-cyanoacetylhydrazobenzene (LXVI) with acetic anhydride for 1 hr. was unsuccessful; cyanoacylation of N-acetylhydrazobenzene also failed. N-Cyanoacetylhydrazobenzene was insoluble in aqueous mineral acid and aqueous sodium hydroxide as was 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV). Diazomethane did not react with either N-cyanoacetylhydrazobenzene or 3-imino-5-oxo-1,2-diphenylpyrazolidine; the latter compound gave a red colouration with ferric chloride.

The ultraviolet absorption of N-cyanoacetyl-hydrazobenzene (LXVI) showed a bathochromic shift from 238 mu to 255 mu on passing from neutral to alkaline solvent while 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) showed no effective change in the position (256 mu) or



(LXV)



(XIV) (XIVa) (LXXI)

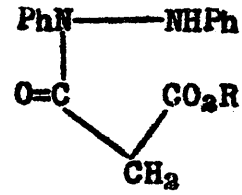
intensity of the longer wavelength ultraviolet maximum when the determination was done in neutral, acid or alkaline solution, i.e. no increase in conjugation. This was in contrast to 3,5-dioxo-1,2-diphenylpyrazolidine (XIV) the ultraviolet absorption spectrum of which was 248 mu in ethanol and 253 mu in alkaline solution suggesting an increase in conjugation in keeping with (XIV) going to (XIVa). (XIVa) was substantiated by the fact that on

treatment with diazomethane, 3-methoxy-5-oxo-1,2--diphenylpyrazoline (LXXI) was obtained. 3-Imino-5--oxo-1,2-diphenylpyrazolidine (LXV) cannot be completely represented by a single structure but more probably by a tautomeric equilibrium of structures (LXV), (LXVa) and (LXVb), with the equilibrium favouring the latter. This question of tautomers is further discussed on page 55.

A suspension of 3-imino-5-oxo-1,2-diphenyl-pyrazolidine (LXV) in aqueous sodium hydroxide was shaken for three days at room temperature in an unsuccessful attempt to convert it to the alkali soluble 3,5-dioxo-1,2-diphenylpyrazolidine (XIV). However heating (LXV) with alkali split the pyrazolidine ring, hydrazobenzene being obtained.

Hydrolysis of N-cyanoacetylhydrazobenzene (LXVI) and 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) with aqueous ethanolic hydrochloric acid gave the same products, a bicarbonate soluble compound A, an alkali soluble compound B and a neutral compound C. The alkali soluble compound was readily identified as 3,5-dioxo-1,2-diphenylpyrazolidine (XIV). Compound A, which was an acid, could be thermally decarboxylated to N-acetylhydrazobenzene. Compound A was therefore N-(β-carboxyacetyl)-hydrazobenzene

(LXXII; R = H), which since its a β-keto acid should

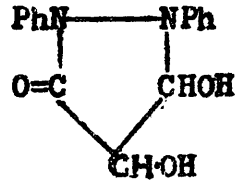


(LXXII)

readily decarboxylate. The infrared spectrum of compound C suggested that it was an ester and since the hydrolysis was carried out in ethanol, it was reasonable to assume that compound C was the ethyl ester of the acid (LXXII; R = H). Treatment of (LXXII; R = H) with diazoethane yielded N-(β-ethoxycarbonylacetyl)-hydrazobenzene (LXXII; R = Et) which was identical with compound C. The ester (LXXII; R = Et) could be cyclised by refluxing with ethanolic sodium ethoxide with the formation of 3,5-dioxo-1,2-diphenylpyrazolidine (XIV).

In an attempt to prepare acyl derivatives of hydrazobenzene, Tsumaki (17) prepared 3,5-dioxo-1,2--diphenylpyrazolidine (XIV) by the action of malonyl chloride on hydrazobenzene. He found that (XIV) was fairly stable and was not decomposed by dilute acid or alkali. However on heating with concentrated alcoholic potash solution, (XIV) seemed to be hydrolysed although he could not detect hydrazobenzene or benzidene in the decomposition product. In addition to 3,5-dioxo-1,2-diphenylpyrazoli-

dine (XIV) another substance $C_{15}H_{14}O_3N_2$ was obtained as a by-product, m.p.160-162°, which seemed somewhat decomposed before melting. This compound was soluble in sodium carbonate and sodium hydroxide solutions and was reprecipitated unchanged by the addition of acid. From its mode of formation Tsumaki proposed two structures namely (LXXII; R = H) and (LXXIII). Tsumaki reasoned

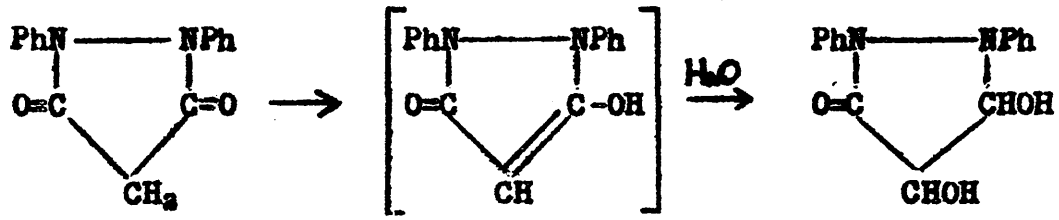


(LXXIII)

that if (LXXII; R = H) was correct then on thermal decomposition azobenzene, acetanilide and carbon dioxide would have been formed, by analogy with the distillation of hydrazobenzene, as had been reported by Melms (59) and Lermonton (60) and with the distillation of N-acetyl-hydrazobenzene (61). Since Tsumaki could detect none of these decomposition products he therefore chose structure (LXXIII) for the compound.

Tsumaki (17) also obtained this compound by the action of dilute hydrochloric acid on a chloroform-ethanol solution of 3,5-dioxo-1,2-diphenylpyrazolidine (XIV).

To account for this Tsumaki argued that 3,5-dioxo-1,2--diphenylpyrazolidine (XIV) was simply hydrated, the acid acting as a catalyst.



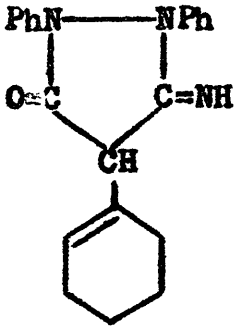
(XIV) (XIVa) (LXXIII)

Now since (XIV) was not hydrolysed to hydrazobenzene as mentioned above, even with concentrated hydrochloric acid, Tsumaki considered that the formation of (LXXII; R = H) from (XIV) by hydrolysis was very unlikely. In view of these facts Tsumaki advanced structure (LXXIII) namely 4,5-dihydroxy-3-oxo-1,2--diphenylpyrazolidine.

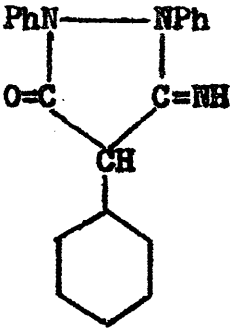
When 3,5-dioxo-1,2-diphenylpyrazolidine (XIV) was hydrolysed, using the same conditions as for N-cyanoacetyl hydrazobenzene (LXVI) and 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV), it was partly converted into a mixture of N-(β-carboxyacetyl)-hydrazobenzene (LXXII; R = H) and its ethyl ester (LXXII; R = Et). When an aqueous dioxan solution was used in place of ethanol in the hydrolysis, only the acid (LXXII; R = H) was obtained. The acid and its ethyl ester were also obtained when we repeated

Tsumaki's hydrolysis conditions. Since N-(β-carboxyacetyl)--hydrazobenzene (LXXII; R = H) melts at 133-134° (decomp.) and N-acetylhydrazobenzene has m.p. 160-161°, the author is of the opinion that Tsumaki's product was probably (LXXII, R = H) but that his melting point determination method resulted in slow decomposition to N-acetylhydrazobenzene, whose m.p. was thus ultimately determined.

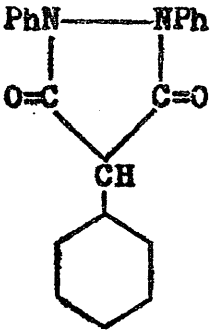
3-Imino-5-oxo-1,2-diphenylpyrazolidine (LXV), in contrast to 3,5-dioxo-1,2-diphenylpyrazolidine (XIV), does not condense readily with aldehydes and ketones. Whereas the latter will form an isopropylidene derivative by simply refluxing in acetone (17), the former will condense with only a few carbonyl compounds. On refluxing 3,5-dioxo--1,2-diphenylpyrazolidine (XIV) with cyclohexanone a yellow crystalline compound was obtained which was the 4-cyclohexylidene derivative (XVII) (17). 3-Imino-5-oxo-1,2-diphenylpyrazolidine (LXV) on heating with cyclohexanone gave a colourless compound $C_{21}H_{21}ON_3$ which is regarded as 4-cyclohexenyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (LXXIV). The lack of conjugation between the double bond and the heterocyclic system in (LXXIV) is also apparent (58) from its ultraviolet spectrum which has the longer wavelength maximum at 255mu whereas (XVII) has absorption maxima at 255, 360 and 372 mu. (LXXIV) on catalytic hydrogenation gave the 4-cyclohexyl derivative (LXXV). Aqueous ethanolic



(LXXIV)



(LXXV)

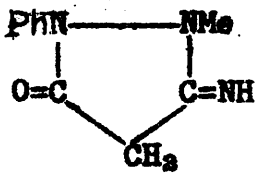


(LXXVI)

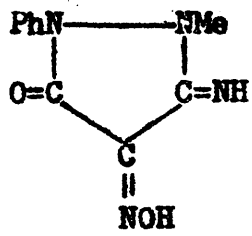
acid hydrolysis of (LXXV) afforded 4-cyclohexyl-3,5--dioxo-1,2-diphenylpyrazolidine (LXXVI), which was also obtained by catalytic hydrogenation of 4-cyclohexylidene-3,5-dioxo-1,2-diphenylpyrazolidine (XVII). (LXXIV) was also prepared, in low yield, by refluxing N-cyanoacetyl-hydrazobenzene with cyclohexanone, the N-cyanoacetyl-hydrazobenzene (LXVI) being presumably cyclised to 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) before condensing.

Both 3,5-dioxo-1,2-diphenylpyrazolidine (XIV) and 3-imino-2-methyl-5-oxo-1-phenylpyrazolidine (LXXVII) on treating with nitrous acid gave coloured isonitroso--derivatives (XX) (17) and (LXXVIII) (46) respectively. Under the same conditions 3-imino-5-oxo-1,2-diphenyl-pyrazolidine (LXV) gave 3-imino-4-isonitroso-5-oxo-1,2-

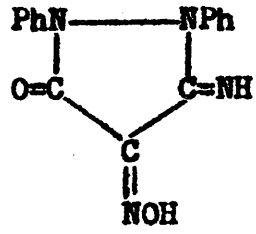
-diphenylpyrazolidine (LXXIX), which was converted into (XX) by aqueous ethanolic acid hydrolysis. (LXV), coupled with benzenediazonium chloride, furnished 3-imino-5-oxo--4-phenylazo-1,2-diphenylpyrazolidine (LXXX). Reduction



(LXXVII)

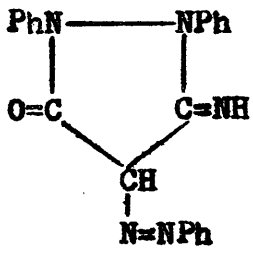


(LXXVIII)

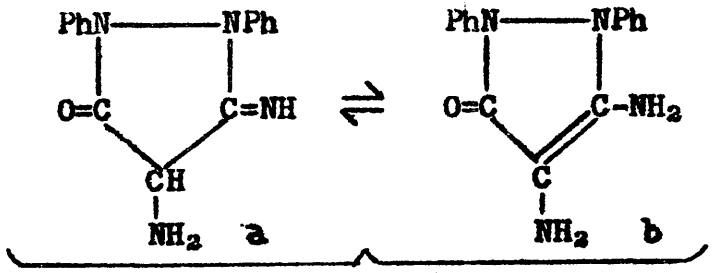


(LXXIX)

of (LXXIX), using zinc dust-hydrochloric acid at 0° afforded 3,4-diamino-5-oxo-1,2-diphenylpyrazoline (LXXXI).



(LXXX)

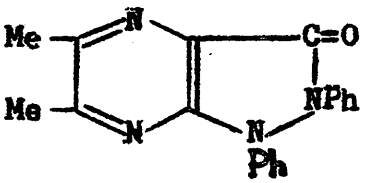


(LXXXI)

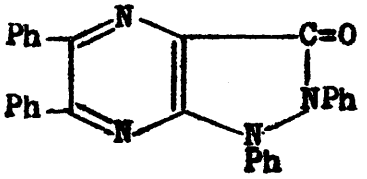
Attempts to prepare the 4-amino derivative (LXXXI) by catalytic hydrogenation of the 4-phenylazo derivative (LXXX) and the 4-isonitroso derivative (LXXIX) using both Raney nickel and platinum oxide were unsuccessful.

The α-diamino system in (LXXXI) proved reactive towards α-dioxo-compounds, as expected. 3,4-Diamino-5-

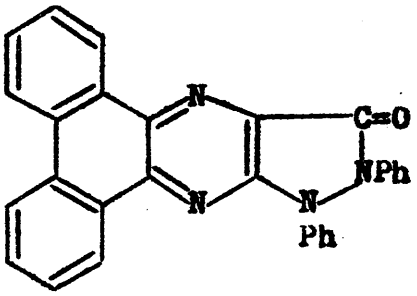
-oxo-1,2-diphenylpyrazoline (LXXXIb) condensed with diacetyl at room temperature giving 5,6-dimethyl-3-oxo--1,2-diphenylpyrazolo-[2,3b]-pyridazine (LXXXII), and on refluxing an acetic acid solution of the diamine (LXXXI) with benzil, 3-oxo-1,2,5,6-tetraphenylpyrazolo-[2,3b]-pyridazine (LXXXIII) was obtained. Under similar conditions to the latter, (LXXXI) condensed with phenanthraquinone to give (LXXXIV)



(LXXXII)



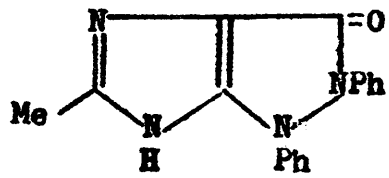
(LXXXIII)



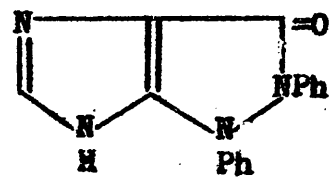
(LXXXIV)

Attempts to cyclise 3,4-diamino-5-oxo-1,2-diphenyl-pyrazoline (LXXXI) to give the iminazolo-[3,4d]-pyrazoline ring system were undertaken. (LXXXI) was refluxed with acetic anhydride but a compound analysing

for a monoacetate derivative of the diamine (LXXXI) was obtained, cyclisation failing to take place to give (LXXXV). Refluxing the monoacetate of (LXXXI) in xylene also failed to bring about cyclisation. Similarly prolonged treatment of (LXXXI) with formic acid was again unsuccessful, a monoformate derivative being obtained



(LXXXV)



(LXXXVI)

and not the cyclised compound (LXXXVI). However using more forceful conditions it should be possible to form (LXXXVI) and its derivatives e.g. (LXXXV).

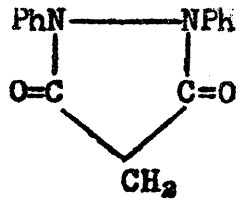
S E C T I O N II

Acyl Derivatives of 3-Imino-5-oxo-1,2-diphenylpyrazolidine.

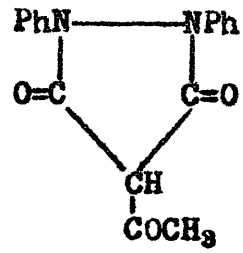
The acylation of 3,5-dioxo-1,2-diphenylpyrazolidine (XIV) using acetic anhydride-pyridine (23) or more prolonged treatment with acetic anhydride alone gives the alkali soluble 4-acetyl-3,5-dioxo-1,2-diphenylpyrazolidine (XXIII). Since (XIV) is also alkali soluble and reacts with diazoethane to give 3-ethoxy-5-oxo-1,2-diphenyl-pyrazoline (LXXXVII;) it would be reasonable to expect the O-acetyl derivative (LXXXVIII)to be also formed; this however is not the case.

3-Imino-5-oxo-1,2-diphenylpyrazolidine (LXV) on acetylation could give three possible monoacetates namely the 4-acetyl derivative (LXXXIX) the N-acetyl derivative (XCI) and the O-acetyl derivative (XC).

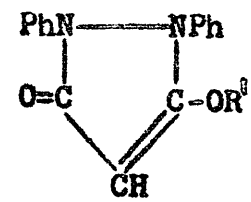
On heating 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) with acetic anhydride a mixture of two isomeric mono-acetates was obtained which was conveniently separated by the solubility of one constituent in alkali. The alkali soluble acetate was called acetate A and the neutral one was called acetate B. The latter was also prepared exclusively by treatment of (LXV) with acetyl chloride in pyridine at 0°. On refluxing a chloroform solution of (LXV) with acetyl chloride alone, acetate A was obtained in low yield together with more than 50% of the starting material.



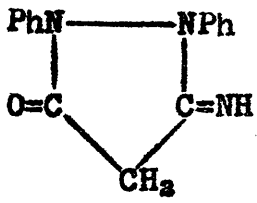
(XIV)



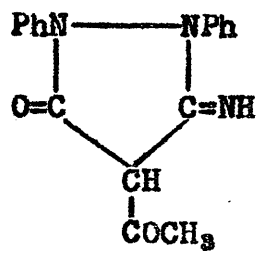
(XXIII)



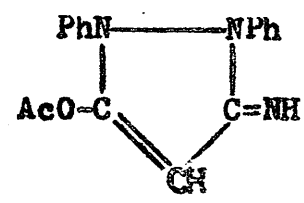
(LXXXVII) R = Et
(LXXXVIII) R = Ac



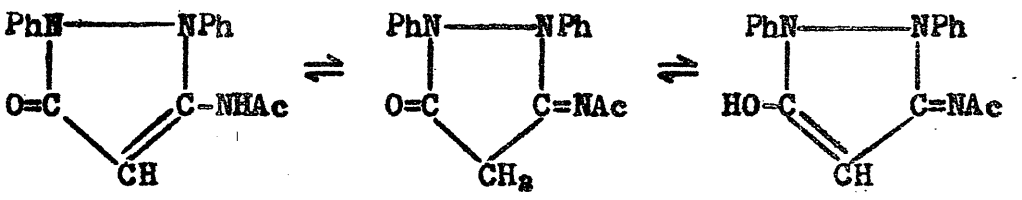
(LXV)



(LXXXIX)



(XC)



a b c

(XCI)

On heating 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) with a minimum amount of acetic anhydride at 100°, until (LXV) had completely dissolved, usually 30-40 min., a compound was obtained along with acetate A and acetate B and which differed from acetates A and B. This

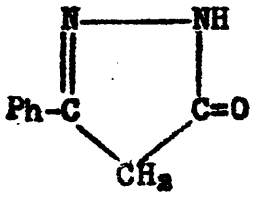
compound, designated acetate C, analysed for a monoacetate and gave a red ferric colour. It is noteworthy that in this reaction, acetate C occurred in 30% yield whereas the yield of acetate A was greatly reduced but that of acetate B was only slightly diminished.

When acetate A was hydrolysed with aqueous ethanolic sodium carbonate solution, (LXV) was obtained in very good yield. Acetate B, however, was unaffected by heating either with aqueous ethanolic solutions of sodium carbonate or sodium hydroxide. Acetate C was also hydrolysed to (LXV) with ethanolic sodium carbonate solution. This difference in stability of the three monoacetates to alkaline hydrolysis made it necessary for a study of the relative resistance to alkaline hydrolysis of the C-, N- and O- acetyl groups.

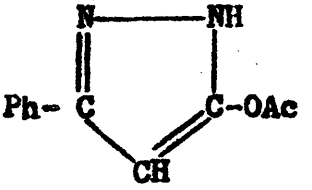
5-Acetoxy-3-phenylpyrazole (XCIII), obtained by Weissberger and Porter (62) from 5-oxo-3-phenylpyrazoline (XCII) using acetic anhydride-pyridine, was insoluble in carbonate and was readily hydrolysed to (XCII). They found that on shaking with a 2% aqueous sodium hydroxide solution, (XCIII) dissolved in about 10 min., to give (XCII) on acidification. This illustrates clearly the susceptability of an O-acetyl group to hydrolysis.

The acetylation of 3-imino-2-phenyl-5-oxopyrazoli-

dine (XCIV) gives the C-acetyl derivative (XCV) (63) and when excess acetic anhydride is used a triacetate (XCVI) is produced. (XCV) is soluble in carbonate which excludes

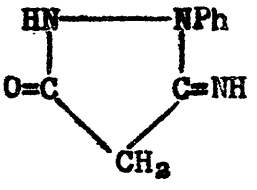


(XCII)

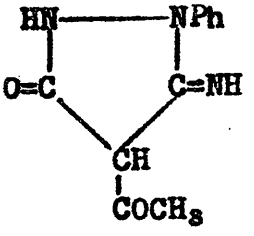


(XCIII)

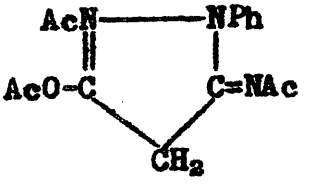
O-acetylation; (XCV) is very stable to alkaline hydrolysis, 70% being obtained after heating in 10% sodium hydroxide solution at 100° for 2 hr. This stability to hydrolysis is characteristic of C-acetyl compounds. (XCVI) on hydrolysis with hot 10% sodium



(XCIV)



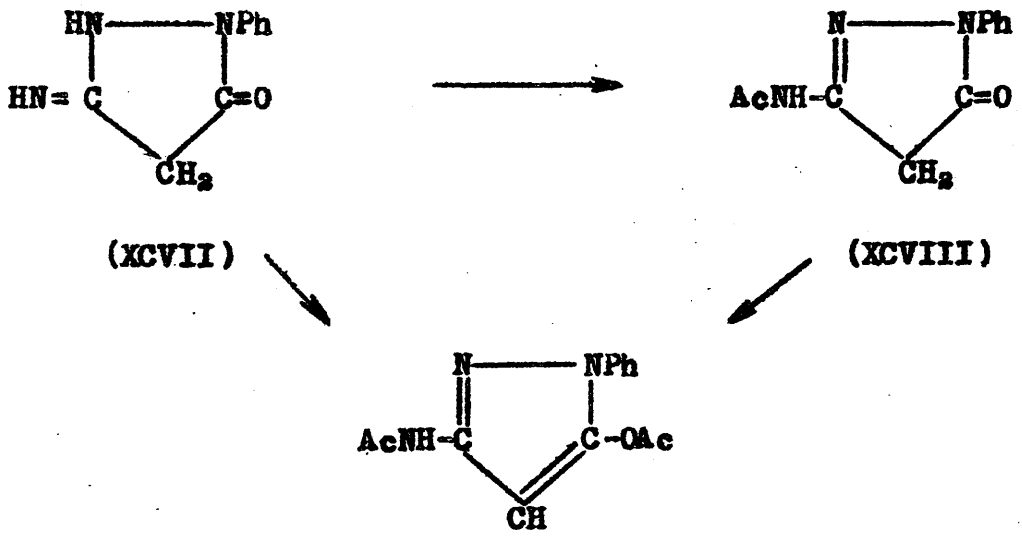
(XCV)



(XCVI)

hydroxide gives (XCIV) i.e. showing the absence of a C-acetyl group. It was also found that 4-acetyl-3,5--dioxo-1,2-diphenylpyrazolidine (XXIII) was stable to alkaline hydrolysis.

Also acetylation of (XCVII) (64), isomeric with (XCIV), using acetyl chloride gives a monoacetate (XCVIII) and when excess acetic anhydride is used a diacetate (XCIX) is obtained. When (XCIX) is treated with 2% sodium hydroxide in the cold, (XCVIII) is obtained, illustrating once more the facile hydrolysis of the O-acetyl group.



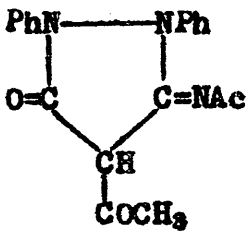
(XCVII) (XCVIII)

(XCIX)

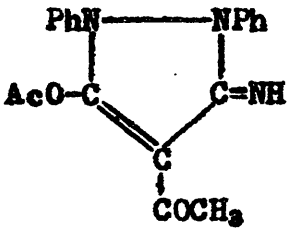
Thus it can be seen that the C,-N- and O- acetyl group can be distinguished by the degree of resistance which each offers to alkaline hydrolysis. The C- acetyl group is the most stable, being unaffected by hot sodium hydroxide solution, whereas N- and O- acetyl groups are

hydrolysed under these conditions. The O- acetyl group is the least stable being hydrolysed by sodium hydroxide in the cold, an N- acetyl group being unattacked under these conditions.

Since the neutral monoacetate B is stable to hydrolysis, it must therefore be 4-acetyl-3-imino-5-oxo--1,2-diphenylpyrazolidine (LXXXIX) and this structure is in keeping with acetate B giving a red ferric chloride colour. The longer wavelength maxima of the ultraviolet of the latter and (XXIII) are similar being respectively 265 and 264 mu in ethanol and 264 mu in aqueous ethanolic alkali. 4-Acetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (LXXXIX) was heated in ethanolic hydrochloric acid for 24 hr. in an attempt to convert it into the alkali soluble 4-acetyl-3,5-dioxo-1,2-diphenylpyrazolidine (XXIII), but without success. In the hope of preparing a diacetyl derivative of (LXV), e.g. (C) or (CI), (LXXXIX) was refluxed with acetyl chloride. However (LXXXIX) was the only compound isolated.

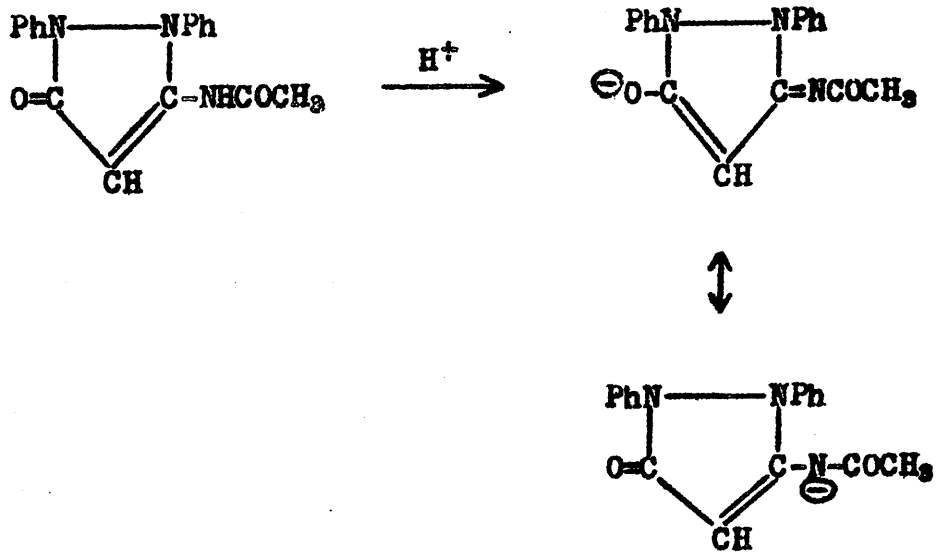


(C)



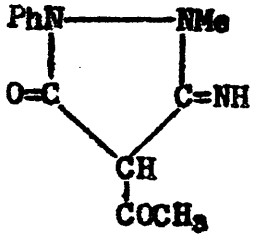
(CI)

The alkali soluble monoacetate of (LXV) was next examined. Its facile hydrolysis, to which reference has already been made, suggested the presence of an N- or O-acetyl group but the red ferric chloride colour favoured structure (XCI). Acetate A is therefore 3-acetylimino--5-oxo-1,2-diphenylpyrazolidine (XCI). The alkali solubility of (XCI) is attributed to the vinylogous imide feature which allows the formation of the ion as indicated:

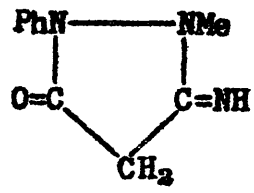


Support for this process comes from the bathochromic shift in the longer wavelength ultraviolet maximum from 260 mu in neutral solution and 280 mu in alkaline solution, indicating an increase in conjugation.

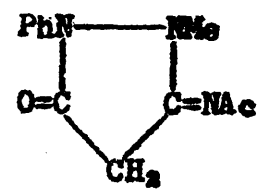
The acylation of 3-imino-2-methyl-5-oxo-1-phenylpyrazolidine (CII) (46), a compound closely related in structure to 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV), may also deserve some comment.



(CIV)



(CII)



(CIII)

The reaction of acetyl chloride on (CII) afforded the alkali soluble N-acetyl derivative (CIII) and when acetic anhydride was used, the neutral 4-acetyl-3-imino--2-methyl-5-oxo-1-phenylpyrazolidine (CIV) was obtained. These results are in agreement with those already discussed for the acetylation of (LXV). Unfortunately no ultraviolet or infrared data were available for (CIII) and (CIV).

Besides the above evidence, it was desirable to substantiate structures (XCI) and (LXXXIX) for acetates A and B respectively. Acetate B is a methyl ketone and as such it should react with a solution of sodium hypoiodite to give iodoform. 4-Acetyl-3,5-dioxo-1,2--diphenylpyrazolidine (XXIII) is also a methyl ketone and

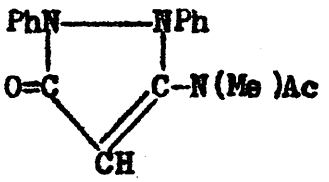
it was decided to use it in a trial reaction. On treating a solution of (XXIII) in dioxan (65) with hypoiodite, only the characteristic odour of iodoform was observed, no solid iodoform being isolated. Similarly a dioxan solution of acetate B yielded no solid iodoform but only the odour of iodoform. On the other hand when a dioxan solution of acetate A and a blank dioxan solution were treated with hypoiodite under the same conditions as for (XXIII), not even the odour of iodoform was detected. These observations are in agreement with the structures assigned to acetates A and B.

The structures of acetate A and acetate B have been established as (XCI) and (LXXXIX) respectively and therefore only structure (XC) i.e. the O-acetyl derivative, was left to accommodate acetate C. Although the facile hydrolysis of acetate C supported this structure, there remained an anomalous piece of evidence against it i.e. acetate C gave a red ferric colour. In an attempt to establish if acetate C was acidic, a solution of the latter in chloroform and ethanol was washed with dilute aqueous sodium hydroxide. The neutral extract yielded 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) in 33% yield and the basic extract, on acidification afforded 3-acetylimino-5-oxo-1,2-diphenylpyrazolidine (XCI) in 60%

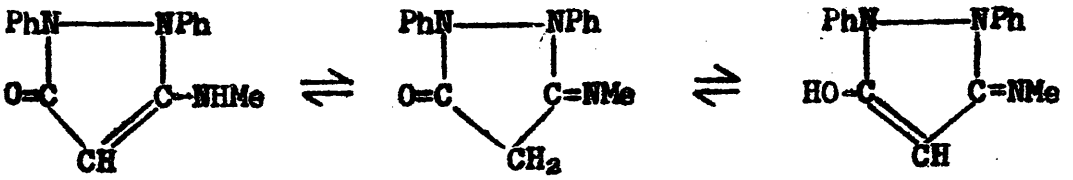
yield. Acetate C was thus in fact a mixture and not a homogeneous compound as was first thought. From the above observations acetate C appeared to be a mixture of either 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) and 3-acetylimino-5-oxo-1,2-diphenylpyrazolidine (XCI) or a mixture of the former and 5-acetoxy-3-imino-1,2-diphenylpyrazoline (XC), the unacetylated pyrazolidine (LXV) being obtained as the hydrolysis product of (XC), since O-acetyl derivatives are hydrolysed by cold alkali. Either of these mixtures would account for the red ferric colour given by acetate C. The composition of the mixture was shown to consist of 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) and 3-acetylimino-5-oxo-1,2-diphenylpyrazolidine (XCI) because on crystallising a mixture of these two compounds acetate C was obtained. That acetate C was a mixture and not an addition compound of the two components followed from the isolation of 4-acetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (LXXXIX) along with 3-acetylimino-5-oxo-1,2-diphenylpyrazolidine (XCI), after treatment of acetate C with acetic anhydride.

4-Acetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (LXXXIX) did not react with diazomethane, whereas prolonged treatment of 3-acetylimino-5-oxo-1,2-diphenylpyrazolidine (XCI) with diazomethane gave an alkali insoluble methyl

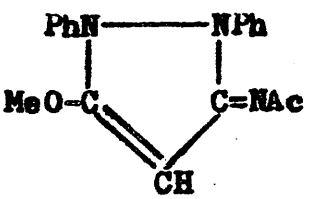
derivative which is formulated as (CV) formed from tautomer (XCIa); hydrolysis of (CV) with sodium carbonate afforded 3-methylimino-5-oxo-1,2-diphenyl-pyrazolidine (CVI), different from 3-imino-4-methyl-5--oxo-1,2-diphenylpyrazolidine (LXX) and giving a red ferric chloride colour indicating that N-methylation had been achieved. If O-methylation of (XCI) had taken place



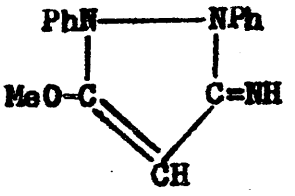
(CV)



(CVI)



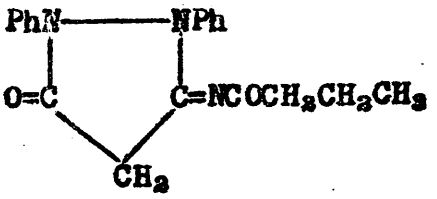
(CVII)



(CVIII)

giving (CVII) then hydrolysis would have afforded 3-imino--5-methoxy-1,2-diphenylpyrazoline (CVIII) which could not give a red ferric chloride colour.

In the reaction between 3-imino-5-oxo-1,2--diphenylpyrazolidine (LXV)and butyric anhydride, only one monoacylated derivative of (LXV) was obtained, which is in contrast to acetic anhydride. This monobutyryl derivative was alkali soluble and by analogy with (XCI) it must therefore be 3-butyrylimino-5-oxo-1,2-diphenyl-pyrazolidine (CIX). The ultraviolet absorption spectrum of (CIX) confirmed N-acylation since it showed a batho-chromic shift in the longer wavelength maximum from 261 mu

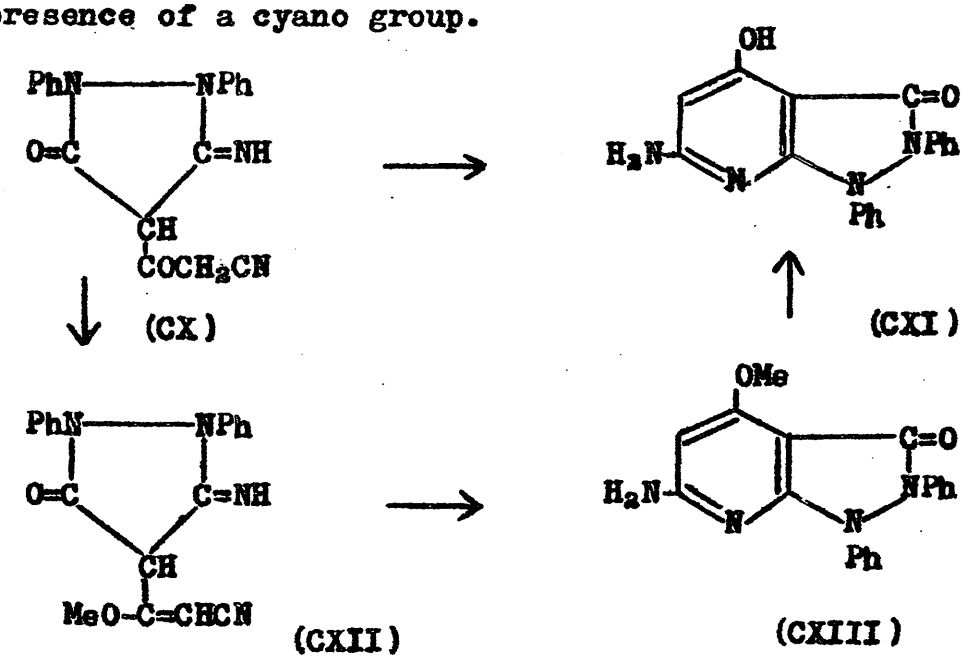


(CIX)

in neutral to 288 mu in alkaline solution, which is in agreement with the bathochromic shift observed for (XCI) to which reference has already been made.

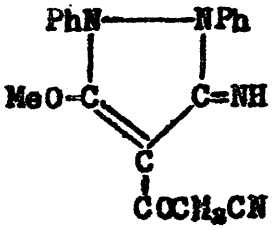
From the condensation of cyanoacetyl chloride and hydrazobenzene in the presence of pyridine, an alkali soluble compound was obtained (Section I), which could also be prepared by treatment of 3-imino-5-oxo-1,2--diphenylpyrazolidine (LXV) with cyanoacetyl chloride in

the presence of pyridine. When this condensation product was heated in an acidic medium followed by basification, 4-acetyl-3-imino-5-oxo-1,2-diphenyl-pyrazolidine (LXXXIX) was obtained. From its mode of formation and its hydrolysis product the compound must therefore be 4-cyanoacetyl-3-imino-5-oxo-1,2-diphenyl-pyrazolidine (CX). The infrared spectrum confirms the presence of a cyano group.



4-Cyanoacetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (CX) on heating with either sodium hydroxide or better with sodium carbonate, was isomerised to an alkali soluble compound which gave a deep red ferric colour and showed hydrogen bonded hydroxyl absorption but no cyano-band in the infrared. It is believed that cyclisation has

taken place with the formation of 6-amino-4-hydroxy-3-oxo--1,2-diphenylpyrazolido-[2 , 3 b]-pyridine (CXI). Methylation of the latter compound with diazomethane yielded a methyl ether which must be 6-amino-4-methoxy-3--oxo-1,2-diphenylpyrazolido-[2 , 3 b]-pyridine (CXIII) since it was also formed by successive reaction of (CX) with diazomethane to give 3-imino-4-(α-methoxy-β-cyano-vinyl)-5-oxo-1,2-diphenylpyrazolidine (CXII), followed by heating to 200°. This series of reactions rules out the possibility of the methylated product being 4-cyanoacetyl--3-imino-5-methoxy-1,2-diphenylpyrazoline (CXIV) instead of (CXII), since the former would not give (CXIII) on cyclisation. Structure (CXII) is also substantiated by



(CXIV)

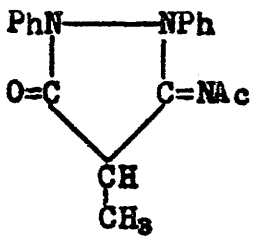
infrared evidence. Kitson and Griffith (66) have found that in saturated nitriles the C≡N frequency lies between 2260 cm.$^{-1}$ and 2240 cm.$^{-1}$. Nitriles, in which the C≡N was conjugated with a double bond, have a strong band between 2232 cm.$^{-1}$ and 2218 cm.$^{-1}$. These results have

been supplemented by further work by Felton and Orr (67) and by Skinner and Thompson (68). Kitson and Griffith (66) have also studied the intensity of the nitrile absorption band. They found a marked variation in intensity in various types of nitriles so that the band varies from strong to undetectable. Conjugation appears to increase the intensity; 2250 cm.$^{-1}$ band of benzonitrile has been reported as being about twice the intensity of either of two non-conjugated materials (69). On the other hand the introduction of a neighbouring oxygenated group into the molecule results in a reduction of the C≡N absorption intensity to a remarkable extent (68). The infrared spectrum of (CX) shows a low intensity band at 2273 cm.$^{-1}$ which is in agreement with it being a saturated nitrile and also the carboxyl group α to the C≡N accounts for the low intensity of the band. In structure (CXII) the nitrile is conjugated with a double bond and therefore the C≡N absorption should appear at a lower frequency and have a greater intensity. This is in complete agreement with the observed results, (CXII) showing a band at 2217 cm.$^{-1}$ and having twice the intensity of the C≡N band in (CX).

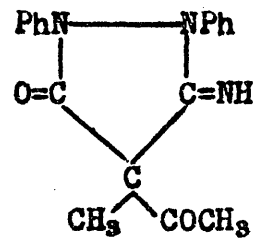
Acyl Derivatives of 4-substituted 3-Imino-5-oxo--1,2-diphenylpyrazolidines.

The acylation of 3-imino-4-methyl-5-oxo-1,2-

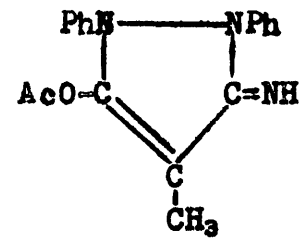
-diphenylpyrazolidine (LXX) has been investigated and differs from its lower homologue. There is the possibility once more of forming three monoacetates with structures (CXV), (CXVI) and (CXVII). Reaction of (LXX) with acetyl chloride at 0° in the presence of pyridine afforded an



(CXV)



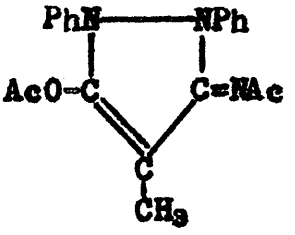
(CXVI)



(CXVII)

alkali siluble monoacetate, which gave a red ferric chloride colour. With these properties the monoacetate can only be 3-acetylimino-4-methyl-5-oxo-1,2-diphenyl-pyrazolidine (CXV) since both (CXVI) and (CXVII) would not give a red ferric colour. Also (CXV) showed similar ultraviolet properties to (XCI). It is noteworthy that no C-acetylation, i.e. the formation of (CXVI), was observed although C-acetylation occurred readily under these conditions when the 4-position is unsubstituted. The monoacetate (CXV) was also obtained in over 70% yield by the reaction of (LXX) with acetic anhydride. Treatment of the latter compound with acetic anhydride gave a neutral diacetate, which was also formed by more drastic

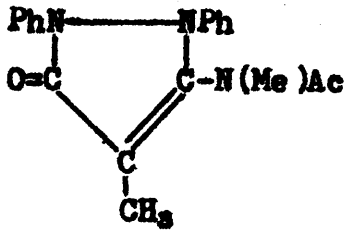
reaction of (LXX) with acetyl chloride and pyridine (58) and along with (CXV) by the action of acetic anhydride on (LXX). Since the diacetate was hydrolysed by sodium carbonate to the monoacetate (CXV), the second acetyl group must be attached to the oxygen and the diacetate therefore has structure (CXVIII). Hydrolysis of the



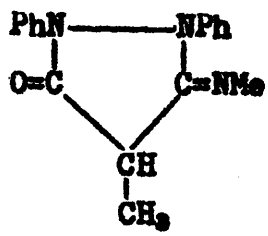
(CXVIII)

monoacetate (CXV) with sodium carbonate gave the parent pyrazolidine (LXX) in over 50% yield, some unchanged starting material being recovered. When sodium hydroxide was used (CXV) and (CXVIII) were both completely hydrolysed to (LXX). It may also dererve some comment that in the 4-methyl series, hydrolysis of an N-acetyl group requires more drastic conditions than in the series where the 4-position is unsubstituted.

Methylation of 3-acetylimino-4-methyl-5-oxo-1,2--diphenylpyrazolidine (CXV) by prolonged treatment with diazomethane afforded 3-acetylmethylamino-4-methyl-5-oxo--1,2-diphenylpyrazoline (CXIX) which was insoluble in alkali and gave no colour with ferric chloride. The



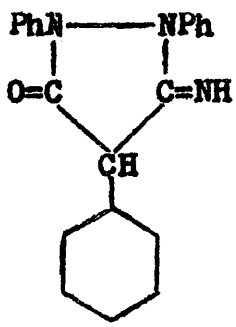
(CXIX)



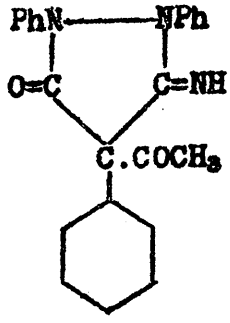
(CXX)

hydrolysis of (CXIX) to 4-methyl-3-methylimino-5-oxo-1,2-diphenylpyrazolidine (CXX) was effected by sodium hydroxide (58).

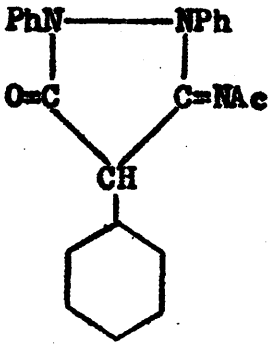
Because of the differences observed in the acylation of 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) and its 4-methyl derivative (LXX) it was decided to investigate the acylation of another 4-substituted derivative of (LXV) namely 4-cyclohexyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (LXXV). On heating the latter with acetic anhydride a neutral monoacetate was obtained which did not give a red ferric chloride colour. Attempts to hydrolyse the monoacetate using 15% sodium hydroxide proved unsuccessful, which ruled out the possibility of an O-acetyl group.



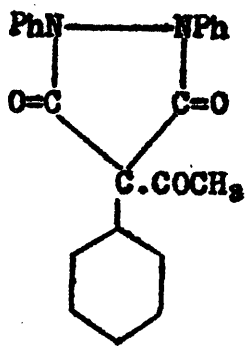
(LXXV)



(CXXI)



(CXXII)



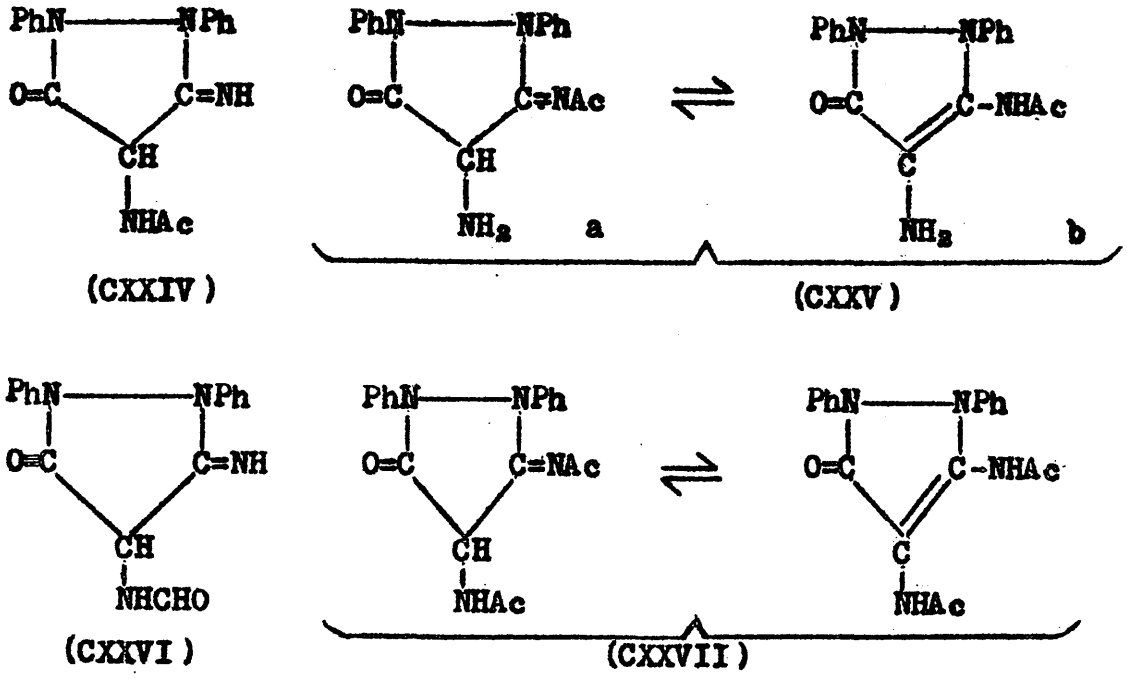
(CXXIII)

This leaves (CXXI) and (CXXII) as possible structures. As was mentioned previously the acylation of 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (LXX) using acetyl chloride-pyridine or acetic anhydride failed to produce a 4-acyl derivative of (LXX) and with the presence of a cyclohexyl ring in the 4-position, the formation of (CXXI) would appear even more unlikely to occur and therefore structure (CXXII) was assigned to the monoacetate of (LXXV). Support for this structure also comes from a similarity in the ultraviolet absorption spectra of (CXXII) and (CXV) [see Table I]. A substituent in the 4-position of 3,5-dioxo-1,2-diphenylpyrazolidine (XIV) also appears to block acylation of that position because 4-cyclohexyl--3,5-dioxo-1,2-diphenylpyrazolidine was unaffected by treatment with acetic anhydride-pyridine. The presence of a substituent in the 4-position also increases the resistance of an N-acetyl group to alkaline hydrolysis e.g.

the difference in stability to hydrolysis between 3-acetylimino-5-oxo-1,2-diphenylpyrazolidine (XCI) and its 4-methyl homologue (XV), which has already been discussed, and so (CXXII) should show a similar increase in resistance to hydrolysis; this is in agreement with the observed results since (CXXII) is unaffected by alkaline hydrolysis.

The rate of hydrolysis of an N-acetyl group in the imino-oxopyrazolidines must be dependent on (a) the presence of a substituent in the 4-position and (b) the size of the substituent. This means that with a substituent in the 4-position the 3-acetylimino group must be sterically hindered and the rate of hydrolysis will thus decrease as the size of the substituent in the 4-position increases

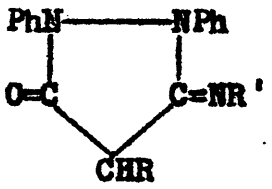
From the attempts to cyclise 3,4-diamino-5-oxo-1,2-diphenylpyrazoline (LXXXI) to give the iminazolo-[3,4d]--pyrazoline ring system [see Section I page 32], a neutral monoacetate and a neutral monoformate of the former were isolated. The monoacetyl derivative was also prepared by treatment of the diamine (LXXXI) with acetyl chloride at room temperature. On refluxing the monoacetate with acetyl chloride a neutral diacetyl derivative of (LXXXI) was obtained which must be 3,4-diacetylamino-5-oxo-1,2--diphenylpyrazoline (CXXVII).



The monoacetyl derivative of (LXXXI) can have either structure (CXXIV) or (CXXV). However from a consideration of the ultraviolet absorption spectra of 4-substituted imino-oxopyrazolidines and their monoacetyl derivatives (Table I), structure (CXXIV) is preferred to (CXXV). The products of acylation of (CXXIV) and other 4-substituted pyrazolidines e.g. (LXX) and (LXXV) show similar longer wavelength absorption maxima both in neutral and alkaline solution. By analogy the monoformyl derivative of the diamine (LXXXI) must be 4-formylamino--3-imino-5-oxo-1,2-diphenylpyrazolidine (CXXVI).

TABLE I.

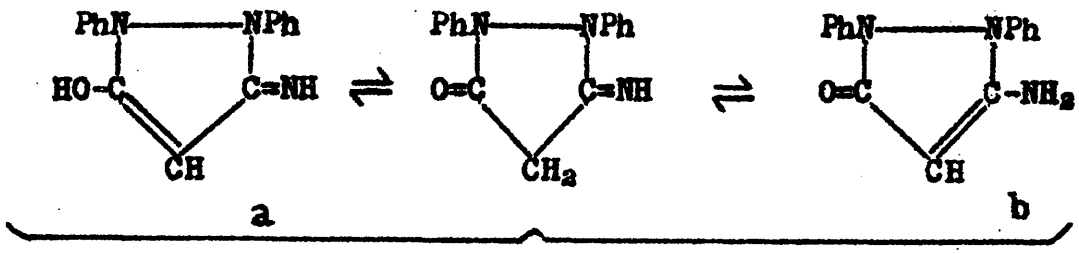
Ultraviolet absorption of 4-substituted imino-oxopyrazolidines.



Formula	R	R'	λ_{max}^{EtOH} mμ	$\lambda_{max.}^{NaOH}$ mμ
(LXX)	Me	H	206, 264	264
(CXV)	Me	Ac	205, 242, 276	272
(LXXV)	C_6H_{11}	H	204, 262	223, 263
(CXXII)	C_6H_{11}	Ac	206, 251, 278	277
(LXXXI)	NH_2	H	206, 252	-
(CXXIV)	NHAc	H	206, 257	256
(CXXVII)	NHAc	Ac	207, 232, 276	231, 278
(CXXVI)	NHCHO	H	206, 259	256

Infrared Absorption of Imino-oxopyrazolidines.

An examination of the infrared absorption spectra of 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) and its 4-substituted derivatives, was undertaken to determine whether (LXV) existed as the imino compound (LXVa) or as the amino compound (LXVb).



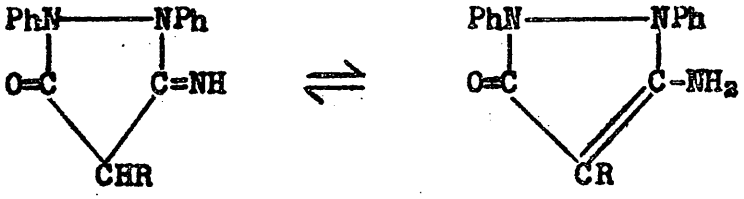
(LXV)

Primary amines in dilute solution in a non polar solvent give two absorption bands in the region 3500-3300 cm.$^{-1}$. The first of these, which is due to the asymmetric stretching mode, is usually found near 3500 cm.$^{-1}$, and the second, which arises from the corresponding symmetrical mode, near 3400 cm.$^{-1}$ (70). Both of these are subject to substantial changes in concentrated solutions in which intermolecular association can occur. On the other hand, secondary amines and imines show only a single NH stretching absorption in dilute solutions. Colthup (71) quotes an overall range of 3400-3300 cm.$^{-1}$ for imines (-C:NH), but little or no information is available in the literature generally.

Intermolecular and/or intramolecular hydrogen bonding effects are shown by most amines under suitable conditions. The effect of this is to lower the frequency usually by less than 100 cm.$^{-1}$ Sutherland (72) has indicated that, in general association with ketonic groups gives absorption in the range 3320-3240 cm.$^{-1}$ and with other nitrogen atoms within the range 3300-3150 cm.$^{-1}$.

3-Imino-5-oxo-1,2-diphenylpyrazolidine (LXV) shows two sharp absorption bands in the range 3300-3100 cm.$^{-1}$, one at 3300cm.$^{-1}$ and the other at 3115 cm.$^{-1}$ (Table II), when the determination is carried out in a Nujol mull. This can only mean that (LXV) is in the amine form i.e. (LXVb) which is in agreement with the conclusion already expressed on page 25. Intermolecular hydrogen bonding effects would almost certainly occur in Nujol mull and would account for the shift from 3500 cm.$^{-1}$ and 3400 cm.$^{-1}$ (free NH) to 3300 cm.$^{-1}$ and 3115 cm.$^{-1}$ (bonded NH). However the infrared spectrum of (LXV) in chloroform shows the two

T A B L E II



Formula	R	ν Nujol max. cm.$^{-1}$	ν $CHCl_3$ max. cm.$^{-1}$
(LXV)	H	3300(s) 3115(s)	3448(w) 3356(m)
(LXX)	Me	3279(s) 3100(s)	3420(w) 3333(m)
(LXXV)	C_6H_{11}	3356(w) 3257(w) 3100(w)	3448(m) 3333(m)
(LXXXI)	NH_2	3236(s) 3086(s)	3390(w) 3333(m)

bands with much lower intensities, at 3448 $cm.^{-1}$ and 3356 $cm.^{-1}$ indicating a breaking of the hydrogen bonds. It could also be argued that the two absorption bands at 3300 $cm.^{-1}$ and 3115 $cm.^{-1}$ arise from the NH stretching absorption of the imino group and the absorption of the hydroxy group in (LXVb). However this seems unlikely because 3,5-dioxo-1,2-diphenylpyrazolidine (XIVb), which is alkali soluble and will react with diazomethane, shows no absorption in the region 3500 $cm.^{-1}$ - 3100 $cm.^{-1}$.

The NH deformation absorption, which is a strong to medium band in primary amines and is extremely weak in secondary aliphatic amines, occurs in the range 1650-1590 $cm.^{-1}$. With 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) the position is confused to some extent by the presence of the aromatic ring vibration near 1600 $cm.^{-1}$ and no assignment of bands due to the NH deformation mode could thus be made with any degree of certainty.

The structures of the acyl derivatives of 3-imino--5-oxo-1,2-diphenylpyrazolidines were determined chiefly by chemical methods. The infrared spectra of these compounds further substantiate these structures and show that in the equilibrium between the secondary and tertiary amide structure, the equilibrium lies well over to the right i.e.

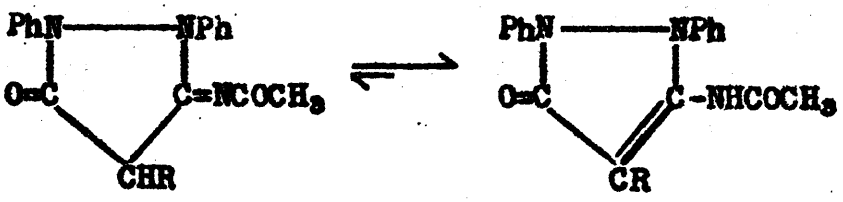


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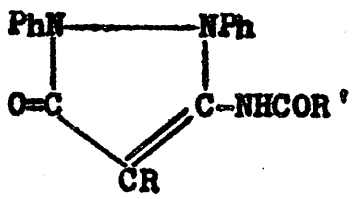
TABLE III



Formula	R	R'	NH stretching ($cm.^{-1}$) ν_{max}^{nujol}	$\nu_{max.}^{CHCl_3}$	Amide II Band ($cm.^{-1}$) $\nu_{max.}^{nujol}$
(XCI)	H	Me	3100(w)	3333(w)	1538
(CIX)	H	Et	3215(w)	3333(w)	1534
			3289(w)	3333(w)	
(CXV)	Me	Me	3077(w)	3226(w)	1526
(CXXII)	C_6H_{11}	Me	3115(m)	3145(w)	1524

Simple secondary amides in dilute solution show a single characteristic band, due to NH stretching, in the 3460-3420 $cm.^{-1}$ range (73-76). With open-chain secondary amides the NH absorption occurs near 3270 $cm.^{-1}$ in the solid state (73,75-77) i.e. bonded NH absorption.

Secondary amides also exhibit a strong band (Amide II band) at lower frequencies the origin of which is the subject of much controversy. It has been variously assigned as an NH deformation mode, a C-N stretching and as a mixed vibration involving both types of motion (70). The frequency range found for this band is 1570-1515 cm.$^{-1}$, for materials examined in the solid state (78). Tertiary amides on the other hand cannot exhibit either the NH stretching or the amide II bands.

The amides (XCI), (CIX), (CXV) and (CXXII) all exhibit the NH stretching band and the amide II band (Table III), indicating that the secondary amide structure predominates in the equilibrium as mentioned above.

In addition to the NH absorption, all amides (R.CO.NH-) can be expected to show a carbonyl absorption which will be affected to a small extent by the nature of the R group adjacent to the carbonyl. This absorption is termed the amide I band and is common to all types of amide, including cyclic forms. The CO frequency for neutral amides is found to be within the range 1680-1630 cm.$^{-1}$. However no precise correlations of the amide I band have been developed yet. In the case of the amides under discussion, the matter is further complicated by the presence of the ring carbonyl, and no assignment of the amide I band arising from the CO of the acetyl group and from the ring carbonyl could be made.

EXPERIMENTAL

All m.ps. are uncorrected. Infrared spectra were determined in nujol unless otherwise stated. Identities were confirmed by infrared comparison in nujol. Ultraviolet spectra in alkali were determined in a mixture of equal parts 2N NaOH and ethanol and in acid, equal parts of 2N hydrochloric acid and ethanol.

Cyanoacetyl Chloride (52,79). - A solution of cyanoacetic acid (53 g.) in dry ether (350 c.c.) was cooled in a freezing mixture and phosphorus trichloride (95 g.) was added with stirring. Liquid chlorine (35 c.c.) was now added portionwise with stirring and the solution stirred for a further 30 min. Removal of the excess phosphorus trichloride and ether under reduced pressure gave a liquid which was redistilled to give cyanoacetyl chloride (30 g.) as a colourless liquid b.p. 48°/0.2 mm.; Schroeter and Zink (79) gave b.p. 59°/0.2 m.m., 61°/0.1 mm. and 68°/0.2 mm.; Weissberger and Porter (52) gave b.p. 58-59°/0.5 mm. Cyanoacetyl chloride on treatment with concentrated ammonia gave cyanoacetamide m.p. 120-121° (lit. 119-120°).

N-Cyanoacetylhydrazobenzene. - To a well stirred solution of hydrazobenzene (13.8 g.) in chloroform (300 c.c.) and pyridine (100 c.c.), cooled to -10°, a

solution of freshly prepared cyanoacetyl chloride (21.5 g.; 3 moles) in chloroform (75 c.c.) was added over a period of 1 hr. The reaction mixture was allowed to attain room temperature during 3 hr., then kept overnight and poured into water (500 c.c.). The chloroform phase was washed with water (100 c.c.), hydrochloric acid (3 x 150 c.c.; 2N), aqueous sodium hydroxide (3 x 150 c.c.; 2N), (Extract A) and finally water and dried (Na_2SO_4). Evaporation of the chloroform and crystallisation of the residue from ethanol gave N-cyanoacetylhydrazobenzene (5.4 g.; 29%) as plates, m.p. 172-173° (lit. (55) m.p. 172-173°).

Found: C,71.5; H,5.1%

$C_{15}H_{13}ON_3$ requires: C,71.7; H,5.2%

λ_{max}^{EtOH} 208(ε = 16,000) and 237 mμ (ε = 18,000); $\lambda_{max.}^{NaOH}$ 254 mμ (ε = 23,900); $\lambda_{max.}^{HCl}$ 205 (ε = 36,000) and 236 mμ (ε = 24,000); ν max. 3306 (NH), 2245 (CN) and 1667 $cm.^{-1}$ (CO).

3-Imino-5-oxo-1,2-diphenylpyrazolidine. -

(a) Concentration of the ethanolic mother liquors of the crystallisation of cyanoacetylhydrazobenzene in the previous experiment yielded 3-imino-5-oxo-1,2-diphenylpyrazolidine (1.6 g.; 9%) as plates, m.p. 222-223°; it was sublimed at 0.1 mm. for analysis.

Found: C,71.45; H,5.2%

$C_{15}H_{13}ON_3$ requires: C,71.7; H,5.2%

λ_{max}^{EtOH} 206 (ε = 17,000) and 254 mμ (ε = 23,000); $\lambda_{max.}^{NaOH}$ 225 (ε = 61,000) and 255 mμ (ε = 22,000); $\lambda_{max.}^{HCl}$ 206 (ε = 19,000) and 252 mμ (ε = 22,000) $\nu_{max.}$ 3333, 3175 (NH), 1675 cm.$^{-1}$ (CO). An ethanolic solution of the compound gave a red colour with aqueous ferric chloride.

(b) A solution of N- cyanoacetylhydrazobenzene (500 mg.) in ethanol (18 c.c.) and aqueous sodium carbonate (18 c.c.; 2M) was refluxed for 4 hours. The cooled solution was diluted with water (50 c.c.) and extracted with chloroform (3 x 50 c.c.), the combined extracts washed with water and dried (Na_2SO_4). Evaporation of the chloroform and crystallisation of the residue from ethanol gave 3-imino--5-oxo-1,2-diphenylpyrazolidine (400 mg.; 80%) m.p. and mixed m.p. with preparation (a) m.p. 220-222° (Found: C,71.7; H,5.3%). The infrared spectrum was identical with that of preparation (a).

(c) N-Cyanoacetylhydrazobenzene (225 mg.) was dissolved in ethanolic sodium ethoxide from sodium (20 mg.) and ethanol (15 c.c.) and the solution refluxed for 3 hr., cooled, and diluted with water and the product isolated using chloroform. Crystallisation from methylene chloride n-hexane gave 3-imino-5-oxo-1,2-diphenylpyrazolidine (75 mg.) as prisms, m.p. 220-222° alone or mixed with preparation (a) (Found: C,71.7; H,5.2%). The infrared spectra of the specimens were identical. A similar yield

of the product was obtained using methanolic sodium methoxide.

(d) A solution of sodium ethoxide in ethanol from sodium (4.5 g.) and dry ethanol (90 c.c.) was treated successively with ethyl cyanoacetate (10.6 g.) and hydrazobenzene (18 g.) and the mixture refluxed for 17 hr. in a nitrogen atmosphere (bath temperature, 115-125°; internal temperature 86-88°). Then ethanol (60 c.c.) was distilled off at atmospheric pressure, the internal temperature rising to 126°. The reaction mixture was cooled, treated with ether (250 c.c.) and water (250 c.c.) with stirring and shaking and the insoluble material (1.0 g.) separated giving an aqueous phase (B) and ethereal phase (C). The pale yellow solid, which had the properties of a sodium salt, was treated with hydrochloric acid (d, 1.15) and the aqueous suspension extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4) and evaporated. The residue crystallised from ethanol to give 3-imino-5-oxo--1,2-diphenylpyrazolidine (550 mg.) as plates, m.p. 220-222° alone or mixed with an authentic specimen. Phase C was dried (Na_2SO_4) and evaporated and the reddish solid crystallised from chloroform-methanol to give hydrazobenzene (9.37 g.) as plates, m.p. 126-128° after washing with light petroleum (b.p. 60-80°) to remove the

orange colour. Evaporation of the light petroleum washings yielded azobenzene (2.5 g.) m.p. 67°. The aqueous alkaline phase B on keeping, deposited solid (1.0 g.) m.p. 222°. Evaporation of the mother liquor to one third bulk under reduced pressure, and keeping gave a further crop (0.3 g.) m.p. 220° and from the mother liquor through chloroform extraction a further 0.3 g. m.p. 210-220° was isolated. Combination of these crops and crystallisation from ethanol yielded 3-imino--5-oxo-1,2-diphenylpyrazolidine m.p. 220-222° alone or mixed with an authentic specimen. An infrared comparison between both samples prepared by this method and authentic material confirmed their identity. Acidification of the aqueous alkaline liquor with 2N hydrochloric acid precipitated a brown solid (2.2 g.) m.p. 300° which could not be crystallised and which was not further examined.

(c) A solution of chloroacetylhydrazobenzene (1.5 g.) in ethanol (25 c.c.) was refluxed with a solution of potassium cyanide (2.5 g.) in water (15 c.c.) for 7 hr. The solution was diluted with water (50 c.c.) and extracted with chloroform (3 x 50 c.c.). The combined chloroform extracts were washed with water (2 x 25 c.c.), dried (Na_2SO_4) and evaporated. Crystallisation from chloroform-ethanol gave 3-imino-5-oxo-1,2-diphenylpyrazolidine (0.8 g.; 57%), m.p. 221-222° alone or mixed with an authentic

specimen; an infrared comparison confirmed the identity of the preparations.

N-Cyanoacetyl-pp'-dimethylhydrazobenzene. - To a well stirred solution of pp'-dimethylhydrazobenzene (9.2 g.) in chloroform (150 c.c.) and pyridine (50 c.c.), cooled in an ice bath, a solution of cyanoacetyl chloride (15.6 g.) in chloroform (40 c.c.) was added dropwise over 1 hr. The cooling bath was then removed and the stirring continued for a further 2 hr. The reaction solution was then treated with water and the chloroform layer washed successively with 3N hydrochloric acid, water, 3N sodium hydroxide, water and dried (Na_2SO_4). The chloroform solution was evaporated under reduced pressure and the residue crystallised from chloroform-methanol giving pp'-dimethylhydrazobenzene (1.0 g.), m.p. and mixed m.p. 132-134° as the fraction of lesser solubility. Concentration of the mother liquor gave a crystalline solid which was digested with cold benzene and the residue separated. Recrystallisation from acetone-methanol gave N-cyanoacetyl-pp'-dimethylhydrazobenzene (2.8 g.) as needles, m.p. 144-145°.

Found: C, 73.4; H, 6.0%

$C_{17}H_{17}ON_3$ requires: C, 73.1; H, 6.1%.

$\lambda^{EtOH}_{max.}$ 209 (ε = 20,000) and 238 mu (ε = 21,000); $\lambda^{NaOH}_{max.}$ 225 (ε = 66,000) and 254 mu (ε = 30,000); $\lambda^{HCl}_{max.}$ 207

(ε = 23,000) and 238 mu (ε = 20,000); $\nu_{max.}$ 3333 (NH), 2273 (CN) and 1692 cm.$^{-1}$ (CO).

3-Imino-5-oxo-1,2-di-p-tolylpyrazolidine. - (a) Using the same conditions as described for the cyclisation of N-cyanoacetylhydrazobenzene using sodium carbonate, N-cyanoacetyl-pp'-dimethylhydrazobenzene (1.0 g.) gave 3-imino-5-oxo-1,2-di-p-tolylpyrazolidine (800 mg.) which separated from acetone-n-hexane as stout needles, m.p. 212-213°.

Found: C,72.9; H,5.9%

$C_{17}H_{17}ON_3$ requires: C,73.1; H,6.1%

$\lambda^{EtOH}_{max.}$ 207 (ε = 25,000) and 254 mu (ε = 29,500); $\lambda^{NaOH}_{max.}$ 254 mu (ε = 52,000); $\lambda^{HCl}_{max.}$ 209 (ε = 28,000) and 250 mu (ε= 30,000); $\nu_{max.}$ 3390, 3185 (NH), 1675 (CO) and 1647 cm.$^{-1}$ An ethanolic solution of the compound gave a red colour with aqueous ferric chloride.

(b) Ethyl cyanoacetate (10,6 g.) and pp'-dimethylhydrazobenzene (21 g.) in ethanolic sodium ethoxide from sodium (4.8 g.) and dry ethanol (150 c.c.) were refluxed for 17 hr. in an atmosphere of nitrogen. The reaction was worked up as described for the similar preparation of 3-imino-5-oxo--1,2-diphenylpyrazolidine into an ethereal phase, an interfacial solid and an aqueous alkaline phase. The dried (Na_2SO_4) ethereal phase was evaporated giving a bright orange solid residue which was triturated with several

portions of light petroleum (b.p. 40-60°) and the residue crystallised from chloroform-light petroleum (b.p.40-60°) to give pp'-dimethylhydrazobenzene (10.6 g.) as plates, m.p. and mixed m.p. 128°. The combined light petroleum washings on concentration yielded pp'-dimethylazobenzene (6.1 g.) as orange blades m.p. and mixed m.p. 142°.

The interfacial solid was combined with further solid which separated from the aqueous alkaline phase on standing and crystallised from chloroform-light petroleum (b.p. 40-60°) to give 3-imino-5-oxo-1,2-di-p-tolylpyrazolidine (1.2 g.) as stout needles, m.p. 213° undepressed on mixing with preparation (a) which had an identical infrared spectrum.

The aqueous phase was continuously extracted with chloroform for 5 hr. Removal of the chloroform gave uncrystallisable material. The aqueous alkaline solution on acidification with hydrochloric acid (d,1.15) gave a brown solid (1.8 g.), m.p. ca. 320° which could not be crystallised.

α-Chloropropionylhydrazobenzene. - A solution of α-chloropropionylchloride (40 g.) in chloroform (30 c.c.) was added dropwise to an ice cooled solution of hydrazobenzene (25 g.) in chloroform (300 c.c.) and pyridine (100 c.c.) with stirring over 1 hr. The ice bath was then removed and stirring continued for a further 2 hr.

The reaction solution was washed with hydrochloric acid (500 c.c.; 2N), water (300 c.c.) and dried (Na_2SO_4). Concentration and cooling and crystallisation of the solid which separated, from ethanol gave α-chloropropionylhydrazobenzene (40 g.) as prisms, m.p. 149°

Found: C,65.22; H,5.9%

$C_{15}H_{15}ON_2Cl$ requires: C,65.5; H,5.5%

λ_{max}^{EtOH} 206 (ε = 28,000) and 238 mμ (ε = 20,000); $\nu_{max.}$ 3250 (NH) and 1642 $cm.^{-1}$ (CO).

3-Imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine. - (a) A solution of α-chloropropionylhydrazobenzene (2.5 g.) and potassium cyanide (3.0 g.) in ethanol (25 c.c.) and water (8 c.c.) was refluxed for 5 hr. The cooled solution was diluted with water and the product isolated using chloroform. 3-Imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) separated from chloroform as plates, m.p. 180°.

Found: C,72.1; H,5.45%

$C_{15}H_{15}ON_3$ requires: C,72.4; H,5.7%

$\lambda_{max.}^{EtOH}$ 206 (ε = 22,000) and 264 mμ (ε = 25,000); $\lambda_{max.}^{NaOH}$ 263 mμ (ε = 19,500); $\nu_{max.}$ 3874 (NH), 3278 (OH) and 1640 $cm.^{-1}$ (CO).

The compound gave a red colour in ethanol with aqueous ferric chloride.

Attempted Condensation of Ethyl Cyanoacetate and Hydrazobenzene using an Acidic Condensing Agent. - A solution of hydrazobenzene (9.2 g.) in ether (500 c.c.) was cooled to 0°C, ethyl cyanoacetate (5.7 g.) was added and the solution stirred. Hydrochloric acid gas was bubbled through the solution for 2 hr. A white solid separated out after 15 min. The freezing mixture was removed and the stirring continued for a further 3 hr. and the solution left overnight at room temperature. The white precipitate was filtered off, washed with ether and dried under vacuum. The solid (5 g.) was dissolved in water (200 c.c.) and basified with 2N sodium hydroxide when a white flocculent precipitate was obtained. The solution was extracted with ether, washed with water and dried (Na_2SO_4). Evaporation of the ether and crystallisation of the residue from methylene chloride-*n*-hexane gave benzidine as needles, m.p. and mixed m.p. 126-128° (*lit.* 128°). The ethereal filtrate was washed with water, sodium hydroxide (3 x 50 c.c.; 2N), water and dried (Na_2SO_4). Evaporation of the ether gave a red residue which on crystallisation from aqueous ethanol gave azobenzene, m.p. 67-68° (lit. 66°). The alkaline washings were acidified with concentrated hydrochloric acid (*d*,1.15), extracted with ether. The ethereal extract was washed with water and the dried (Na_2SO_4) solution evaporated to dryness giving only a trace of material which was not

investigated.

Attempted Condensation of Ethyl Cyanoacetate and Hydrazobenzene with Basic Condensing Agents.

(a) Hydrazobenzene (2 g.) was dissolved in pyridine (15 c.c.), ethyl cyanoacetate (1.4 g.) was added and the solution left standing for 2 days at room temperature in an atmosphere of nitrogen. The solution was poured into water, extracted with ether, and the ether extract washed successively with hydrochloric acid (3 x 50 c.c.; 4N), when a white crystalline solid separated out and was separated off, sodium hydroxide (3 x 50 c.c.; 3N), water and dried (Na_2SO_4). Evaporation of the ether and crystallisation of the residue from aqueous ethanol gave azobenzene, m.p. 66-68°. The crystalline solid (m.p. 300°) was dissolved in water (100 c.c.) and basified with dilute sodium hydroxide. Ether extraction in the usual way gave benzidine, m.p. and mixed m.p. 126-127°. The alkaline washings were acidified with dilute hydrochloric acid, extracted with ether and evaporation of the dried (Na_2SO_4) ether extract gave a residue which on crystallisation from methylene chloride-n-hexane gave a brown crystalline material, m.p. 141-145°. Lack of material prevented further investigation of the compound.

(b) To a solution of ethanol (120 c.c.) and sodium (460 mg.) was added hydrazobenzene (3.7 g.) and ethyl cyano-

acetate (2.3 g.). The solution was left for 2 days at room temperature under a nitrogen atmosphere. The solution was worked up into neutral and acidic fractions as described in the previous experiment. The neutral fraction gave hydrazobenzene (3.3 g.), m.p. and mixed m.p. 126-128°. The acidic fraction gave only a small quantity of a gum from which no solid material could be obtained.

(c) A solution of hydrazobenzene (3.7 g.) in ethyl cyanoacetate (2.3 g.) in N-methylmorpholine (10 c.c.) was left overnight at room temperature in a nitrogen atmosphere. The solution was worked up as described above and only hydrazobenzene (3.4 g.), m.p. and mixed m.p. 125-126° was obtained.

Attempted Preparation of N-Acetyl-N'-cyanoacetylhydrazobenzene. - (a) A solution of N-cyanoacetylhydrazobenzene (200 mg.) in pyridine (4 c.c.) and acetic anhydride (4 c.c.) was heated on the steam bath for 1 hr. The solution was poured into water and extracted with ether. The ethereal extract was washed with hydrochloric acid (3 x 30 c.c.; 3N), water and dried (Na_2SO_4). The ether was evaporated giving a gum from which no solid material could be obtained.

(b) N-Cyanoacetylhydrazobenzene (100 mg.) was heated on the steam bath with acetic anhydride (10 c.c.) for 1 hr.

Water was added and the solution evaporated to dryness. The residue was crystallised from ethanol to give unchanged starting material, m.p. and mixed m.p. 172-173°.

(c) N-Cyanoacetylhydrazobenzene (100 mg.) was refluxed with acetic anhydride (15 c.c.) for 1 hr. The reaction was worked up as described in (b) to give unchanged starting material, m.p. and mixed m.p. 172-173°.

(d) To a solution of N-acetylhydrazobenzene (2.9 g.) in chloroform (80 c.c.) and pyridine (30 c.c.), cooled in a freezing mixture, a solution of cyanoacetyl chloride (1.8 g.) in chloroform (25 c.c.) was added with stirring over a period of 15 min. The freezing mixture was removed and worked up into neutral and acidic fractions. Crystallisation of the product, obtained from the neutral fraction, from ethanol gave unchanged N-acetylhydrazobenzene (2.5 g.), m.p. and mixed m.p. 164-165° (lit.159°). No solid material could be obtained from the acidic fraction.

N-Carboxyacetylhydrazobenzene. - (a) A solution of N-cyanoacetylhydrazobenzene (500 mg.) in ethanol (18 c.c.), water (18 c.c.) and hydrochloric acid (1 c.c.; d,1.15) was refluxed for 1 hr. The reaction solution was separated into an ethereal neutral fraction (C) and an alkali soluble fraction. Acidification of the alkaline solution

and isolation using ether followed by crystallisation from methylene chloride-n-hexane gave N-carboxyacetyl-hydrazobenzene (300 mg.) as needles, m.p. 133-134° (decomp.)

Found: C,66.32; H,5.39%

$C_{15}H_{14}O_3N_2$ requires: C,66.65; H,5.22%

$\lambda^{EtOH}_{max.}$ 208 (ε = 17,000) and 236 mu (ε = 14,500);

$\nu_{max.}$ 3390-3175 (NH and OH), 1724 $cm.^{-1}$ (CO)

(b) A solution of 3-imino-5-oxo-1,2-diphenylpyrazolidine (220 mg.) in ethanol (9 c.c.), water (9 c.c.) and hydrochloric acid (0.5 c.c.; d,1.15) was refluxed for 1 hr. The reaction solution was separated using ether into a neutral fraction D and an acidic fraction which crystallised from methylene chloride-n-hexane to give N-carboxyacetyl-hydrazobenzene (100 mg.) as needles, m.p. and mixed m.p. 133-134° (decomp.).

(c) A solution of 3,5-dioxo-1,2-diphenylpyrazolidine (1.0 g.) in dioxan (20 c.c.) and hydrochloric acid (0.5 c.c.; 2N) was kept at room temperature for 6 days with occasional shaking. Water was added and the solution was extracted with chloroform and the combined chloroform extracts washed with aqueous sodium hydrogen carbonate, aqueous sodium hydroxide, water and dried (Na_2SO_4). From the sodium hydrogen carbonate solution by acidification and isolation using ether N-carboxyacetylhydrazobenzene (260 mg.), m.p. and mixed m.p. 130-132° was obtained

crystallising from methylene chloride-n-hexane as needles. The sodium hydroxide extract on acidification yielded 3,5-dioxo-1,2-diphenylpyrazolidine (450 mg.) m.p. and mixed m.p. 175-178°. No crystalline material was isolated from the neutral fraction.

N-Acetylhydrazobenzene. - N-Carboxyacetyl-hydrazobenzene (150 mg.) was heated for 15 min. at 140°. The cooled mass was dissolved in ether and the ethereal solution washed with aqueous sodium hydroxide (2N), water and dried (Na_2SO_4). The ethereal solution was evaporated and the residue crystallised from chloroform-ethanol to give N-acetylhydrazobenzene (60 mg.) as needles, m.p. 161-162° alone or mixed with an authentic sample (lit. m.p. 159°). The infrared spectra of the two samples were identical.

N-Ethoxycarbonylacetylhydrazobenzene. - (a) N-Carboxyacetylhydrazobenzene (30 mg.) was added to an excess of ethereal diazoethane and the solution left standing overnight at room temperature. The solution was evaporated to dryness and the residue crystallised from methylene chloride-n-hexane to give N-ethoxycarbonylacetyl-hydrazobenzene (20 mg.) as needles, m.p. 98-100°.

Found: C,68.4; H,5.7%

$C_{17}H_{18}O_3N_2$ requires: C,68.4; H,6.1%

$\lambda_{max.}^{EtOH}$ 208 (ε = 26,400) and 236 mμ (ε = 18,000); $\nu_{max.}$ 3333 (NH) and 1739 cm.$^{-1}$ (ester carbonyl).

(b) Removal of ether from neutral fraction C of the hydrolysis of N-cyanoacetylhydrazobenzene and crystallisation of the residue from methylene chloride-n-hexane gave N-ethoxycarbonylacetylhydrazobenzene (150 mg.) as needles, m.p. and mixed m.p. 99-100°.

(c) Neutral fraction D from the action of aqueous ethanolic hydrochloric acid on 3-imino-5-oxo-1,2-diphenylpyrazolidine was evaporated to dryness and the residue crystallised from methylene chloride-n-hexane to give N-ethoxycarbonylacetylhydrazobenzene as needles, m.p. 97-98°, alone or mixed with an authentic specimen.

(d) A solution of 3,5-dioxo-1,2-diphenylpyrazolidine (500 mg.) in ethanol (18 c.c.), water (18 c.c.) and hydrochloric acid (1c.c.; d,1.15) was refluxed for 1 hr. The cooled solution was separated in the usual way into neutral and alkali soluble fractions. The neutral fraction crystallised from methylene chloride-n-hexane to give N-ethoxycarbonylacetylhydrazobenzene (80 mg.) as needles, m.p. and mixed m.p. 97-99°. N-Carboxyacetylhydrazobenzene, m.p. and mixed m.p. 130-132° (decomp.) was obtained from the acidic fraction along with starting material, m.p. and mixed m.p. 175-178°.

Comparison of the infrared spectra of preparations (a), (b), (c) and (d) confirmed their identity.

3,5-Dioxo-1,2-diphenylpyrazolidine. - (a) N-Ethoxycarbonylacetylhydrazobenzene (50 mg.) was added to a solution of sodium ethoxide from sodium (40 mg.) and ethanol (15 c.c.) and refluxed for 2 hr. on the steam bath. The solution was evaporated to dryness under reduced pressure, the residue dissolved in water and the solution acidified with hydrochloric acid (d,1.15) and extracted with ether (3 x 30 c.c.). The combined ethereal extracts were washed with water, dried (Na_2SO_4) and the ether evaporated. Crystallisation of the residue from ethanol gave 3,5-dioxo-1,2-diphenylpyrazolidine (30 mg.) as plates, m.p.178-179°, alone or mixed with an authentic specimen. The infrared spectrum was also identical with that of the authentic specimen.

(b) Concentration of the methylene chloride-n-hexane mother liquor from the crystallisation of N-carboxyacetylhydrazobenzene obtained from N-cyanoacetylhydrazobenzene gave 3,5-dioxo-1,2-diphenylpyrazolidine (20 mg.) which separated from ethanol as plates, m.p. and mixed m.p. 175-178°.

(c) A solution of 3-imino-5-oxo-1,2-diphenylpyrazolidine (1.2 g.) in ethanol (20 c.c.), water (20 c.c.) and

hydrochloric acid (2 c.c.; d,1.15) was refluxed for 1 hr. The reaction solution was diluted with water (50 c.c.) and extracted with chloroform. The chloroform extract was washed with aqueous sodium hydrogen carbonate, aqueous sodium hydroxide, water and dried (Na_2SO_4). From the sodium hydroxide solution by acidification, with hydrochloric acid (d,1.15), and isolation using chloroform, 3,5-dioxo-1,2-diphenylpyrazolidine (100 mg.)m.p. and mixed m.p. 177-178° was obtained crystallising from chloroform-ethanol as plates. N-Carboxyacetylhydrazobenzene (480 mg.) separated out as needles from the sodium hydrogen carbonate solution on acidification with dilute hydrochloric acid and standing. Evaporation of the neutral fraction yielded N-ethoxycarbonylacetylhydrazobenzene (80 mg.) m.p. and mixed m.p. 96-98°.

Action of Alkali on 3-Imino-5-oxo-1,2-diphenylpyrazolidine. - (a) 3-Imino-5-oxo-1,2-diphenylpyrazolidine (300 mg.) was suspended in a 1% aqueous sodium hydroxide solution and shaken for 5 days at room temperature. The solution was filtered and unchanged starting material (300 mg.) was recovered m.p. and mixed m.p. 220-222°. (b) 3-Imino-5-oxo-1,2-diphenylpyrazolidine (500 mg.) was refluxed with ethanolic sodium hydroxide (25 c.c.; N) for 1 hr. The solution was cooled and a solid separated out

which was filtered off and dried. Crystallisation of the solid from ethanol gave hydrazobenzene (83 mg.) m.p. 125° alone or when mixed with an authentic sample. Dilution of the filtrate with water caused the precipitation of more solid which on crystallisation from ethanol gave unchanged starting material (160 mg.) m.p. and mixed m.p. 220-222°.

Action of Diazomethane on 3-Imino-5-oxo-1,2-diphenylpyrazolidine. - A solution of 3-imino-5-oxo-1,2-diphenylpyrazolidine (30 mg.) in methanol (20 c.c.) was treated with a large excess of an ethereal solution of diazomethane and left overnight at room temperature. The reaction solution was treated with acetic acid to destroy excess diazomethane and evaporated to dryness under reduced pressure. Crystallisation of the residue from chloroform-ethanol gave unchanged starting material, m.p. and mixed m.p. 222-223°.

3-Methoxy-5-oxo-1,2-diphenylpyrazoline. - A solution of 3,5-dioxo-1,2-diphenylpyrazolidine (1 g.) in chloroform (50 c.c.) was treated with an excess of an ethereal diazomethane solution and left at room temperature for 24 hr. The chloroform solution was washed with dilute sodium hydroxide solution (3 x 20 c.c.), with water and dried (Na_2SO_4). Evaporation of the chloroform

solution to dryness under reduced pressure and crystallisation of the residue from chloroform-petroleum ether gave 3-methoxy-5-oxo-1,2-diphenylpyrazoline (650 mg.) as colourless needles, m.p. 171-173°.

Found: C,72.15; H,5.4%

$C_{16}H_{14}O_2N_2$ requires: C,72.16; H,5.3%

$\lambda^{EtOH}_{max.}$ 204 (ε = 27,000) and 250 mu (ε = 17,000); $\lambda^{NaOH}_{max.}$ 248 mu (ε = 16,000); $\nu_{max.}$ 1701 $cm.^{-1}$ (CO).

3-Ethoxy-5-oxo-1,2-diphenylpyrazoline. - A solution of 3,5-dioxo-1,2-diphenylpyrazolidine (500 mg.) in chloroform (30 c.c.) was treated with an excess of an ethereal diazoethane solution and left at room temperature for 24 hr. Working up as above, the product was crystallised from methylene chloride-n-hexane to give 3-ethoxy-5-oxo-1,2-diphenylpyrazoline (240 mg.) as colourless needles, m.p. 155-156°.

Found: C,72.5; H,5.5%

$C_{17}H_{16}O_2N_2$ requires: C,72.84; H,5.23%

$\nu_{max.}$ 1689 $cm.^{-1}$ (CO).

4-cycloHexenyl-3-imino-5-oxo-1,2-diphenylpyrazolidine. - (a) 3-Imino-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) was refluxed with cyclohexanone (10 c.c.) for 1 hr. The solution was evaporated to dryness under reduced pressure and the residue crystallised from ethanol-light petroleum

(b.p. 60-80°) to give 4-cyclohexenyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) as prims, m.p. 188-189°

Found: C,75.84; H,6.03%

$C_{21}H_{21}ON_3$ requires: C,76.1; H,6.4%

$\lambda^{EtOH}_{max.}$ 205 (ε = 29000) and 255 mu (ε = 22000); $\lambda^{NaOH}_{max.}$ 228 (ε = 6000) and 254 mu (ε = 24000); ν max. 3356 (NH) and 1664 $cm.^{-1}$ (CO). An ethanolic solution of the compound gave a reddish brown colour with aqueous ferric chloride.

(b) Cyanoacetylhydrazobenzene (500 mg.) was refluxed for 6 hr. with cyclohexanone (10 c.c.). Isolation as in the preceding experiment and crystallisation from chloroform-methanol gave 4-cyclohexenyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (30 mg.) as prisms, m.p. and mixed m.p. 185-186°.

4-cycloHexyl-3-imino-5-oxo-1,2-diphenylpyrazolidine.- A solution of 4-cyclohexenyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) in ethyl acetate (250 c.c.) was shaken at room temperature and atmospheric pressure in the presence of platinum from Adams catalyst (500 mg.). When absorption was complete (ca. 2 hr.) the filtered solution was evaporated to dryness under reduced pressure and the residue crystallised from methylene chloride-n--hexane to give 4-cyclohexyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) as needles, m.p. 223-225°.

Found: C,75.2; H,6.8; N,12.9%

$C_{21}H_{23}ON_3$ requires: C,75.6; H,6.95; N,12.6%

$\lambda_{max.}^{EtOH}$ 204 (ε = 24,000) and 262 mu (ε = 25,000); λ_{max}^{NaOH} 223 (ε = 45,000) and 263 mu (ε = 19,000); $\nu_{max.}$ 3226, 3106 and 1618 $cm.^{-1}$ (CO).

An ethanolic solution of the compound gave a reddish-brown colour with aqueous ferric chloride.

4-cycloHexylidene-3,5-dioxo-1,2-diphenylpyrazolidine (17). - 3,5-Dioxo-1,2-diphenylpyrazolidine (1.0 g.) was refluxed with cyclohexanone (10 c.c.). The solution was evaporated to dryness under reduced pressure and the residue crystallised from ethanol to give 4-cyclohexylidene-3,5-dioxo-1,2-diphenylpyrazolidine (900 mg.) as yellow needles, m.p. 172-173°. An ethanolic solution of the compound gave no colour with aqueous ferric chloride.

4-cycloHexyl-3,5-dioxo-1,2-diphenylpyrazolidine. - (a) A solution of 4-cyclohexylidene-3,5-dioxo-1,2-diphenylpyrazolidine (400 mg.) in ethyl acetate (40 c.c.) was shaken at room temperature and atmospheric pressure with platinum from Adams catalyst (140 mg.) until absorption was complete (ca. 1 hr.). The filtered solution was evaporated under reduced pressure and the residue crystallised from chloroform-methanol to gave 4-cyclohexyl-3,5-dioxo-1,2-diphenylpyrazolidine (350 mg.) as needles,

m.p. 176-178° (lit.(15)m.p. 177°).
$\lambda_{max.}^{EtOH}$ 207 (ε = 19,000) and 268 mu (ε = 22,000), $\lambda_{max.}^{NaOH}$ 270 mu (ε = 23,000); νmax. 1754 and 1730 cm.$^{-1}$ (both CO).

An ethanolic solution of the compound gave no colour with aqueous ferric chloride.

(b) A solution of 4-cyclohexyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (740 mg.) in ethanol (20 c.c.) water (20 c.c.) and hydrochloric acid (2 c.c.; d,1.15) was refluxed for 1 hr. The cooled solution was extracted with chloroform (3 x 40 c.c.) and the combined extracts washed with aqueous sodium hydroxide (2 x 50 c.c.; 2N), water and dried (Na_2SO_4). Removal of the chloroform and crystallisation of the residue from chloroform-methanol gave unchanged material (300 mg.) m.p. and mixed m.p.220-222°. Acidification of the combined alkaline washings with 2N hydrochloric acid (Congo red) and isolation of the product using chloroform gave 4-cyclohexyl-3,5-dioxo-1,2-diphenylpyrazolidine (100 mg.) m.p. and mixed m.p. 174-176°.

The infrared spectrum of the compound was identical with that of an authentic specimen.

3-Imino-4-isonitroso-5-oxo-1,2-diphenylpyrazolidine.- To a solution of 3-imino-5-oxo-1,2-diphenylpyrazolidine (3.0 g.) in ethanol (50 c.c.) was added crushed ice (50 gm.) and hydrochloric acid (100 c.c.; 2N). An ice-cold aqueous

solution of sodium nitrite (100 c.c.; 2N) was now added slowly with stirring. The solution turned yellow and after half of the nitrite solution had been added a pink precipitate separated out. When the addition of the nitrite solution had been completed the solution was placed in the refrigerator for 2 hr. The pink precipitate was filtered off, washed with water and sucked dry at the water pump. Crystallisation of the solid from aqueous ethanol gave 3-imino-4-isonitroso-5-oxo-1,2-diphenyl-pyrazolidine (3.0 g.) as red prismatic needles, m.p.247-248° (decomp.).

Found: C,64.04; H,4.23%

$C_{15}H_{12}O_2N_4$ requires: C,64.27; H,4.32%

$\lambda^{EtOH}_{max.}$ 208 (ε = 19,000), 318 mu (ε = 16,000) and $\lambda_{inflex.}$ 228 mu (ε = 18,000); $\lambda^{NaOH}_{max.}$ 250 (ε = 15,000) and 308 mu (ε = 13,000); ν max. 3226 (NH), 1712 and 1667 $cm.^{-1}$ (C=O)

3-Imino-5-oxo-4-phenylazo-1,2-diphenylpyrazolidine

Aniline (3 c.c.) was added to hydrochloric acid (20 c.c.; 6N) and was diazotised at 0°C by the gradual addition of aqueous sodium nitrite solution (18 c.c.; 2N). Five minutes after the addition was complete, excess nitrous acid was destroyed by the addition of urea. The ice-cold diazo solution was now poured into a stirred solution of 3-imino-5-oxo-1,2-diphenylpyrazolidine (1 g.) in ethanol (20 c.c.), cooled in an ice bath. The pH of the resulting

solution was brought to ca.4 by the addition of concentrated aqueous sodium acetate solution. The solution was stirred for 1 hr. and left overnight in the refrigerator. The solution was filtered and the yellow precipitate washed with water and sucked dry at the water pump. Crystallisation of the solid from aqueous ethanol or better from methylene chloride-n-hexane gave 3-imino--5-oxo-4-phenylazo-1,2-diphenylpyrazolidine (1.1 g.) as yellow needles m.p. 218-219°.

Found: C,70.89; H,5.14%

requires: C,70.96; H,4.82%

$\lambda_{max.}^{EtOH}$ 205 (ε = 25,000), 245 (ε = 19,000) and 360 mu (ε = 22,000), λ_{inflex} 260 mu (ε = 16,000); $\nu_{max.}$ 3333 (NH) and 1667 $cm.^{-1}$ (C=O).

3,5-Dioxo-4-isonitroso-1,2-diphenylpyrazolidine (17)

(a) 3,5-Dioxo-1,2-diphenylpyrazolidine was treated with nitrous acid as described above to give 3,5-dioxo-4-isonitroso-1,2-diphenylpyrazolidine as red needles (hydrated). The anhydrous compound, which is dark red in colour has m.p. 160-162°.

(b) A suspension of 3-imino-4-isonitroso-5-oxo-1,2--diphenylpyrazolidine (50 mg.) in sulphuric acid (25 c.c.; 2N) was heated on the steam bath for 45 min. when the solid went into solution. On cooling 3,5-dioxo-4-

-isonitroso-1,2-diphenylpyrazolidine (20 mg.) separated out as red needles. On drying it had m.p. 160-161°, undepressed when mixed with the specimen prepared in (a).

3,4-Diamino-5-oxo-1,2-diphenylpyrazoline. - (a) 3-Imino-4-isonitroso-5-oxo-1,2-diphenylpyrazolidine (800 mg.) was added portionwise over 20 min. to a vigorously stirred solution of hydrochloric acid (10 c.c.; d,1.15), crushed ice (50 gm.) and zinc dust (3.0 gm.), cooled in an ice bath. The solution was stirred for a further 90 min., filtered to remove the zinc and poured into ammonium hydroxide (15 c.c.; d,0.88). A white solid separated out as needles which on standing gradually turned yellow. The solid was filtered off, washed with water and sucked dry. Crystallisation of the solid from methylene chloride-n-hexane gave 3,4-diamino-5-oxo-1,2--diphenylpyrazoline (600 mg.) as yellow needles, m.p. 163-164° (decomp.).

Found: C,67.46; H,5.23%

$C_{15}H_{14}ON_4$ requires: C,67.65; H,5.3%

λ_{max}^{EtOH} 206 (ε = 19,000) and 252 mu (ε = 18,000);

ν max. 3236, 3086 (both NH) and 1688 cm.$^{-1}$ (CO);

$\nu_{max.}^{CHCl_3}$ 3390, 3333 (both NH) and 1695 (shoulder) and 1647 cm.$^{-1}$ (CO).

5,6-Dimethyl-1,2-diphenyl-3-oxopyrazolo[2,3b]-pyridazine. - A solution of 3,4-diamino-5-oxo-1,2-diphenylpyrazoline (50 mg.) in diacetyl (5 c.c.) was left standing overnight at room temperature. Water (3 c.c.) was added and on further standing needle like crystals appeared, which were filtered off and dried. Crystallisation from methylene chloride-n--hexane gave 5,6-dimethyl-1,2-diphenyl-3-oxopyrazolo--[2,3b]-pyridazine (40 mg.) as needles, m.p. 203-205°.

Found: C,71.89; H,5.09%

$C_{19}H_{16}ON_3$ requires: C,72.13; H,5.01%

$\lambda_{max.}^{EtOH}$ 206 (ε = 24,000), 274 mu (ε = 18,000), λ_{inflex} 295 mu (ε = 14,000); $\lambda_{max.}^{NaOH}$ 231 (ε = 20,000), 270 mu (ε = 18,000), λ_{inflex} 298 mu (ε = 14,000); $\lambda_{max.}^{HCl}$ 207 (ε = 24,000), 270 mu (ε = 18,000) and $\lambda_{inflex.}$ 294 mu (ε = 13,000); $\nu_{max.}$ 1709 cm.$^{-1}$ (C = 0).

3-Oxo-1,2,5,6-tetraphenylpyrazolo-[2,3b]-pyridazine. - A solution of 3,4-diamino-5-oxo-1,2-diphenylpyrazoline (130 mg.) and benzil (150 mg.) in

glacial acetic acid (50 c.c.) was refluxed for 20 hr. The cooled solution was poured into water (200 c.c.) and extracted with chloroform. The chloroform extract was washed with sodium bicarbonate solution, water and dried (Na_2SO_4). Evaporation of the chloroform to dryness under reduced pressure gave a red gum which on crystallisation from methylene chloride-ethanol gave 3--oxo-1,2,5,6-tetraphenylpyrazolo-[2,3b]-pyridazine (70 mg.) as yellow needles, m.p. 255-256°

Found: C,79.38; H,4.51%

$C_{29}H_{20}ON_4$ requires: C,79.07; H,4.58%

$\lambda^{EtOH}_{max.}$ 209 (ε = 36,000) and 294 mu (ε = 22,000), $\lambda_{inflex.}$ 220 (ε = 29,000) and 340 mu (ε = 15,000); ν max. 1695 $cm.^{-1}$ (C = O).

Phenanthraquinone Derivative of 3,4-Diamino--5-oxo-1,2-diphenylpyrazoline. - A solution of 3,4-diamino-5-oxo-1,2-diphenylpyrazoline (200 mg.) and phenanthraquinone (180 mg.) in glacial acetic acid was refluxed for 2 hr. The solution rapidly turned very dark red in colour. The

cooled solution was poured into water (100 c.c.) and extracted with chloroform. The chloroform extract was washed with sodium bicarbonate solution, water and the dried (Na_2SO_4) extract evaporated to dryness under reduced pressure. A red-brown solid was obtained which on repeated crystallisation from chloroform-methanol gave the phenanthraquinone derivative of 3,4-diamino-5-oxo-1,2-diphenylpyrazoline (80 mg.) as yellow needles, m.p. 312-313°.

Found: C,77.98; H,4.43%

$C_{29}H_{18}ON_4$ + $0.5CH_3OH$ requires: C,77.96; H,4.4%

$\lambda_{max.}^{EtOH}$ 205 (ε = 30,000), 253 (ε = 33,000), 306 (ε = 20,000), 317 (ε = 15,000) and 377 mu (ε = 12,000); ν max. 1709 $cm.^{-1}$ (C = O).

4-Acetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine. - (a) 3-Imino-5-oxo-1,2-diphenylpyrazolidine (2.0 g.) was heated on the steam bath with acetic anhydride (25 c.c.) for 2 hr. The warm solution was treated with water (20 c.c.) and evaporated to dryness under reduced pressure.

The solid residue was dissolved in chloroform (50 c.c.) and the solution washed with aqueous sodium hydroxide (3 x 30 c.c.; 2N) [Extract B], water (30 c.c.) and dried (Na_2SO_4). Removal of the chloroform and crystallisation of the residue from methylene chloride-n-hexane gave 4--acetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (500 mg.) as stout needles, m.p. 207-208°.

Found: C,69.8; H,5.2%
$C_{17}H_{15}O_2N_3$ requires: C,69.6; H,5.2%

λ_{max}^{EtOH} 208 (ε = 20000), 233 (ε = 22,500) and 265 mu (ε = 20,000); $\lambda_{max.}^{NaOH}$ 235 (ε = 17,000) and 264 mu (ε = 15,000). $\nu_{max.}$ 3333, 3175 (NH) and 1695 $cm.^{-1}$ (C = O); $\nu_{max.}^{CHCl_3}$ 3425, 3268 (NH) and 1692 $cm.^{-1}$ (CO).

An ethanolic solution of the compound gave a red colour with aqueous ferric chloride.

(b) A well stirred solution of 3-imino-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) in pyridine (50 c.c.) and dioxan (25 c.c.) cooled in an ice bath, was treated dropwise with a solution of pure acetyl chloride (3.0 g.) in dry ether (25 c.c.) over 30 min. The reaction mixture was kept overnight, water added, and extracted with chloroform. The chloroform extract was washed with 2N sodium hydroxide, water, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residual solid was crystallised from methylene chloride-n-hexane to give

4-acetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (800 mg.) as stout needles, m.p. and mixed m.p. 206-208°. No identifiable material was obtained from examination of the alkaline washings.

4-Acetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine was recovered unchanged, m.p. and mixed m.p. 207-209° after 4 hr. reflux with 50% aqueous ethanolic sodium carbonate (M) solution and after 1 hr with 80% aqueous ethanolic sodium hydroxide solution (3N).

3-Acetylimino-5-oxo-1,2-diphenylpyrazolidine. - (a) Alkaline extract B from the reaction between 3-imino-5-oxo-1,2-diphenylpyrazolidine and acetic anhydride was acidified (Congo red) with 2N hydrochloric acid. Isolation of the product using chloroform followed by crystallisation from methylene chloride-n-hexane gave 3-acetylimino-5-oxo-1,2-diphenylpyrazolidine (300 mg.) as needles, m.p. 204-205°.

Found: C,69.6; H,5.1%

$C_{17}H_{15}O_2N_3$ requires: C,69.6; H,5.2%

λ_{max}^{EtOH} 204 (ε = 20,000) and 260 mu (ε = 18,000); $\lambda_{max.}^{NaOH}$ 280 mu (ε = 23,000); $\nu_{max.}$ 3100 and 1718 cm.$^{-1}$ (C = O); $\nu_{max.}^{CHCl_3}$ 3333, 1733 (C = O) and 1681 cm.$^{-1}$ (C = O).

An ethanolic solution of the compound gave a red colour with aqueous ferric chloride.

(b) 3-Imino-5-oxo-1,2-diphenylpyrazolidine (1.0 g.) in dioxan (10 c.c.) was treated with acetyl chloride (20 c.c.) and the solution heated on the steam bath for 2 hr. The cooled solution was diluted with water (50 c.c.) and extracted with chloroform (3 x 50 c.c.). The chloroform extract was washed with aqueous sodium hydroxide (3 x 30 c.c.; 2N) then with water and dried (Na_2SO_4). The combined alkaline washings were acidified (Congo red) with 2N hydrochloric acid and the product isolated using chloroform. Crystallisation from methylene chloride-n-hexane gave 3-acetylimino-5-oxo--1,2-diphenylpyrazolidine (50 mg.) as needles, m.p. and mixed m.p. 202-204°. Evaporation of the chloroform solution of the neutral material under reduced pressure and crystallisation of the residue from methylene chloride-n-hexane gave back 3-imino-5-oxo-1,2-diphenyl-pyrazolidine (600 mg.) m.p. and mixed m.p. 221-223°.

Alkaline Hydrolysis of 3-Acetylimino-5-oxo-1,2--diphenylpyrazolidine to 3-Imino-5-oxo-1,2-diphenyl-pyrazolidine. - 3-Acetylimino-5-oxo-1,2-diphenylpyrazo-lidine (100 mg.) in ethanol (7 c.c.) and aqueous sodium carbonate (7 c.c.; 2M) was refluxed for 2 hr. The cooled solution was extracted with chloroform, the chloroform extract evaporated under reduced pressure, and the residue crystallised from acetone-light petroleum (b.p.

60–80°) to give 3-imino-5-oxo-1,2-diphenylpyrazolidine (80 mg.) as plates, m.p. and mixed m.p. 221–223°.

Acetate C. – (a) A solution of 3-imino-5-oxo-1,2-diphenylpyrazolidine (2 g.) in acetic anhydride (10 c.c.) was heated on the steam bath for 1 hr. Water was added and the solution evaporated to dryness under reduced pressure. The residue was digested with hot chloroform and the insoluble solid filtered off. Crystallisation of the solid from a mixture of chloroform, ethanol-petroleum ether gave acetate C (500 mg.), m.p. 237–239°

Found: C,69.44; H,5.09; N,15.31%

C,69.28; H,5.02%

$\lambda_{max.}^{EtOH}$ 206 (ε = 25,000) and 257 mu (ε = 2,500); $\lambda_{max.}^{NaOH}$ 264 mu (ε = 19,000); $\nu_{max.}$ 3260, 3096 (NH), and 1709 $cm.^{-1}$ (CO).

The chloroform filtrate after washing with sodium hydroxide afforded 4-acetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (320 mg.) as needles m.p. and mixed m.p. 207–208°. Acidification of the alkaline washings followed by chloroform extraction yielded 3-acetylimino--5-oxo-1,2-diphenylpyrazolidine (70 mg.) as needles m.p. and mixed m.p. 205–206°.

(b) A mixture of 3-imino-5-oxo-1,2-diphenylpyrazolidine (50 mg.) and 3-acetylimino-5-oxo-1,2-diphenylpyrazolidine

(50 mg.) was crystallised from a mixture of chloroform, ethanol-petroleum ether to give acetate C (60 mg.) m.p. 237-238°. There was no depression when mixed with the sample prepared in (a). The infrared spectra were also identical.

A solution of acetate C in ethanol gave a red colouration with aqueous ferric chloride.

Alkaline Hydrolysis of Acetate C to 3-Imino-5-oxo-1,2-diphenylpyrazolidine. - A solution of acetate C (80 mg.) in ethanol (9 c.c.) and aqueous sodium carbonate (9 c.c.; 2M) was refluxed for 4 hr. The cooled solution was diluted with water and extracted with chloroform. The chloroform solution was washed with water and the dried (Na_2SO_4) extract evaporated to dryness under reduced pressure. Crystallisation of the residue from ethanol-petroleum ether gave 3-imino-5-oxo-1,2-diphenylpyrazolidine (50 mg.) m.p. and mixed m.p. 220-222°.

Action of Cold Alkali on Acetate C. - A cold solution of acetate C (260 mg.) in chloroform (25 c.c.) and ethanol (5 c.c.) was washed with aqueous sodium hydroxide (3 x 30 c.c.; 2N). The chloroform solution was washed with water and the dried (Na_2SO_4) chloroform extract was evaporated under reduced pressure. Crystallisation of the residue from ethanol-petroleum ether gave 3-imino-5-oxo-1,2-diphenylpyrazolidine (84 mg.) m.p. and

mixed m.p. 223-224°. Acidification of the alkaline washings with dilute hydrochloric acid followed by chloroform extraction afforded 3-acetylimino-5-oxo-1,2--diphenylpyrazolidine (104 mg.) as needles, m.p. and mixed m.p. 205-206°.

Action of Acetic Anhydride on Acetate C. - A solution of acetate C (220 mg.) in acetic anhydride (25 c.c.) was heated on the steam bath for 1 hr. Water was added and the solution was evaporated to dryness. The residue was dissolved in chloroform and washed with sodium hydroxide, water and dried (Na_2SO_4). Evaporation of the chloroform and crystallisation of the residue from methylene chloride-n-hexane gave 4-acetyl-3-imino-5-oxo--1,2-diphenylpyrazolidine (38 mg.) as needles m.p. and mixed m.p. 208-209°. Acidification of the alkaline washings with dilute hydrochloric acid followed by chloroform extraction gave 3-acetylimino-5-oxo-1,2-diphenylpyrazolidine (120 mg.) as needles m.p. and mixed m.p. 206-207°.

3-Acetylmethylamino-5-oxo-1,2-diphenylpyrazoline. - A solution of 3-acetylimino-5-oxo-1,2-diphenylpyrazolidine (830 mg.) in methylene chloride (50 c.c.) was treated with a large excess of ethereal diazomethane and kept at 0°C for 10 days. After removal of excess diazomethane by

treatment with glacial acetic acid the ethereal solution was washed with 2N aqueous sodium hydroxide to remove unchanged starting material, then with water and dried (Na_2SO_4). The ether was removed and the residue crystallised from ethanol-n-hexane to give 3-acetylmethylamino-5-oxo-1,2-diphenylpyrazoline (55 mg.) as prisms, m.p. 227-228°, $\lambda_{max.}^{EtOH}$ 205 (ε = 14,000), 244 (ε = 8000) and 281 mu (ε = 7000); $\lambda_{max.}^{NaOH}$ 224 (ε = 8000) and 260 mu (ε =14,000); $\nu_{max.}$ 1681 $cm.^{-1}$ (C = O).

3-Methylimino-5-oxo-1,2-diphenylpyrazolidine. - A solution of 3-acetylmethylamino-5-oxo-1,2-diphenylpyrazoline (23 mg.) in ethanol (5 c.c.) and aqueous sodium carbonate (5 c.c.; 2M) was refluxed for 2 hr. The cooled solution was diluted with water (20 c.c.) and extracted with chloroform (2 x 20 c.c.). The dried (Na_2SO_4) chloroform extract was evaporated under reduced pressure and the residue crystallised from methylene chloride-n-hexane to give 3-methylimino-5-oxo-1,2-diphenylpyrazolidine (15.3 mg.) as needles, m.p. 178-179°.

Found: C,72.09; H,5.56%

$C_{16}H_{15}ON_3$ requires: C,72.43; H,5.7%

$\lambda_{max.}^{EtOH}$ 210 (ε = 13,000) and 256 mu (ε = 22,000); $\lambda_{max.}^{NaOH}$ 256 mu (ε = 27,000); $\lambda_{max.}^{HCl}$ 208 (ε = 18,000) and

256 mu (ε = 18,000); $\nu_{max.}^{CHCl_3}$ 3425 (NH) and 1667 cm.$^{-1}$ (C = O). An ethanolic solution of the compound gave a red colour with aqueous ferric chloride.

3-Butyrylimino-5-oxo-1,2-diphenylpyrazolidine. - A solution of 3-imino-5-oxo-1,2-diphenylpyrazolidine (890 mg.) in butyric anhydride (15 c.c.) was heated for 4 hr. on the steam bath. Water was added to the cooled solution and extracted with chloroform. The chloroform solution was washed with sodium hydroxide, water and the dried (Na_2SO_4) solution, on evaporation to dryness gave a negligible quantity of gum. Acidification of the sodium hydroxide washings with dilute hydrochloric acid, followed by chloroform extraction gave a solid. Crystallisation of the solid from methylene chloride--n-hexane gave 3-butyrylimino-5-oxo-1,2-diphenylpyrazolidine (450 mg.) as colourless needles, m.p. 184-185°.

Found: C,70.84; H,5.71%

$C_{19}H_{19}O_2N_3$ requires: C,71.01; H,5.96%

$\lambda_{max.}^{EtOH}$ 207 (ε = 20,000) and 261 mu (ε = 18,000); $\lambda_{max.}^{NaOH}$ 288 mu (ε = 22,000), ν max. 3215 (NH) and 1718 cm.$^{-1}$ (C = O).

4-Cyanoacetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine. - (a) The aqueous sodium hydroxide extract A from

the preparation of N-cyanoacetylhydrazobenzene (see page 62) was acidified (Congo red) with 2N hydrochloric acid and the product isolated using ether. Crystallisation from methylene chloride-n-hexane gave 4-cyanoacetyl--3-imino-5-oxo-1,2-diphenylpyrazolidine (340 mg.) as plates, m.p. 210-211°.

Found: C,67.7; H,4.5%

$C_{18}H_{14}O_2N_4$ requires: C,67.9; H,4.4%

$\lambda^{EtOH}_{max.}$ 204 (ε = 34,000), 231 (ε = 25,000) and 270 mu (ε = 21,000); νmax. 3534, 3257 (NH), 2288 (C≡N), 1695 (CO) and 1653 $cm.^{-1}$ (CO)

(b) To a well stirred solution of 3-imino-5-oxo-1,2-diphenylpyrazolidine (600 mg.) in dioxan (20 c.c.) and pyridine (5 c.c.), cooled in an ice bath, a solution of cyanoacetyl chloride (1.5 g.) in chloroform (10 c.c.) was added dropwise. After keeping overnight at room temperature the reaction mixture was treated with water (50 c.c.) and extracted with chloroform (3 x 50 c.c.). The combined chloroform extracts were washed successively with hydrochloric acid (3 x 30 c.c.; 2N), water (30 c.c.) and dried (Na_2SO_4). Removal of the chloroform gave a neglibible quantity of gum. The combined alkaline washings were acidified (Congo red) with 2N hydrochloric acid and the product isolated using chloroform.

Crystallisation from acetone-n-hexane gave 4-cyanoacetyl-3--imino-5-oxo-1,2-diphenylpyrazolidine (350 mg.) as plates, m.p. and mixed m.p. 208-210° (Found: C,67.9; H,4.6%). An ethanolic solution of the compound gave a pale brown colour with aqueous ferric chloride.

Hydrolysis of 4-Cyanoacetyl-3-imino-5-oxo-1,2--diphenylpyrazolidine to 4-Acetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine. - A solution of 4-cyanoacetyl-3--imino-5-oxo-1,2-diphenylpyrazolidine (500 mg.) in ethanol (18 c.c.), water (18 c.c.) and hydrochloric acid (9 c.c.; d.1.15) was heated on the steam bath for 3 hr. The solution was evaporated to dryness under reduced pressure and the solid residue treated with aqueous sodium hydrogen carbonate (30 c.c.; 10%) and extracted with ether (3 x 30 c.c.). The ethereal extract was washed with water, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. Crystallisation of the residue from acetone-n-hexane gave 4-acetyl-3-imino-5--oxo-1,2-diphenylpyrazolidine (30 mg.) as needles, m.p. and mixed m.p. 206-208°.

3-Imino-4-(α-methoxy-β-cyanovinyl)-5-oxo-1,2-diphenylpyrazolidine. - A solution of 4-cyanoacetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (730 mg.) in methylene chloride (30 c.c.) was treated with excess ethereal

diazomethane solution and kept overnight. The solution was washed with aqueous sodium hydroxide (2 x 50 c.c.; 2N), water and dried (Na_2SO_4). Evaporation of the ether under reduced pressure and crystallisation of the residue from acetone-n-hexane gave 3-imino-4-(α-methoxy-β-cyano-vinyl)-5-oxo-1,2-diphenylpyrazolidine (300 mg.) as needles, m.p. 183-185°, resolidifying and remelting at 265-270°.

Found: C,68.5; H,5.0%

$C_{19}H_{16}O_2N_4$ requires: C,68.7; H,4.85%

$\lambda_{max.}^{EtOH}$ 207 (ε = 24,000), 297 mu (ε = 33,000), $\lambda_{inflex.}$ 260 mu (ε = 23,000); $\nu_{max.}$ 3333 (NH), 2222 (C N) and 1656 $cm.^{-1}$ (C O).

Using diazoethane 3-imino-4-(α-ethoxy-β-cyano-vinyl)-5-oxo-1,2-diphenylpyrazolidine, m.p. 162-163° was obtained.

Found: C,69.24; H,5.59%

$C_{20}H_{18}O_2N_4$ requires: C,69.35; H,5.24%

6-Amino-4-hydroxy-3-oxo-1,2-diphenylpyrazolido-[2,3b]-pyridine. - (a) 4-Cyanoacetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (1.02 g.) was heated on the steam bath with aqueous sodium carbonate (30 c.c.; M) for 2 hr. The cooled solution was extracted with chloroform and the extract rejected. The aqueous phase was acidified

(Congo red) with 2N hydrochloric acid and extracted with chloroform. An interfacial solid which separated was collected. The chloroform extract was washed with water, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was combined with the interfacial solid and crystallised from tetrahydrofuran-n-hexane to give 6-amino-4-hydroxy-3-oxo-1,2-diphenylpyrazolido-[2,3b]-pyridine (550 mg.) as prisms, m.p. 289-290°

Found: C,67.5; H,4.7%

$C_{18}H_{14}O_2N_4$ requires: C,67.9; H,4.4%

$\lambda_{max.}^{EtOH}$ 208 (ε = 23,000), 230 (ε = 18,000) and 284 mu (ε = 28,000); $\lambda_{max.}^{NaOH}$ 233 (ε = 24,600), 238 (ε = 24,600) and 272 mu (ε = 28,600), $\lambda_{inflex.}$ 295 mu (ε = 16,000); ν max. 3425, 3155 (OH group) and 1667 $cm.^{-1}$ (C=O).

An ethanolic solution of the compound gave a deep red colour with aqueous ferric chloride.

(b) A solution of 4-cyanoacetyl-3-imino-5-oxo-1,2--diphenylpyrazolidine 450 mg.) in aqueous sodium hydroxide (25 c.c.; N) was heated on the steam bath for 1 hr. Acidification of the cooled solution, isolation using ether and crystallisation from chloroform-ethanol gave 6-amino-4-hydroxy-3-oxo-1,2-diphenylpyrazolido--[2,3b]-pyridine (40 mg.) as plates, m.p. and mixed m.p. 288-290°.

6-Amino-4-methoxy-3-oxo-1,2-diphenylpyrazolido-[2,3b]-pyridine. - (a) A solution of 6-amino-4-hydroxy-3-oxo-1,2-diphenylpyrazolido-[2,3b]-pyridine (200 mg.) in acetone (30 c.c.) was treated with an excess of ethereal diazomethane and kept overnight. The solution was washed with aqueous sodium hydroxide (2 x 50 c.c.; 2N), water and dried (Na_2SO_4). Removal of the ether under reduced pressure and crystallisation of the residue from chloroform-methanol gave 6-amino-4-methoxy-3-oxo-1,2 diphenylpyrazolido-[2,3b]-pyridine. (120 mg.) as needles, m.p. 272-273°.

Found: C,68.9; H,4.8%

$C_{19}H_{16}O_2N_4$ requires: C,68.7; H,4.8%

λ_{max}^{EtOH} 206 (ε = 28,000), 230 (ε = 18,000) and 288 mu (ε = 28,000); ν max. 3247, 3145 (both NH) and 1681 $cm.^{-1}$ (C=O); $\nu_{max.}^{CHCl_3}$ 3333 (NH) and 1692 $cm.^{-1}$ (C=O).

(b) 3-Imino-4-(α-methoxy-β-cyanovinyl)-5-oxo-1,2--diphenylpyrazolidine (50 mg.) was heated at 200° for 30 min. After cooling, the solidified melt was crystallised from chloroform-methanol to give 6-amino--4-methoxy-3-oxo-1,2-diphenylpyrazolido-[2,3b]-pyridine (20 mg.) as needles, m.p. and mixed m.p. 271-273°.

3-Acetylimino-4-methyl-5-oxo-1,2-diphenylpyrazolidine. (a) A stirred solution of 3-imino-4-methyl-5-

-oxo-1,2-diphenylpyrazolidine (1.0 g.) in dioxan (25 c.c.) and pyridine (5 c.c.), cooled in an ice-bath, was treated over 30 min. with a solution of pure acetyl chloride (3c.c.) in ether (20 c.c.). After keeping 2 hr. the reaction mixture was diluted with chloroform, washed with 2N hydrochloric acid, water and 2N aqueous sodium hydroxide, the latter washings, on acidification and isolation using chloroform, gave on crystallisation from methanol 3-acetylimino-4-methyl-5-oxo-1,2-diphenyl-pyrazolidine (250 mg.) as plates, m.p. 189°

Found: C, 70.1; H, 5.8%

$C_{18}H_{17}O_2N_3$ requires: C, 70.3; H, 5.6%.

$\lambda_{max.}^{EtOH}$ 205 (ε = 23,000), 242 (ε = 20,000) and 276 mμ (ε = 14,000); $\lambda_{max.}^{NaOH}$ 272 mμ (ε = 24,000); ν max. 3335, 3106 (NH), 1681 cm.$^{-1}$ (C=O). An ethanolic solution of the compound gave a red colour with aqueous ferric chloride. Evaporation of the chloroform solution of the neutral fraction under reduced pressure gave back 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (500 mg.) m.p. and mixed m.p. 180°.

(b) 3-Imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (2.1 g.) was heated on the steam bath for 3 hr. with acetic anhydride (20 c.c.). The cooled solution was treated with water (20 c.c.) and evaporated to dryness under

reduced pressure. The solid residue was taken up in chloroform (50 c.c.) and the solution washed with aqueous sodium hydroxide (3 x 30 c.c.; 2N), water and dried (Na_2SO_4). Acidification of the combined alkaline phase and isolation using chloroform gave 3-acetylimino--4-methyl-5-oxo-1,2-diphenylpyrazolidine (850 mg.) separating from tetrahydrofuran-n-hexane as prisms, m.p. and mixed m.p. 188-189°. 3-Acetylimino-4-methyl--5-oxo-1,2-diphenylpyrazolidine dissolved in aqueous sodium carbonate but was recovered unchanged upon acidification after 2 hr. reflux. When a solution of the compound (250 mg.) in aqueous sodium hydroxide (30 c.c.; 5%) was refluxed for 5 hr. the neutral fraction yielded 3-imino-4-methyl-5-oxo-1,2-diphenylpyrazolidine (150 mg.) m.p. and mixed m.p. 180° and the acid fraction unchanged acetyl compound (80 mg.) m.p. and mixed m.p. 189°.

5-Acetoxy-3-acetylimino-4-methyl-1,2-diphenyl-pyrazoline. - (a) The chloroformic neutral fraction from the action of acetic anhydride on 3-imino-4-methyl--5-oxo-1,2-diphenylpyrazolidine was evaporated to dryness and the residue crystallised from tetrahydrofuran-n--hexane to give 3-imino-4-methyl-5-oxo-1,2-diphenyl-pyrazolidine (400 mg.) m.p. and mixed m.p. 179-180° as

the component of lesser solubility. Concentration of the mother liquors gave 5-acetoxy-3-acetylimino-4-methyl-1,2-diphenylpyrazoline (40 mg.) which separated from chloroform as prisms, m.p. 166-167°.

Found: C,68.2; H,5.2%

$C_{20}H_{19}O_3N_3$ requires: C,68.75; H,5.5%

$\lambda^{EtOH}_{max.}$ 209 (ε = 18,000) 246 (ε = 12,000) and 286 mu (ε = 12,000); $\lambda^{NaOH}_{max.}$ 228 (ε = 49,000) and 278 mu (ε = 17,000); $\lambda^{HCl}_{max.}$ 203 (ε = 18,000), 210 (ε = 11,000) and 257 mu (ε = 15,000); ν max. 1725, 1710 and 1767 $cm.^{-1}$ (CO groups).

3-Acetylimino-4-cyclohexyl-5-oxo-1,2-diphenylpyrazolidine. - A solution of 4-cyclohexyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (220 mg.) in acetic anhydride (10 c.c.) was heated on the steam bath for 4 hr. Water was added to the hot solution which on cooling afforded 3-acetylimino-4-cyclohexyl-5-oxo-1,2-diphenylpyrazolidine (150 mg.) as needles, m.p. 296-300°. On recrystallisation from tetrahydrofuran-petroleum ether the acetate crystallised as prisms, m.p.302-304°.

Found: C,73.47; H,6.98%

$C_{23}H_{23}O_2N_3$ requires: C,73.57; H,6.7%

λ^{EtOH}_{max} 206 (ε = 21,000), 251 (ε = 13,000) and 278 mu (ε = 13,000); $\lambda^{HCl}_{max.}$ 206 (ε = 18,000) 250 (ε = 11,000)

and 280 mu (ε = 11,000); $\lambda_{max.}^{NaOH}$ 277 mu (ε = 19,000) and $\lambda_{inflex.}^{NaOH}$ 230 mu (ε = 10,000).

$\nu_{max.}$ 3125 (NH) and 1704 $cm.^{-1}$ (CO); $\nu_{max.}^{CHCl_3}$ 3145 (NH) and 1709 (CO).

4-Acetylamino-3-imino-5-oxo-1,2-diphenylpyrazolidine. - (a) A solution of 3,4-diamino-5-oxo-1,2-diphenylpyrazoline (350 mg.) in acetic anhydride (20 c.c.) was heated on the steam bath for 1 hr. Water was added and the solution evaporated to dryness under reduced pressure. The residue was dissolved in chloroform and the chloroform solution washed with aqueous sodium hydroxide solution (2 x 50 c.c.; 2N), water and dried (Na_2SO_4). Evaporation of the chloroform solution and crystallisation of the residue from chloroform-ethanol gave 4-acetylamino-3--imino-5-oxo-1,2-diphenylpyrazolidine (260 mg.) as colourless needles, m.p. 261-262°.

Found: C,66.15; H,5.38%

$C_{17}H_{16}O_2N_4$ requires: C,66.22; H,5.23%

$\lambda_{max.}^{EtOH}$ 206 (ε = 24,000) and 257 mu (ε = 24,000); $\lambda_{max.}^{NaOH}$ 256 mu (ε = 22,000); $\lambda_{max.}^{HCl}$ 206 (ε = 26,000) and 254 mu (ε = 23,000).

ν max. 3333, 3226 (both NH), 1689 (C=O) and 1669 $cm.^{-1}$ (CO).

An ethanolic solution of the compound gave a brown colour

with aqueous ferric chloride. The monoacetate was recovered after 5 hr. reflux in xylene.

(b) A solution of 3,4-diamino-5-oxo-1,2-diphenylpyrazoline (250 mg.) in acetic anhydride (10 c.c.) was refluxed for 1 hr. Methanol was added and the solution evaporated to dryness under reduced pressure. Working up as in (a), 4-acetylamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (150 mg.) m.p. and mixed m.p. 261-262° was obtained.

(c) To a stirred solution of 3,4-diamino-5-oxo-1,2-diphenylpyrazoline (260 mg.) in chloroform (25 c.c.) at room temperature a solution of acetyl chloride (5 c.c.) in chloroform (15 c.c.) was added dropwise over 30 min. The solution was stirred for a further hour and the chloroform solution washed with aqueous sodium hydroxide (3 x 30 c.c.; 2N), water and the dried (Na_2SO_4) solution evaporated to dryness under reduced pressure. Crystallisation of the residue from chloroform-methanol gave 4-acetylamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (100 mg.) m.p. and mixed m.p. 260-261°.

4-Formylamino-3-imino-5-oxo-1,2-diphenylpyrazolidine. - A solution of 3,4-diamino-5-oxo-1,2-diphenylpyrazoline (330 mg.) in formic acid (3 c.c.) was heated on the steam bath for 2 hr. The cooled solution was

made just alkaline by the addition of dilute aqueous sodium hydroxide and the solution was extracted with chloroform. The chloroform extract was washed with water and the dried (Na_2SO_4) solution evaporated to dryness under reduced pressure. Crystallisation of the residue from ethanol-petroleum ether gave 4-formylamino--3-imino-5-oxo-1,2-diphenylpyrazolidine (210 mg.) as colourless needles, m.p. 182-183°.

Found: C,64.43; H,5.24%

$C_{16}H_{14}O_2N_4 + 0.5\ CH_3CH_2OH$ requires: C,64.34; H,5.36%

$\lambda_{max.}^{EtOH}$ 206 (ε = 20,000) and 259 mu (ε= 20,500); $\lambda_{max.}^{NaOH}$ 256 mu (ε= 18,000).

ν max. 3534, 3175 (both NH) and 1672 $cm.^{-1}$ (C=O); $\nu_{max.}^{CHCl_3}$ 3333, 3175 (both NH) and 1681 $cm.^{-1}$ (C = O).

4-Formylamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (120 mg.) m.p. and mixed m.p. 180-181° was recovered unchanged after being refluxed for 7 hr. with excess formic acid.

3,4-Diacetylamino-5-oxo-1,2-diphenylpyrazoline. - A solution of 4-acetylamino-3-imino-5-oxo-1,2-diphenylpyrazolidine (100 mg.) in chloroform (10 c.c.) and redistilled acetyl chloride was refluxed for 4 hr. Water was added cautiously to the cooled solution and then

extracted with chloroform. The chloroform extract was then washed with aqueous sodium bicarbonate solution, water and the dried (Na_2SO_4) extract evaporated to dryness under reduced pressure. Crystallisation of the solid residue from ethanol-petroleum ether gave 3,4-diacetylamino-5-oxo-1,2-diphenylpyrazoline (70 mg.) as needles, m.p. 222-223°.

Found: C,64.51; H,5.66%.

C,64.45; H,5.55%

$C_{19}H_{18}O_3N_4$ + 0.5 CH_3CH_2OH requires: C,64.34; H,5.63%

$\lambda^{EtOH}_{max.}$ 207 (ε = 22,000) and 276 mu (ε = 15,000); $\lambda^{NaOH}_{max.}$ 231 (ε = 14,000) and 278 mu (ε = 21,000).

ν max. 3390, 3155 (both NH), 1709 (C=O) and 1631 $cm.^{-1}$;

$\nu^{CHCl_3}_{max.}$ 3390, 3226 (both NH), 1709 (C=O) and 1642 $cm.^{-1}$.

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SUMMARY

Section I.

Cyclisation of cyanoacetylhydrazobenzene (LXVI) or the reaction of ethyl cyanoacetate with hydrazobenzene gave 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) and its pp'-dimethyl derivative (LXVIII). (LXV) and its 4-methyl derivative (LXX) were best prepared by the action of potassium cyanide on the appropriate α-haloacylhydrazobenzene. Ring opening studies have been made on 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV), which has also been converted into 3,5-dioxo- 1,2-diphenylpyrazolidine (XIV). Ethanolic hydrochloric acid hydrolysis of (LXV) and (XIV) opened the pyrazolidine ring giving the same products, namely N-(β-carboxyacetyl)-hydrazobenzene (LXXII; R = H) and its ethyl ester (LXXII; R = Et); the latter compound was cyclised to (XIV) using alkali. 3-Imino--5-oxo-1,2-diphenylpyrazolidine (LXV) condensed with cyclohexanone giving 4-cyclohexenyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (LXXIV) which on catalytic hydrogenation yielded 4-cyclohexyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (LXXV). Acid treatment of the latter converted it into the corresponding 3,5-dioxo-compound. The 4-isonitroso derivative (LXXIX) and the 4-phenylazo derivative (LXXX) of 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) were also prepared. Reduction of the former gave 3,4--diamino-5-oxo-1,2-diphenylpyrazoline (LXXXIb) which on condensation with diacetyl and benzil gave 5,6-dimethyl-3-oxo-1,2-diphenylpyrazolo-[2,3b]-pyridazine and 3-oxo-1,2,5,6-tetraphenyl-

pyrazolo-[2,3b]-pyridazine respectively.

Section II.

Acetylation of 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) using acetic anhydride gave 3-acetylimino-5-oxo-1,2--diphenylpyrazolidine (XCI) and 4-acetyl-3-imino-5-oxo-1,2-diphenyl-pyrazolidine (LXXXIX). The latter could also be prepared exclusively using acetyl chloride-pyridine. (LXV) was also converted into its N-butyryl derivative. The N-acetyl derivative (XCI) was readily hydrolysed to (LXV) using alkali but the 4-acetyl derivative (LXXXIX) was stable to alkaline hydrolysis. Acetic anhydride on 3-imino-5-oxo-1,2-diphenylpyrazolidine (LXV) also gave a mixed crystal of (LXV) and (XCI). The N-monoacetyl compound (XCI) was acidic and on treatment with diazomethane N-methylation took place yielding 3-acetylmethylamino-5-oxo-1,2-diphenylpyrazoline (CV); the latter on alkaline hydrolysis gave 3-methylimino-5-oxo-1,2-diphenylpyrazolidine (CVI). 4-Cyano-acetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine (CX) was also prepared and acid hydrolysis converted it into 4-acetyl-3-imino--5-oxo-1,2-diphenylpyrazolidine (LXXXIX). On treatment with alkali 4-cyanoacetyl-3-imino-5-oxo-1,2-diphenylpyrazolidine was cyclised to the isomeric 6-amino-4-hydroxy-3-oxo-1,2-diphenyl-pyrazolido-[2,3b]-pyridine (CXI). The latter on treatment with diazomethane afforded 6-amino-4-methoxy-3-oxo-1,2-diphenylpyrazo-

lido-[2,3b]-pyridine (CXIII) which was also formed by successive reaction of (CX) with diazomethane to give 3-imino-4-(α-methoxy-β-cyanovinyl)-5-oxo-1,2-diphenylpyrazolidine (CXII), followed by heating to 200°. 3-Imino-4-methyl-5-oxo-1,2-diphenyl-pyrazolidine (LXX) on acetylation gave an N-acetyl derivative (CXV) and 5-acetoxy-3-acetylimino-4-methyl-1,2-diphenylpyrazoline (CXVIII). Both (CXV) and (CXVIII) on alkaline hydrolysis yielded the parent pyrazolidine (LXX). 3-Acetylimino-4-cyclohexyl-5--oxo-1,2-diphenylpyrazolidine (CXXII) was also prepared. Treatment of 3,4-diamino-5-oxo-1,2-diphenylpyrazoline (LXXXIb) with acetic anhydride gave 4-acetylamino-3-imino-5-oxo-1,2-diphenyl-pyrazolidine (CXXIV), which could also be prepared by the reaction of the diamino-compound (LXXXIb) with acetyl chloride at room temperature. On refluxing (CXXIV) with acetyl chloride, 3,4--diacetylamino-5-oxo-1,2-diphenylpyrazoline (CXXVII) was produced. 4-Formylamino-3-imino-5-oxo-1,2-diphenylpyrazolidine was obtained from the action of formic acid on (LXXIb).

N.B. (Roman numerals) refer to the corresponding compounds in Ph.D. Thesis 1959.

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