THE PREPARATION AND PROPERTIES OF SOME PYRAZOLO|1,5-c|PYRIMIDINES AND PYRAZOLO|1,5-c|QUINAZOLINES

Thesis presented for the Degree of Master of Philosophy

by Peter Robert Morris

Department of Pharmacy

The University of Aston in Birmingham

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PYRAZOLO|1,5-c|PYRIMIDINES

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Summary

Four types of pyrazolopyrimidines can theoretically exist. Pyrazolo |3,4-d| pyrimidines and pyrazolo|4,3-d|pyrimidines do not contain a bridgehead nitrogen atom, and their syntheses and properties are reported elsewhere. Pyrazolo|1,5-a|pyrimidines and pyrazolo|1,5-c|pyrimidines contain a nitrogen atom, common to both the pyrazole and pyrimidine rings. The syntheses and properties of pyrazolo|1,5-a|pyrimidines are comprehensively reviewed here. Pyrazolo|1,5-c|pyrimidines were, at the commencement of this work, unreported in the literature (the ring index refers to this heterocycle, but the subject of the reference therein is a pyrazolo|1,5-a| pyrimidine) but in 1972 a synthesis of this ring system was reported and some electrophilic substitution reactions were mentioned. These are reported in the introduction.

The preparations of pyrazolo|1,5-a|quinazolines and pyrazolo|1,5-c| quinazolines, the tricyclic analogues of the fused pyrimidines mentioned above, are reviewed here, partly because of their similarity to the pyrazolopyrimidines structurally, but also because of the biological activities (psychomotor depression and antibacterial activity) reported for the|1,5-c|series.

Many references to the preparation and properties of pyrazolo|1,5-a| pyrimidines mention biological activity; antiimflammatory, analgesic, anti-tumour activities are reported. Derivatives of pyrazoles from which these compounds are synthesised have for many years been recognised to possess anti-inflammatory activity but anti-tumour properties have also been attributed to some derivatives[123], which include the fused pyrazolo|3,4-d| pyrimidines[124]. Pyrazolo|4,3-d|pyrimidines also possess biological activity and their syntheses are reported elsewhere.

It seemed desirable then to inovate the synthesis of pyrazolo|1,5-c| pyrimidines for two reasons; a) this heterocycle was unreported in the literature b) since other pyrazolopyrimidines possess biological activity, the possibility of activity in the pyrazolo|1,5-c|pyrimidines should be investigated. (Biological reports have not yet been received).

The great activity of the C- and N- glycosides of many heterocyclic compounds suggests that the ribosylation of pyrazolo|1,5-c|pyrimidines and pyrazolo|1,5-c|quinazolines might produce compounds of greater potency, and therefore, the activity of these heterocycles to electrophilic reagents was investigated experimentally.

A successful route to pyrazolo|1,5-c|pyrimidines from 3-formyl-5-methylpyrazole was obtained. A route from 4-methylpyrimidines was less successful. 2-methylpyrazolo|1,5-c|quinazoline was prepared essentially by methods reported in the literature and the novel 2-hydroxy derivative was obtained by a similar procedure.

Electrophilic substitution was possible only with the stronger electrophiles ($\overset{+}{N}O_2$, Br_2, ^{+}CHO). 2-Hydroxy pyrazolo|1,5-c|quinazoline appeared to be less reactive to electrophiles than the 2-methyl derivative, and was less stable in dilute acid. Ring cleavage occurred over a period of thirty minutes.

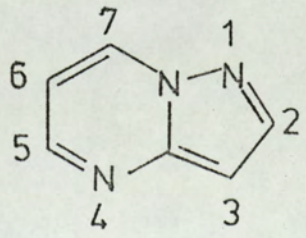
INTRODUCTION

PYRAZOLO|1,5-a|PYRIMIDINES

SYNTHESIS

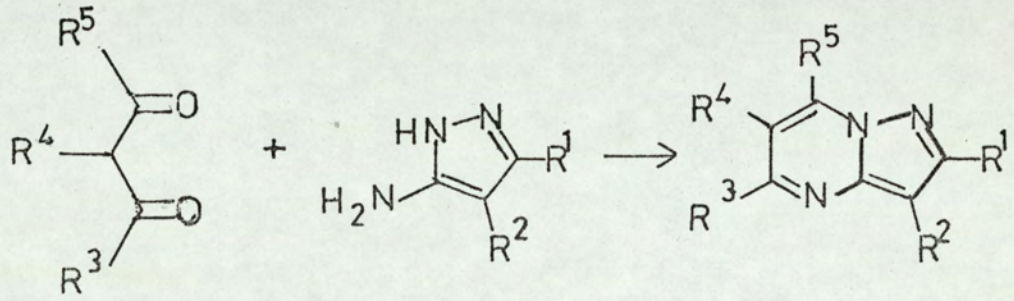
This ring system has been described in the early literature as a pyrazolo|2,3-a|pyrimidine. More recent literature has adopted the title pyrazolo|1,5-a|pyrimidine to describe the method of fusion of the pyrazole and pyrimidine ring. The latter method makes use of the lower initial number to describe the nitrogen atom at the bridgehead and is now universally adopted, and obeys I.U.P.A.C. rule A.22.

Routes to pyrazolo|1,5-a|pyrimidines can be envisaged which involve the cyclisation of a suitable pyrimidine having an amino group on a 2-carbon chain at C-2 or of a 2-substituted-1-amino pyrimidinone. The use of these types of routes has not been reported. Several methods are described in the literature which involve the condensation of 1,3-bi-functional electrophiles, or potential electrophiles with a 3-aminopyrazole or 3-aminopyrazol-5-one, or with hydrazine if one electrophilic centre is contained in a nitrile group, to afford the pyrazolo|1,5-a|pyrimidines and the 2-hydroxyderivatives. Cyanoacetylhydrazines have also condensed with 1,3-diketones under certain conditions to afford 2-hydroxypyrazolo|1,5-a|pyrimidines usually *via* an isolated hydrazone.



5,7-Dialkylpyrazolo|1,5-a|pyrimidines

The condensation of several 1,3-diketones with 3-aminopyrazoles has afforded 5,7-dialkylpyrazolo|1,5-a|pyrimidines. In acidic, neutral or basic media, acetylacetone[1,2,3], , and dibenzoylmethane[4], produced 5,7-dimethyl- and 5,7-diphenyl- pyrazolopyrimidines (I). 3-Acetamido-, 3-ethyl-, 3-methyl- and 3-phenylazo-pentan-2,4-diones have also been employed to give good yields of the respective 6-substituted pyrazolo-pyrimidines (I; $R^4 = CH_3CONH, C_2H_5, CH_3, PhN_2$)[5,6,7],



(I)

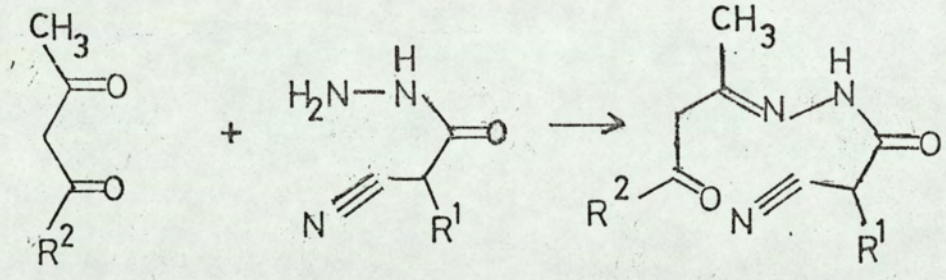
The orientation of the 5- and 7-substituents of the pyrazolo|1,5-a|pyrimidine obtained from the condensation of benzoylacetone and 3-amino pyrazoles was not ascertained[4], although electronic considerations might suggest a preponderance of the 5-methyl-7-phenyl isomer.

3-Methylmercapto-, 3-cyanomethyl-, 3-phenyl-, 4-cyano- and 4-ethoxy-carbonyl- pyrazoles have been used successfully in this reaction[1-4,6,8], 4-cyano- and 4-ethoxycarbonyl- pyrazoles have also been condensed with 2-formylcyclohexanone to afford the respective 6,7-tetramethylenepyrazolo|1,5-a pyrimidines in good yield[9].

3-Aminopyrazol-5-one with benzoyl- and propionyl acetylacetones acetylacetone itself in acidic media, afforded the respective 2-hydroxy-pyrazolo|1,5-a|pyrimidines (4;R^1=H) in good yield[5,10], but acetylacetone in basic conditions gave 4,6-dimethyl-3-hydroxyprazolo|3,4-b|pyridine which on nitrosation gave an unstable compound(unlike the pyrazolo|1,5-a| pyrimidines; see chemical properties, page 12)[3,10].

2-Hydroxy-7-methyl- and-7-phenyl- pyrazolo|1,5-a|pyrimidines (1;R^1=OH, R^2=R^3=R^4=H, R^5=CH_3,Ph) were successfully obtained by the reaction of 1,1-dimethoxy-3-hydroxybutane and benzoylacetaldehyde respectively, in acidic media[5,11].

Cyanoacetylhydrazines (2) with acetylacetone, benzoylacetone, m-nitrobenzoylacetone and propionylacetone afforded the cyanoacetylhydrazones (3) which were cyclised by heat to 5,7-dialkyl-2-hydroxypyrazolo|1,5-a| pyrimidines (4; R_2=CH_3,Ph,(mNO_2)C_6H_4,C_2H_5)[5,10].



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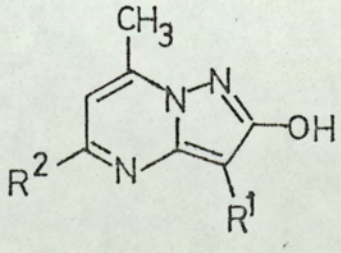
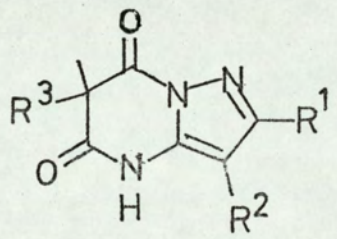


(4)

The condensation of propionylacetone with cyanoacetylhydrazines and 3-aminopyrazol-5-ones was reported to yield only one isomer[5].

Pyrazolo|1,5-a|pyrimidin-5,7(4H,6H)-diones

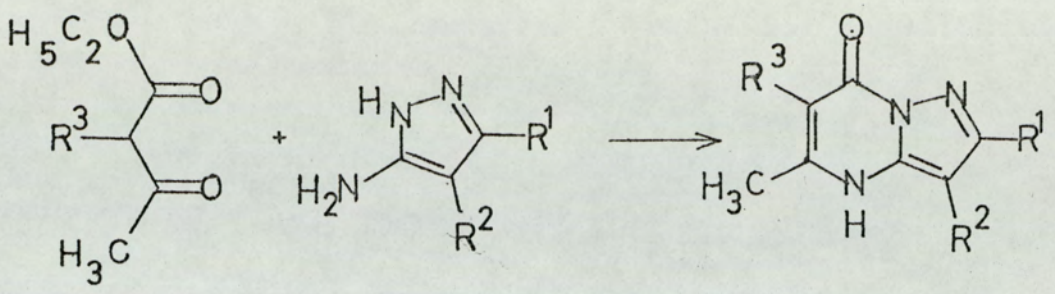
The condensations of diethyl malonate and diethyl 2-phenylazomalonate with 3-amino-5-phenylpyrazole, 3-amino-4-ethoxycarbonylpyrazole and 3-aminopyrazole, to afford 2-phenylpyrazolo|1,5-a|pyrimidin-5,7(4H,6H)-dione (5;R^1=Ph, R^2=H, R^3=H), and the 3-ethoxycarbonyl-6-phenylazo derivative (5; R^1=H, R^2=$COOC_2H_5$, R^3=Ph-N=N), the 3-ethoxycarbonyl derivative (5;R^1=R^3=H, R^2=$COOC_2H_5$) and pyrazolo|1,5-a|pyrimidin-5,7(4H,6H)-dione (5;R^1=R^2=R^3=H) have been reported[1,2,6,12].



(5)

5(7)-alkylpyrazolo|1,5-a|pyrimidin-7(5)(4H)-ones.

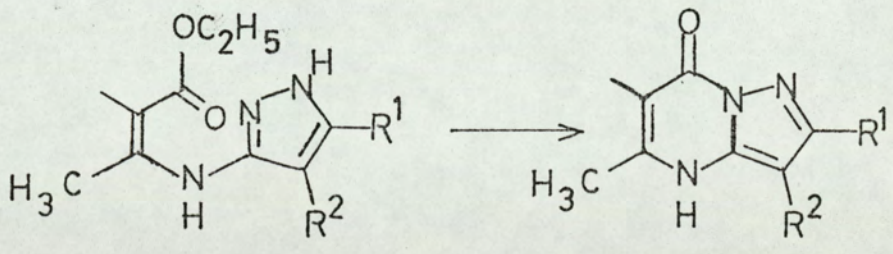
5-Methylpyrazolo|1,5-a|pyrimidin-7(4H)-ones (6) only, have been isolated from the reaction of ethyl acetoacetates with 3-aminopyrazoles[1,2,3,6,7,10,13-19]. 2-methyl-, 2-ethyl-, 2-acetamido-, 2-amino-, 2-(nitrophenyl) diazo- and 2-(halogenophenyl)diazo-acetoacetates have been condensed in the same way to afford the respective 6-substituted pyrazolo|1,5-a|pyrimidinones (6;R^3=CH_3,C_2H_5, CH_3CONH,NH_2,$\underline{m}(NO_2)C_6H_4N_2$,$(Cl)C_6H_4N_2$)[6,7]. 2- and 3-substituted pyrazolo|1,5-a|pyrimidinones were derived from the pyrazole used and include 2-phenyl, 2-methylthio, 2-hydroxyethoxy, 2-hydroxy, 3-methyl, 3-cyano and 3-ethoxycarbonyl derivatives.



(6)

The reaction of 3-aminopyrazol-5-one with ethylacetoacetate in base also yielded pyrazolo|1,5-a|pyrimidines (not pyrazolo|3,4-b|pyridines, see page 3) [5,10,27].

Studies by Checchi[3,18] on the relative reactivities of the exocyclic and endocyclic amine groups of 3-aminopyrazoles allows a prediction of the nature of the final products, while the isolation of the pyrazolylamino-crotonates (7) [1,2,3,17,18], followed by cyclization to pyrazolo|1,5-a| pyrimidinones, suggests the reaction mechanism, and spectroscopic evidence[1,17, 20-22], the nature of the final products.

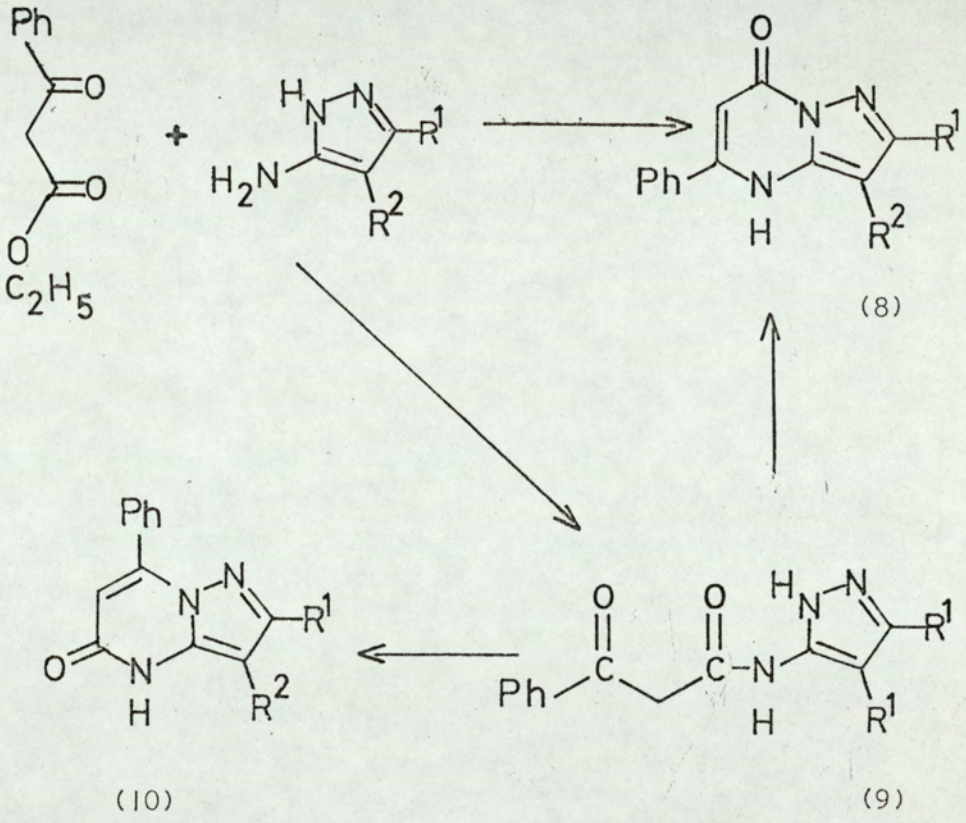


(7)

Orientation specificity was not observed in the products obtained by the condensation of ethyl acetoacetate with 3-anilino-5-methyl- and 4-ethoxycarbonyl-3,5-diamino-pyrazoles. Both 5-methyl- and 7-methyl- pyrazolo

|1,5-a|pyrimidin-5 and 7 (4H)-ones were obtained[23].

Similarly, ethyl benzoylacetate and 3-aminopyrazoles gave 5-phenylpyrazolo|1,5-a|pyrimidin-7(4H)-ones[20] (8) and 3-benzoylacetamidopyrazoles (9) which were cyclized to 7-phenylpyrazolo|1,5-a|pyrimidin-5(4H)-ones (10) in acidic ethanol. The benzoylacetamido pyrazoles(9) by means of a thermal rearrangement at 220° afforded the 5-phenyl isomer(8)[3,18,19].

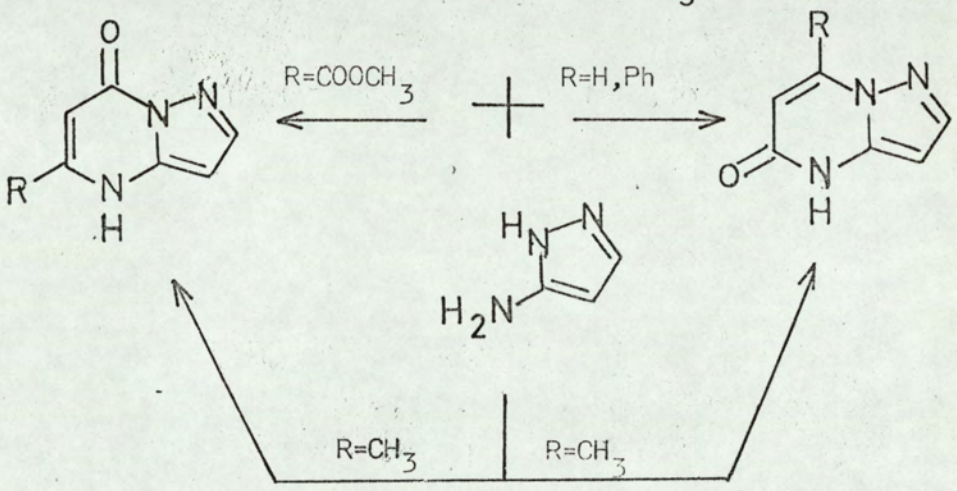


The 7-phenyl isomer(10) has been identified by the cyclization of its 5-hydrazino derivative in triethylorthoformate to a triazolopyrazolopyrimidine[20,21]. The 5-phenyl isomer (8) has been prepared by a proposed

unequivocal synthetic route[19].

3-Aminopyrazole has been condensed with the acetylenic esters, methyl propiolate, methyl phenylpropiolate, dimethyl acetylenedicarboxylate and methyl tetrolate (II, R=H, $COOCH_3$ and CH_3 respectively) to give 7(5)-alkyl(aryl, H)pyrazolo|1,5-a|pyrimidin-5(7)(4H)-ones[19,20,21].

(II)



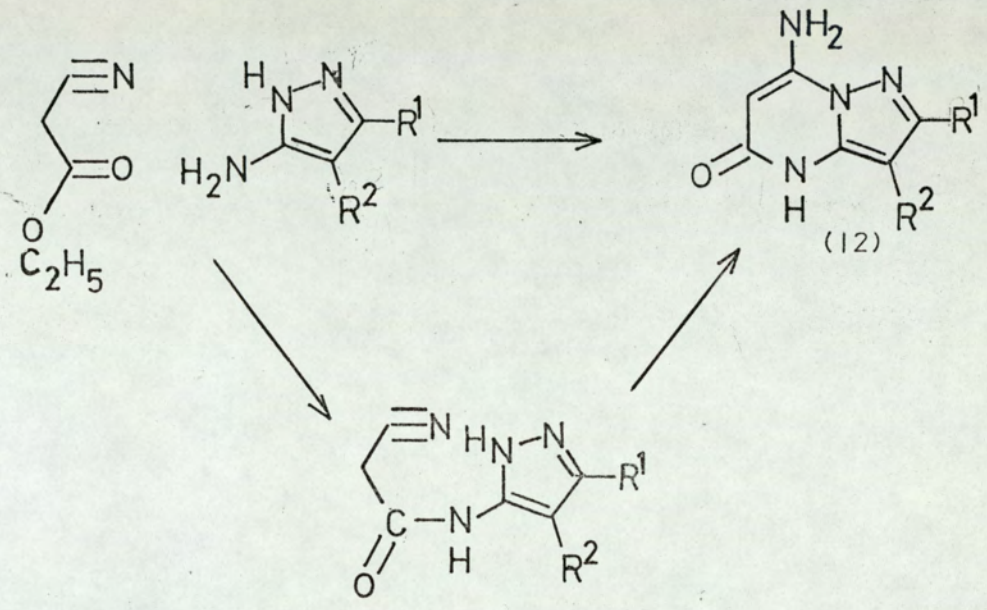
Infrared and ultraviolet absorption spectra show that these compounds exist in the keto tautomeric form[19,20].

Diketene, behaving as a 1,3-diketone, has also been condensed with 3-aminopyrazolones and cyanoacetylhydrazines (see page 3) to afford 5- and 7-methylpyrazolo|1,5-a|pyrimidin-7 and 5(4H)-ones[10,24,25,26].

7-Aminopyrazolo|1,5-a|pyrimidin-5(4H)-ones.

The condensation of ethyl cyanoacetate with 3-aminopyrazole in neutral and acidic conditionshas led to the isolation of 7-aminopyrazolo|1,5-a|pyrimidin-5(4H)-one (12; $R^1=R^2=H$) in good yield[1,2]. The intermediate

3-cyanoacetamidopyrazole (13) characterised by infrared data, has been isolated and cyclized in cold base[1,12] and hot acetic acid[1] to the pyrazolopyrimidine (12). Substituents at C-3 include; cyano, ethoxycarbonyl and methyl and at C-2 include methyl and phenyl groups[1,2,7,28,29].



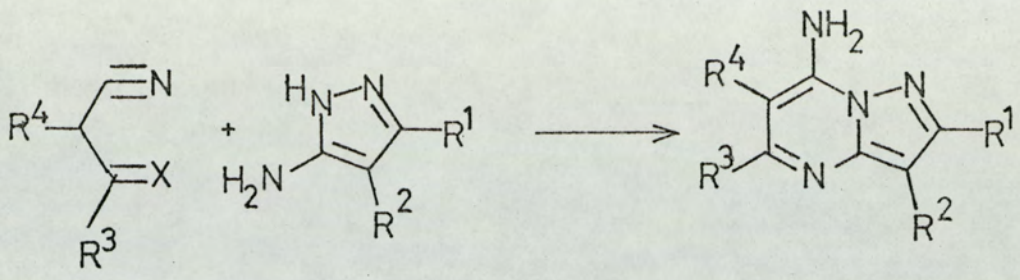
(12)

(13)

The 2-hydroxy derivative (12; R^1=OH, R^2=H) was prepared by the cyanoacetylation of 3-aminopyrazol-5-one using 1-cyanoacetyl-3,5-dimethylpyrazole as the acylating agent followed by a thermally induced cyclization of the resulting 3-cyanoacetamidopyrazol-5-one (13; R^1=OH, R^2=H)[10].

7-Amino-5-alkylpyrazolo|1,5-a|pyrimidines

β-keto and β-iminonitriles (14; X=O, NH, R^3=C_2H_5,Ph,CH_3 H, R^4=CH_3,C_3H_7, Ph,H) with 3-aminopyrazoles[28,30-35] in acidic conditions gave 7-amino-5-alkylpyrazolo|1,5-a|pyrimidines in excellent yields.



(14) (15)

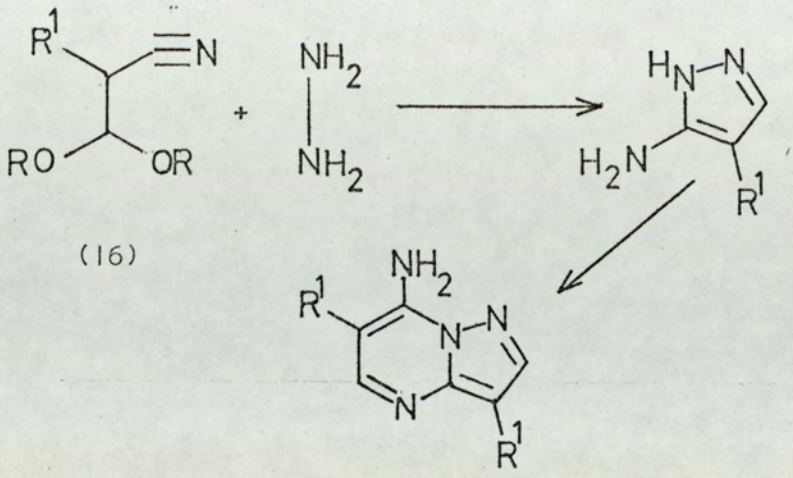
(Substituents at C-2 and -3 can be -methyl, -ethyl or -phenyl). 5-Alkyl-7-amino-3-bromopyrazolo|1,5-a|pyrimidines have also been prepared[35].

Hydrazine and the β-ketonitrile or β-iminonitrile in the molar ratio 1:2, also gave the required pyrazolopyrimidines via an intermediate pyrazole, the final product (15) being symmetrically disubstituted (R^2=R^4, R^1=R^3)[28,35-37].

7-Amino-6-alkylpyrazolo|1,5-a|pyrimidines

2-Dialkoxymethylpropionitriles (16) behave in acidic solution as 2-methylcyanoacetaldehyde. Condensations of these propionitriles and phenylcyanoacetaldehyde with hydrazine hydrochloride proceed via an intermediate pyrazole to 7-amino-3,6-dimethyl- and -3,6-diphenyl-pyrazolo|1,5-a|pyrimidines respectively (17; R^1=CH_3 and Ph)[40,41,44,47]. 3-Aminopyrazoles have also been used to prepare several 2- and 3-alkyl derivatives of (17)[28,43,46,39], the parent compound (17; R^1=H)[28,42] and 2-hydroxy-7-methylpyrazolo|1,5-a|pyrimidines.

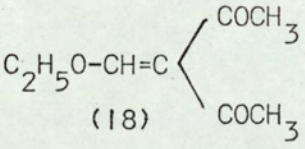
Under more severe conditions dialkoxymethylpropionitriles have been condensed with 3-amino-1-methylpyrazoles to give 1,6-dimethylpyrazolo|1,5-a|pyrimidin-7(1H)-ones[45,47].



(16)

(17)

An interesting series of reactions has been reported by Takamizawa and others, in which the 2-(ethoxyalkylidene)-1,3-bifunctional electrophiles (18-23) were condensed with 3-aminopyrazoles to give good yields of pyrazolo|1,5-a|pyrimidines having electrophilic groups at carbon 6 and either alkyl, keto or amino groups at carbon 7. Position 5 may also be substituted by alkyl groups depending on the alkylidene starting material used. The intermediates (24) were isolated in many cases.



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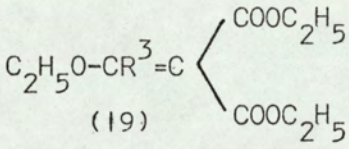

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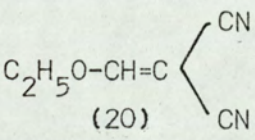

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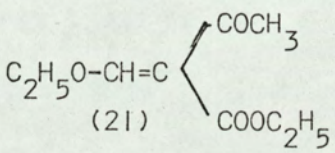

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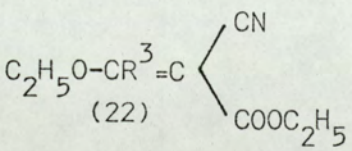

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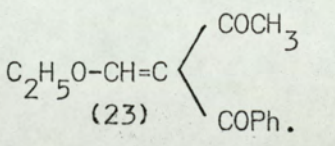
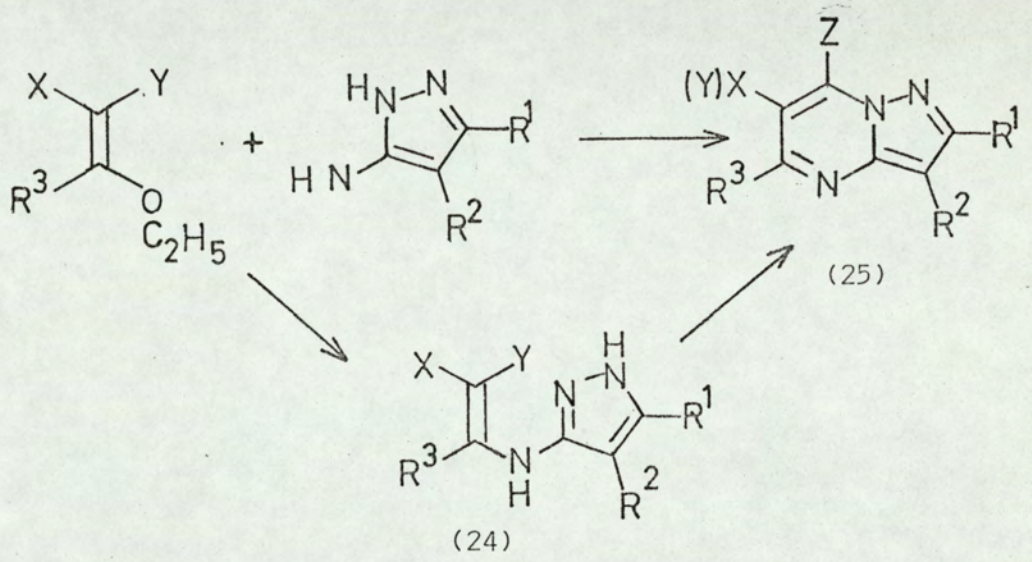


(23)

(z=NH_2, OH, CH_3 or Ph).

Single products were obtained from the reaction of compounds (18-20) with 3-aminopyrazoles[22,49,53] although Ridi[51] reported the isolation of

a pyrazolo|3,4-b|pyridine in 5% yield. The ethoxyalkylidenes, (21 and 23), containing dissimilar electrophilic centres condensed to give 6-ethoxycarbonyl-2-hydroxy-7-methyl- and 6-acetyl-7-phenyl-pyrazolo|1,5-a|pyrimidines(25; z=CH_3, Ph) respectively, as the major products[22,51],mixed products were obtained ,however, when ethyl 2-ethoxyalkylidenecyanoacetate (22) was used[22,28,48,49,50,52,54]. The pH of the cyclizing media influenced the proportions of the components in the mixture.



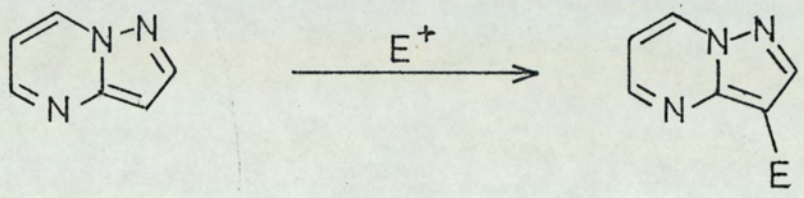
(25)

(24)

An interesting preparation of the parent heterocycle was reported by Khan and Lynch[54a]. 3-Aminopyrazole condensed with malondialdehyde (T.M.A) to afford pyrazolo|1,5-a|pyrimidine 3-Amino-4-cyano- and 3-amino-4-ethoxycarbonyl pyrazoles afforded the respective 3-substituted pyrazolo|1,5-a| pyrimidines but hydrolyses of these functional groups, followed by decarboxylates afforded, by ring cleavage and rearrangement pyrazolo|3,4-b|pyrimidine.

CHEMICAL PROPERTIES

Electrophilic Substitution



Nitration

5,7-Dimethylpyrazolo|1,5-a|pyrimidines have been nitrated successfully with fuming nitric acid in acetic acid. Nitration occurred in the 3 position [10,51]. (The yields of 3-nitro-7-aminopyrazolo|1,5-a|pyrimidines were not high, probably due to oxidation of the amino group. However the oxidation of 3-nitroso groups could offer a good route to these compounds[75].) Potassium nitrate and hydrochloric acid have also been used to effect nitration[60]. Reduction of the 3-nitro group has been accomplished with hydrogen in the presence of a palladium catalyst[10,63].

Nitrosation

7-aminopyrazolo|1,5-a|pyrimidines have been nitrosated at room temperature with mineral acid and sodium nitrite[62]. More severe conditions(40°C [3,10,18], and long periods at ambient temperature[5,10,62] have been employed to successfully nitrosate many 7-alkyl-, 7-amino-, and 7-hydroxy-, pyrazolo|1,5-a|pyrimidines.[5] Reduction of the nitroso group was accomplished as above[10,63] to yield the unstable amine, isolated as the acetyl derivative.

Halogenation

Chlorine and bromine in acetic acid have been employed to effect the halogenation of 5,7-dimethyl-2-hydroxypyrazolo|1,5-a|pyrimidine at C-3. Excess chlorine produced 3-chloro-5-chloromethyl-2-hydroxy-7-methylpyrazolo |1,5-a|pyrimidine, while phosphoryl chloride and phosphorous pentachloride effected in addition, a nucleophilic replacement of the 2-hydroxy group to give 2,3-dichloro-5,7-dimethylpyrazolo|1,5-a|pyrimidine[10].

Several 7-aminopyrazolo|1,5-a|pyrimidines have been brominated at position 3 with molecular bromine[64].

Diazocoupling

2-Hydroxypyrazolo|1,5-a|pyrimidines have been coupled successfully with benzene-, 4-ethoxybenzene- and 2-hydroxynaphthalene- diazonium chlorides[5,26,55], at carbon 3. Coupling at the hydroxy group of 5,7-dimethyl-3-ethyl-2-hydroxypyrazolo|1,5-a|pyrimidine, followed by rearrangement to afford the 3-aryldiazoalkyl derivative, has been reported[55]. The preparation of some biphenyl-4,4' bis(azopyrazolo|1,5-a|pyrimidines) has been reported[5].

Alkylation

3,6-Dimethylpyrazolo|1,5-a|pyrimidine-7(4H)-one, due to the existence of a -7(1H)-one tautomer, has been methylated at position 1 with methyl-iodide in a sealed tube at 140° [18]. Similar conditions have been used to prepare 4-alkyl-7-iminopyrazolo|1,5-a|pyrimidines[18,59,74], which in some cases have been hydrolysed to 4-alkylpyrazolo|1,5-a|pyrimidin-7(4H)-ones, otherwise inaccessible by alkylation of the parent-7(4H)-one[47,57]. Diazomethane was shown to effect 4-alkylation.[20]

Alkylation at position 3 of 2-hydroxy- and 2-phenyl-pyrazolo|1,5-a| pyrimidines was unsuccessful but cyanoethylation has been accomplished to afford 3-cyanoethyl-2-hydroxy-7-methyl-5-phenylpyrazolo|1,5-a|pyrimidine[58].

Acylation

Position 4 has been shown to be susceptible to electrophilic attack by acetyl chloride and acetic anhydride[47]. (However see reference[67])

Nucleophilic substitution

Nucleophilic substitution at C-2 and -7 has been reported. 7-Amino groups have been replaced by hydroxyl groups (with sodium hydroxide)[22] to afford pyrazolo|1,5-a|pyrimidine-7(4H)-ones[22,41,47,57,66,67] and 7-hydroxyl groups by chlorine atoms using phosphoryl chloride[66,68].

7-Chloropyrazolo|1,5-a|pyrimidines have been reacted with methylamine, dimethylamine, piperidine and hydrazine to afford the respective 7-amino compounds[20,21,69] but under certain conditions with hydrazine, ring cleavage has been effected to give a parent pyrazole[47].

Reduction with hydrogen and raney nickel of the 7-chloro compound in acetic acid afforded the parent heterocycle[66 69] while reduction in ethanol has resulted in ring cleavage[51].

2-Hydroxypyrazolo|1,5-a|pyrimidines reacted with phosphoryl bromide to give 2-bromopyrazolo|1,5-a|pyrimidines in good yield. The bromo-compounds when subjected to the conditions of an Ullman reaction were converted to 2-aminopyrazolo|1,5-a|pyrimidines[70].

Ring cleavage has been reported[71] when 2-phenylpyrazolo|1,5-a|pyrimidin-5,7(4H,6H)-dione was heated at 200-250° with simple aliphatic alcohols or ammonia, aniline, piperidine and morpholine to give 3-phenyl pyrazol-5-amidoacetic esters and amides respectively (See also Checchi[12])

Reactions of the side chains

7-Aminopyrazolo|1,5-a|pyrimidines behaved like aniline in the presence of acetyl chloride and chloracetyl chloride. Mono or di-acyl derivatives

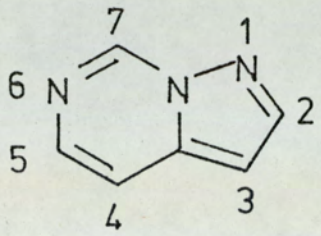
have been formed depending upon the nature of the substituent at carbon 6.[66, 67,72,73]. The chlorine group of the 7-chloracetamido compound is replaceable in the usual way by secondary amines[76].

7-Ethoxycarbamoylpyrazolo|1,5-a|pyrimidines are produced in good yield by the condensation of 7-aminopyrazolo|1,5-a|pyrimidines with ethyl chloroformate. The resulting carbamoates have been condensed with secondary amines and thioethanol to afford the respective amides and the thioester[77]. 2-Amino groups have been acylated and diazotised[70] and 2-hydroxyl groups have been acylated successfully with acetic anhydride[5,70] and alkylated with diazomethane or ethyl 4-toluene sulphonate[5,10,55]. Phosphorylation has also been accomplished[78].

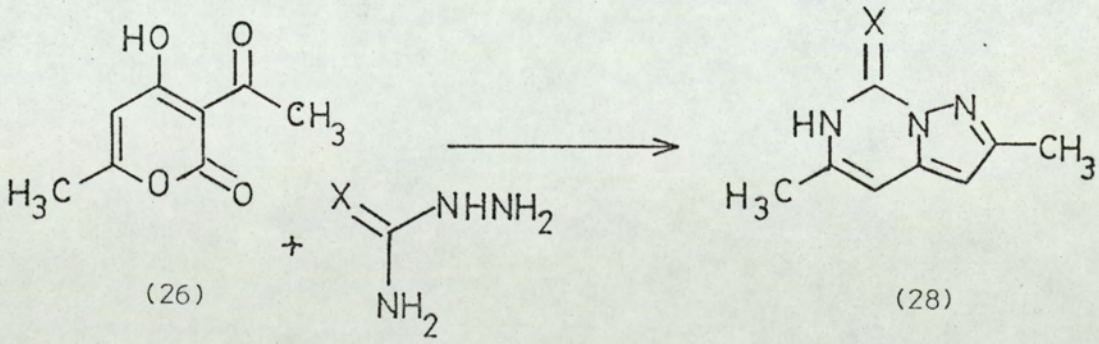
Hydrolysis reactions of esters and nitriles have been reported[1] and also decarboxylation of carboxylic acids[1,29,43] . (A 90% yield of the parent heterocycle was obtained by heating 7-amino-6-carboxy-2,3-dimethylpyrazolo |1,5-a|pyrimidine at 250° for 45 seconds[29]).

PYRAZOLO|1,5-c|PYRIMIDINES

SYNTHESIS



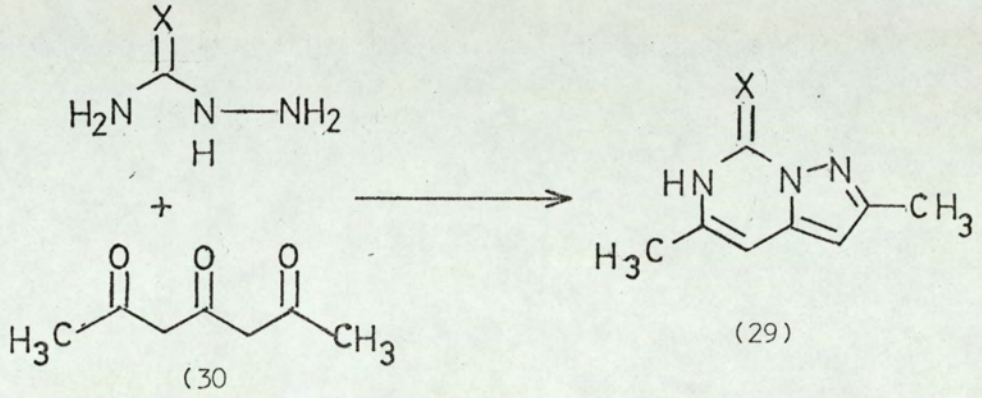
During the course of this work in 1972, this new ring system was prepared by Kranz et al[79], by the reaction of dehydracetic acid (26) with thiosemicarbazide, semicarbazide and aminoguanidine (27; x=O, S, NH_2), which gave 2,5-dimethylpyrazolo|1,5-c|pyrimidin-7(6H)-thione (28;x=S), 2,5-dimethylpyrazolo|1,5-c|pyrimidin-7(6H)-one (28;x=O) and 2,5-dimethyl-6,7-dihydro-7-iminopyrazolo|1,5-c|pyrimidine (28; x=NH).



(26) (27) (28)

Lutidones and 2,6-dimethyl-4-pyrone, isolated from the reaction of (26) and (27) accounted for a considerable proportion of the expected product, hence the yields of the pyrazolopyrimidine (28) were low.

A rationalization of the possible reaction mechanisms indicated that dehydracetic acid (26) might be reacting as a 1,3,5-triketone and in fact yields of the pyrazolopyrimidine (29) were improved when diacetylacetone (30) was used in place of dehydracetic acid.



(30)

(29)

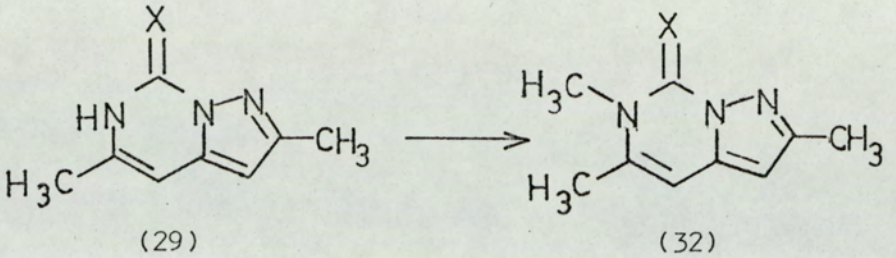
Nuclear magnetic resonance data are given which contain signals attributable to the 3, 4, and in the case of the reduced thio compound, the 7 proton, the chemical shifts of which correspond to those observed in this laboratory (see experimental section). The existence of structures tautomeric with (29) is acknowledged.

CHEMICAL PROPERTIES

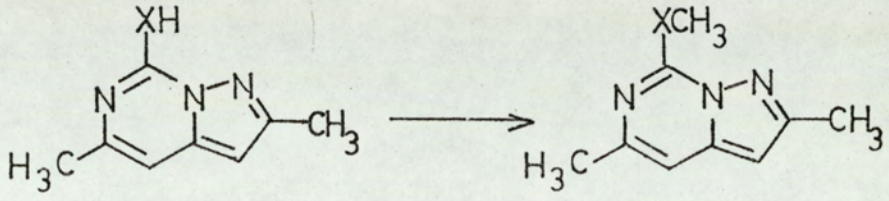
Electrophilic substitution

Methylation:

Tautomeric mixtures of the 6,7-dihydro compounds (29) and the free bases (31) might be expected, and in an attempt to demonstrate the percentage contribution of each tautomer to the resonance hybrid, alkylation experiments were performed[79].



(29) (32)



(31) (33)

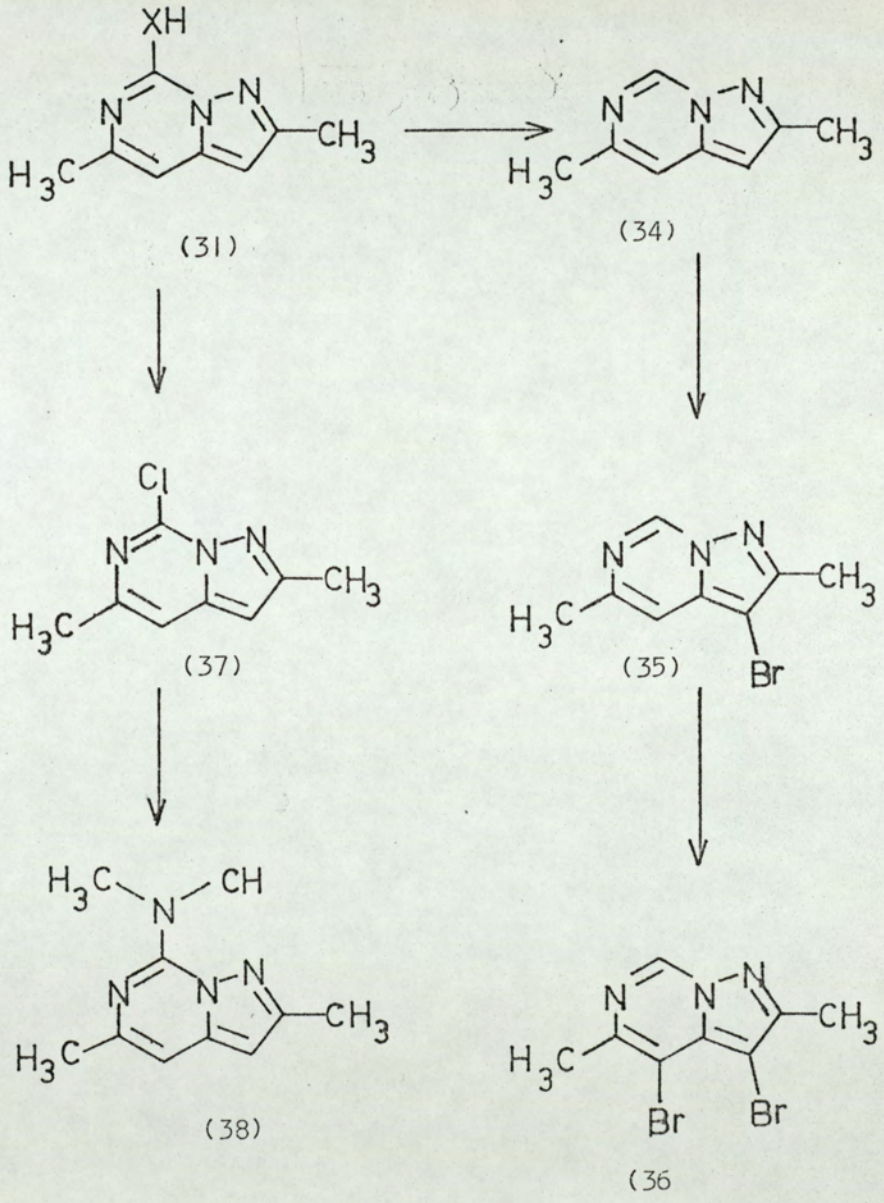
The 7-thio compound(29,31;X=S) with diazomethane gave predominantly the 7-methylmercapto compound (33;X=S, 75%) and some 6-methyl derivative (32;X=S, 15%). 2,5-Dimethyl-7-methylmercaptopyrazolo|1,5-c|pyrimidine , (33;X=S) was obtained in quantitative yield when dimethyl sulphate or methyl iodide were used in place of diazomethane.

High yields of 2,5,6-trimethylpyrazolo|1,5-c|pyrimidin-7(6H)-one (32; X=O) were isolated when methyl iodide or dimethyl sulphate were used to alkylate the 7-one (29; X=O) but low yields were obtained with diazomethane.

7-Amino-2,5-dimethylpyrazolo|1,5-c|pyrimidine(29,31; X=NH) was alkylated only with difficulty to give poor yields of the 6-methyl and

7-methylamino derivatives (32,33; X=NH) in equal proportions. Infrared, ultraviolet, nuclear magnetic resonance, and mass spectral data were given to support the proposed structures of the products. 1-Methyl compounds were apparently not isolated.

Bromination



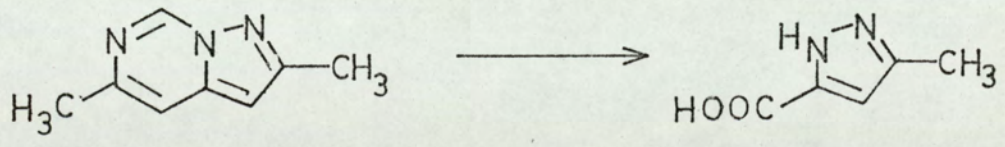
2,5-Dimethylpyrazolo|1,5-c|pyrimidine (34) obtained by the desulphurization of the 7-thio derivative (31; X=S) was successfully brominated with molecular bromine in the presence of triethylamine in chloroform, to afford 3-bromo-2,5-dimethylpyrazolo|1,5-c|pyrimidine in good yield (66%). (35). Further bromination at position 4 occurred when excess bromine was used, to afford the dibromo compound(36).

Nucleophilic Substitution

7-Chloro-2,5-dimethylpyrazolo|1,5-c|pyrimidine (37) was obtained in 30% yield, by the action of phosphoryl chloride on the 7-oxo compound (31; X=O).

The chloro group was replaced by diethylamine to afford the 7-diethylamino derivative (38) in excellent yield.

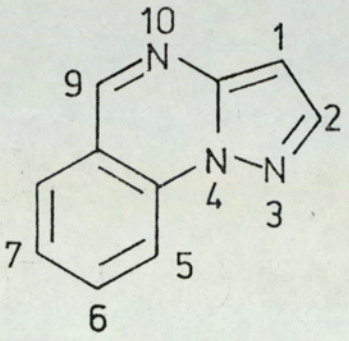
Reduction of 2,5-dimethylpyrazolo|1,5-c|pyrimidine-7-thiol (31;x=S) with raney nickel has already been mentioned and oxidation of 2,5-dimethylpyrazolo|1,5-c|pyrimidine was accomplished with hot aqueous potassium permanganate. Acidification of the reaction mixture produced 3-methylpyrazol-5-carboxylic acid (39) in quantitative yield (see above).



(39)

PYRAZOLO|1,5-a|QUINAZOLINES

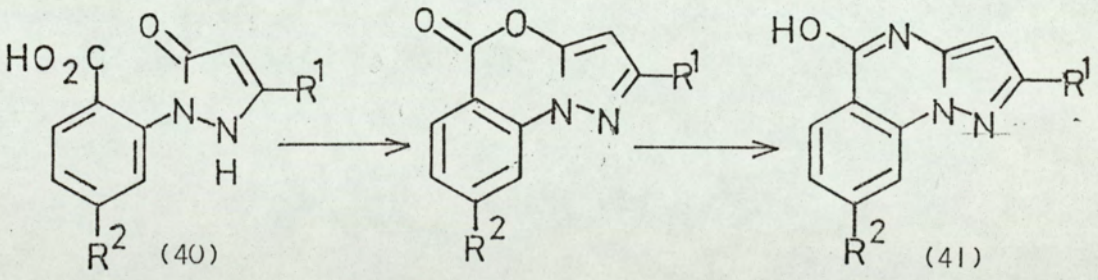
SYNTHESIS



This ring system has not been extensively studied, however the following preparations were reported.

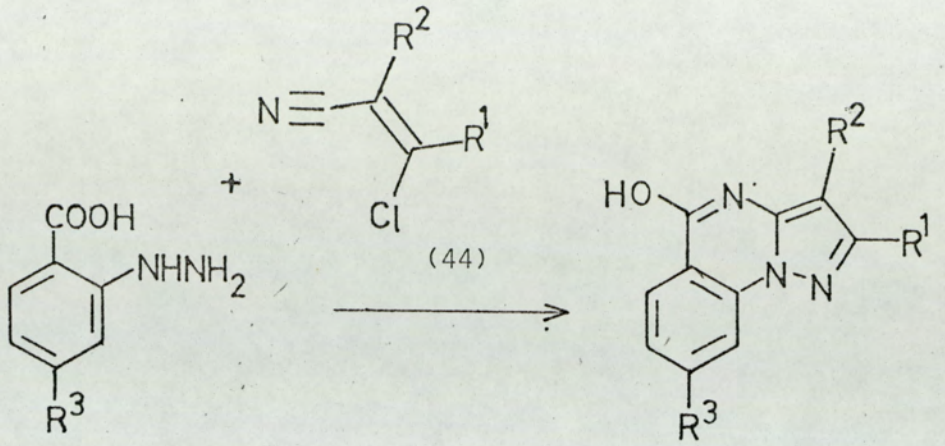
1-(2'-carboxyphenyl)pyrazol-5-ones

1-(2'-Carboxyphenyl) pyrazol-5-one (40; R^1=R^2=H) when treated at 120° for 2 hours with .880 ammonia solution, gave 9-hydroxypyrazolo|1,5-a|quinazoline (41) . 2-Methyl- and 6-chloro-9-hydroxypyrazolo|1,5-a|quinazolines (41; R^1=CH_3,H, R^2=H,Cl) were prepared by the same method[80].



2-Carboxyphenylhydrazines

Several 1- and 2- substituted -9-hydroxypyrazolo|1,5-a|quinazolines (42;R^1=CH_3,C_2H_5,CN or H,R^2=CN,$COOC_2H_5$, or H) have been prepared from 2-carboxyphenylhydrazines (43;R^3=H or Cl) and 3-chloroacrylonitriles (44)

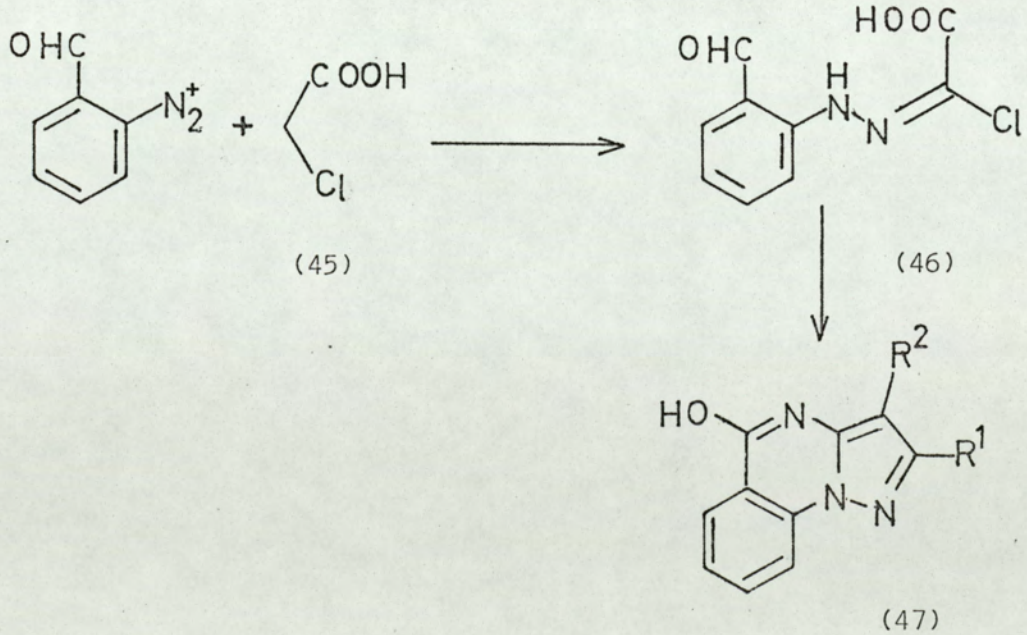


(43) (44) (42)

Nitrile and ester groups at positions 1 and 2 have been hydrolysed[81].

2-Aminobenzaldehyde

2-Aminobenzaldehyde was diazotised and coupled at 2° with ethyl-2-chloroacetoacetate (45) to give the hydrazone (46) which was then condensed with cyanoacetamide, ethyl cyanoacetate and malononitrile in base to afford, 9-hydroxypyrazolo[1,5-a]quinazolines (47; R^1=$CONH_2$, $COOC_2H_5$, CN, R^2=$COOC_2H_5$)[82,83].



(45) (46) (47)

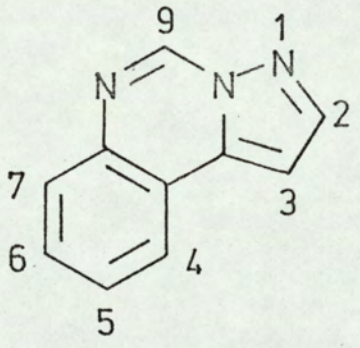
Hydrolyses of the amide, ester or nitrile functions at positions 1 and 2 were described, and decarboxylation of the acids formed gave the parent heterocycle.

The mechanism is somewhat obscure but probably the condensations of the nitriles with hydrazone (46) results in the replacement of the chloro group (by an Sn^2 mechanism). Two consecutive cyclisations then seem to be indicated (cf Wright[81]).

The chemical properties of pyrazolo|1,5-a|quinazolines have not been reported.

PYRAZOLO|1,5-c|QUINAZOLINES

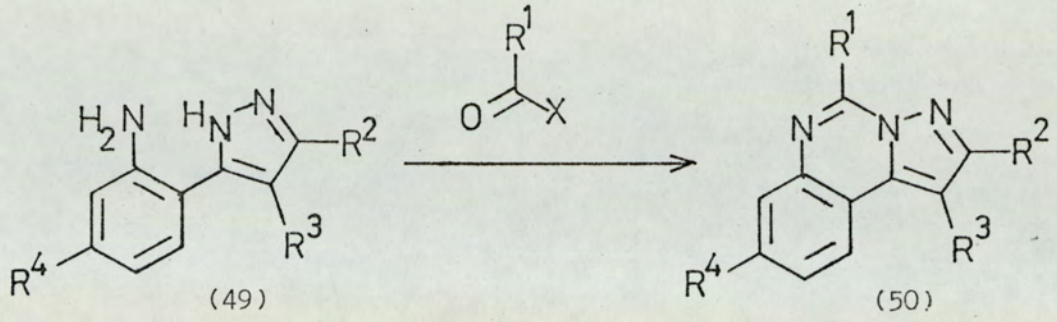
SYNTHESIS



(48)

Pyrazolo|1,5-c|quinazolines (48) have been prepared by the cyclization of 3-(2'-aminophenyl)pyrazoles (49) with a variety of carbonyl compounds. Cyclization with formic acid, acid chlorides and anhydrides and orthoformates afforded the fully aromatic heterocycle (50) but with aldehydes and ketones the 8,9-dihydropyrazolo|1,5-c|quinazolines (53) were obtained. The action of carbonyl chloride and carbon disulphide gave the 9-oxo- and 9-thioxo-pyrazolo|1,5-c|quinazolines (51).

Carboxylic acids and derivatives



(49) (50)

The general reaction illustrated above has been performed with formic acid and benzoyl, cyclohexoyl, cyclophentylacetyl, 1-chloropropionyl and chloroacetyl chlorides to give pyrazolo|1,5-c|quinazolines (48) bearing the respective substituents at postion 9 [84,85,86].

Cyclisation of 3-(2'-aminophenyl)pyrazole (49 ; R^2=R^3=R^4=H) could not be accomplished by heating with acetic anhydride alone but the addition of an equivalent of acetyl chloride to the reaction mixture, followed by heat gave the 9-methylpyrazoloquinazoline (50 ; R^2=R^3=R^4=H, R^1=CH_3)[85,86]

Orthoformates

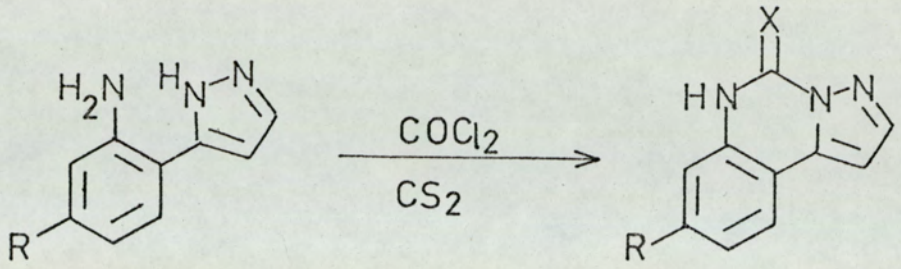
The preparation of 6-chloropyrazolo|1,5-c|quinazoline (50 ; R^1=R^2=R^3=H, R^4=Cl) 2-methylpyrazolo|1,5-c|quinazoline (50 ; R^1=R^3=R^4=H, R^2=CH_3) and the parent heterocycle (48) has been accomplished by refluxing the respective pyrazoles with triethylorthoformate. Good yields were reported[84,87].

Carbonyl chloride ($COCl_2$) and Carbon disulphide (CS_2)

Phosgene has been condensed with 3-(2 -amino-4'-chlorophenyl)pyrazole to give 6-chloropyrazolo|1,5-c|quinazolin-9(8H)-one (51 ; R^1=Cl, X=O) in good yield[87].

Carbon disulphide with 3-(2'-amino-4'-chlorophenyl)pyrazole (52 ; R^1=Cl) afforded the thione (51 ; R=Cl, X=S) and with 3-(2'-aminophenyl)pyrazole

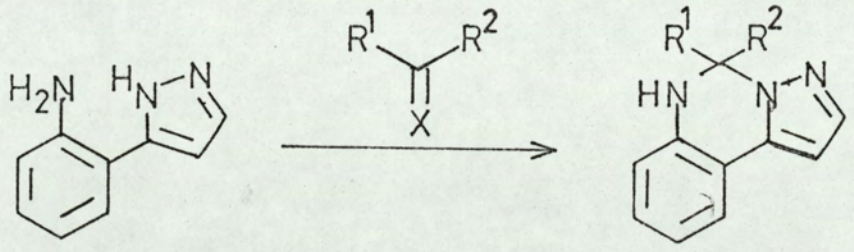
gave pyrazolo[1,5-c]quinazolin-9(8H)-thione (51; R=H, X=S)[87,88].



(52) (51)

Aldehydes and ketones

The condensation of 3-(2'-aminophenyl)pyrazole with formaldehyde, 3-formylpyridine, benazldehyde and 4-chloro-, 3,4-dichloro-, 4-fluoro-, 4-hydroxy- and 3,4,5-trimethoxy-benzaldehydes, gave the respective 3-substituted-8,9-dihydropyrazolo[1,5-c]quinazolines (53; R^1=H, R^2=H,Ph, X-C_6H_4pyridinyl). Good yields were reported in all cases except with formaldehyde[84,85,87].



(53)

Similarly, acetone, chloroacetone and 1,1-dichloroacetone with 3-(2'-aminophenyl)pyrazole, gave (53; R^1=CH_3, R^2=CH_3,CH_2,Cl,$CHCl_2$)[84,85].

CHEMICAL PROPERTIES

Electrophilic substitution into the nucleus of pyrazolo|1,5-c|quinazolines has not been reported. However nucleophilic substitutions into the ring and at the side chain have been mentioned in the literature.

Methylation of pyrazolo|1,5-c|quinazoline-9(8H)-thione was easily accomplished with methyl iodide. The methylmercapto group thus produced, was found to be replaceable with amino, morpholino, 4-ethyl- and 4-methyl-piperidino groups[88].

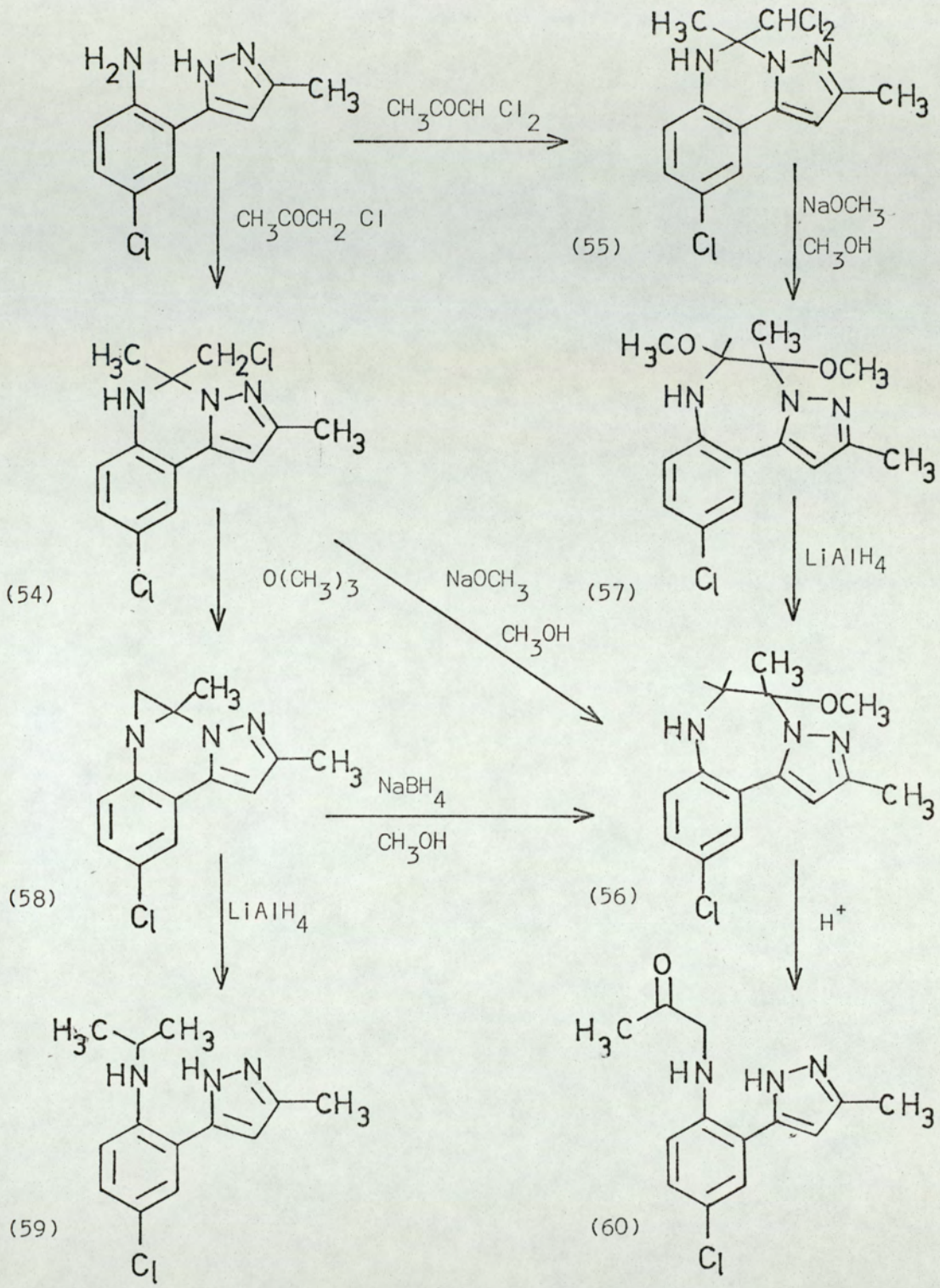
9-Chloromethyl side chains were also found to be susceptible to nucleophilic attack; replacement of the chloro group with methylamino, anilino and 4-fluorobenzylamino groups was reported[85].

Several ring expansion reactions of 5-chloro-9-chloromethyl-8,9-dihydro-2,9-dimethylpyrazolo|1,5-c|quinazoline (54) and 5-chloro-9-dichloro-8,9-dihydro-2,9-dimethylpyrazolo|1,5-c|quinazoline (55)are reported[89]. (See diagram below).

The chloromethyl compound (54), gave, in the presence of methoxide ions, a 9-methoxyazepine (56) which was also obtained by lithium aluminium hydride reduction of 8,9-dimethoxydiazepine (57) produced by the reaction of the dichloromethyl compound (55)with methoxide in methanol.

Treatment of the chloromethyl compound (54)with the tertiary butoxide ion, gave an aziridine (58)which was converted to the 9-methoxydiazepine (56) with sodium borohydride in methanol. Stronger reduction with lithium aluminium hydride caused cleavage of the pyrimidine and aziridine rings of compound (58) to afford the isopropylaminophenylpyrazole (59).

Ring cleavage of the benzodiazepine(56) was accomplished successfully with mineral acid to give 5-(2-acetonylamino-5'-chlorophenyl)-3-methyl-pyrazole (60).


$CH_3COCH\ Cl_2$
$CH_3COCH_2\ Cl$
$NaOCH_3$
CH_3OH
(55)
(54)
$O(CH_3)_3$
$NaOCH_3$
CH_3OH
(57)
$LiAlH_4$
$NaBH_4$
CH_3OH
(58)
(56)
$LiAlH_4$
H^+
(59)
(60)

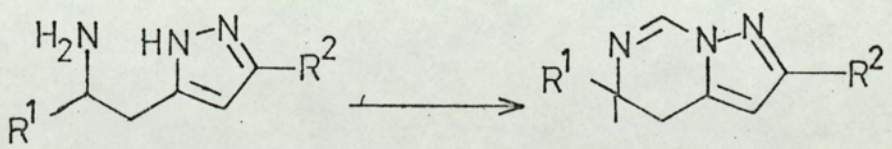
DISCUSSION

SYNTHESIS

PYRAZOLO|1,5-c|PYRIMIDINES

From Pyrazoles

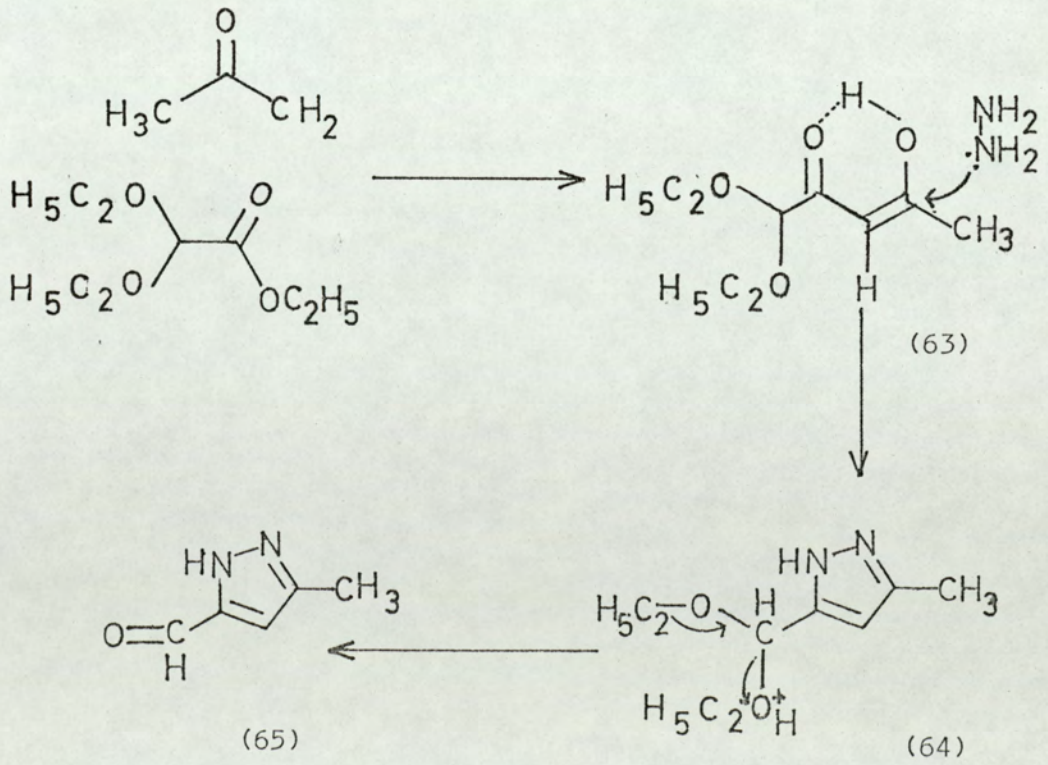
A series of steps outlined by Jones and Mann[96] led to the isolation of 3-(2'-aminoethyl)pyrazole in poor yield. It was envisaged that by the introduction of a one carbon fragment using formic acid, or triethylorthoformate, cyclisation of the aminoethylpyrazole (61 ; $R^1=R^2=H$) to afford a dihydropyrazolo|1,5-c|pyrimidine (62 $R^1=R^2=H$) might be accomplished. Spectral evidence (n.m.r.) indicated that this product (62) might be a component of the reaction mixture but the dihydro compound could not be isolated nor its proportion in the mixture increased. The attempted preparation of 3-(2'-amino propyl)-5-methylpyrazole (61; $R^1=R^2=CH_3$) as described in the literature[96] was not successful.



(61) (62)

Based upon the method of Herz[98] who prepared a pyrrolo[1,2-c]pyrimidine (68) from 2-formylpyrrole and benzoylglycine, a successful route to pyrazolo[1,5-c]pyrimidines, which were unreported at the commencement of this work, was undertaken.

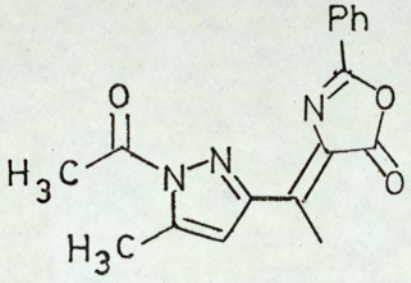
3-Formyl-5-methylpyrazole is easily prepared by the method of Bredereck[97]. 1,1-Diethoxypentan-2,4-dione[116] (63) was prepared by the condensation of ethyl diethoxyacetate[99] and acetone at low temperatures. The n.m.r. spectrum of this compound (63) shows that the enol form is predominant (see experimental section). The dione is then condensed with hydrazine hydrate to afford 3-diethoxymethyl-5-methylpyrazole as a pale yellow oil which is recognisable from the n.m.r. spectrum (see experimental section). Hydrolysis of this acetal gives rise to 3-formyl-5-methylpyrazole (65) as an analytically pure powder in excellent yield.



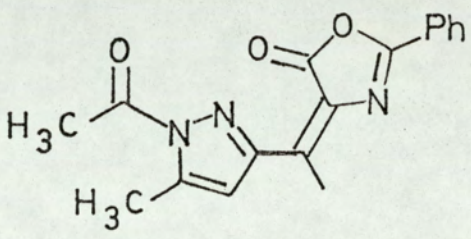
(63) (64) (65)

4-|1'(2')-Acetyl-5'-methylpyrazol-3'-ylidene|-2-phenyloxazo-5(4H)-one (66)

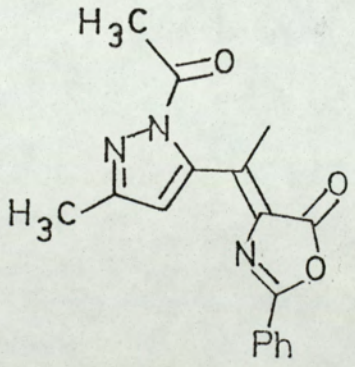
The condensation of 3-formyl-5-methylpyrazole with benzoylglycine results in the isolation of the oxazolone (66) The precise structure of this compound is not clear.



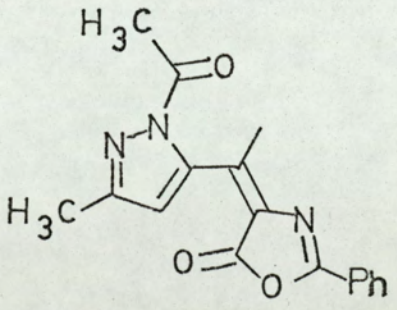
(66(a))



(66(b))

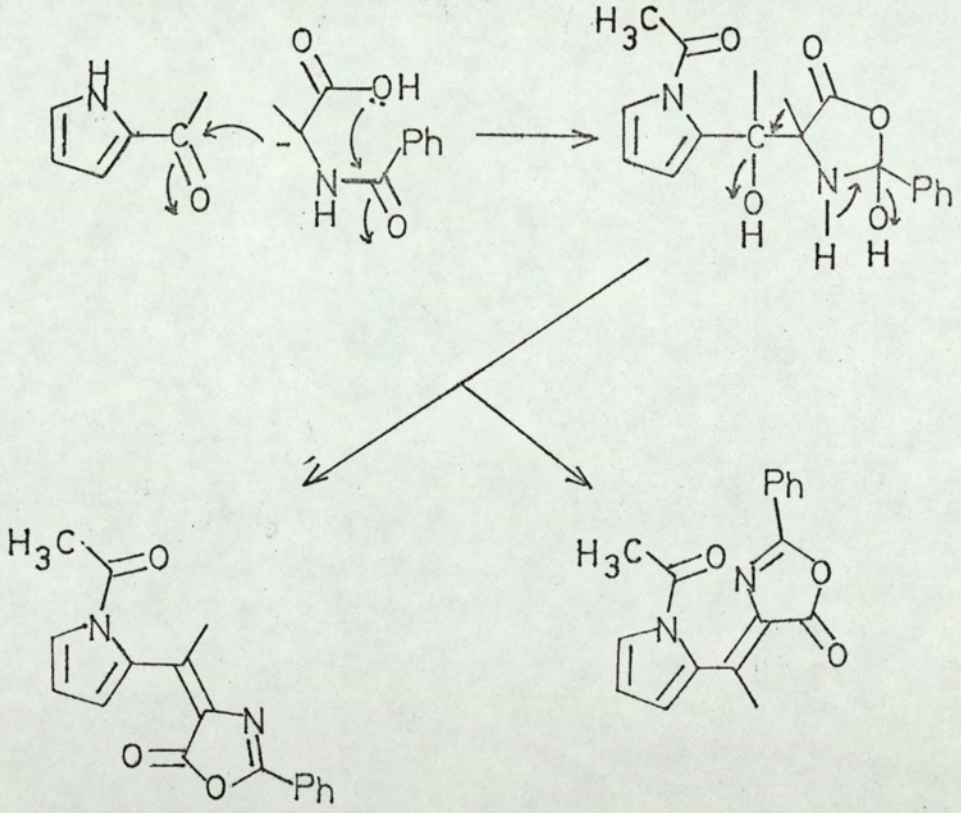


(66(c))



(66(d))

Any one of the four structures (66 a - d) may represent the oxazolone which is isolated. The possibility of the lactam mentioned by Herz was discounted on evidence afforded by infrared spectral data; the carbonyl absorption at 1720cm^{-1} is characteristic of a pyrazolyl-N-acyl group and not a benzamido group. Two compounds were isolated by Herz, melting points 135-145^{o} and 173^{o}. The latter compound alone could be cyclised to afford the pyrrolopyrimidine (68) by the action of hot aqueous sodium hydroxide. Since the infrared spectra of these compounds were similar, <u>cis</u>- and <u>trans</u>- isomers (67a+b) were suspected[98].



(67a; mp. 135-145) (67b; mp. 173)

Two fractions were isolated in this laboratory, by the technique of Herz, from the reaction of 3-formyl-5-methylpyrazole with benzoylglycine.

No difference in melting point or in spectral characteristics was observed between the fractions and both were reacted with sodium hydroxide solution to afford the pyrazolo[1,5-c]pyrimidin -5-carboxylic acid (69)

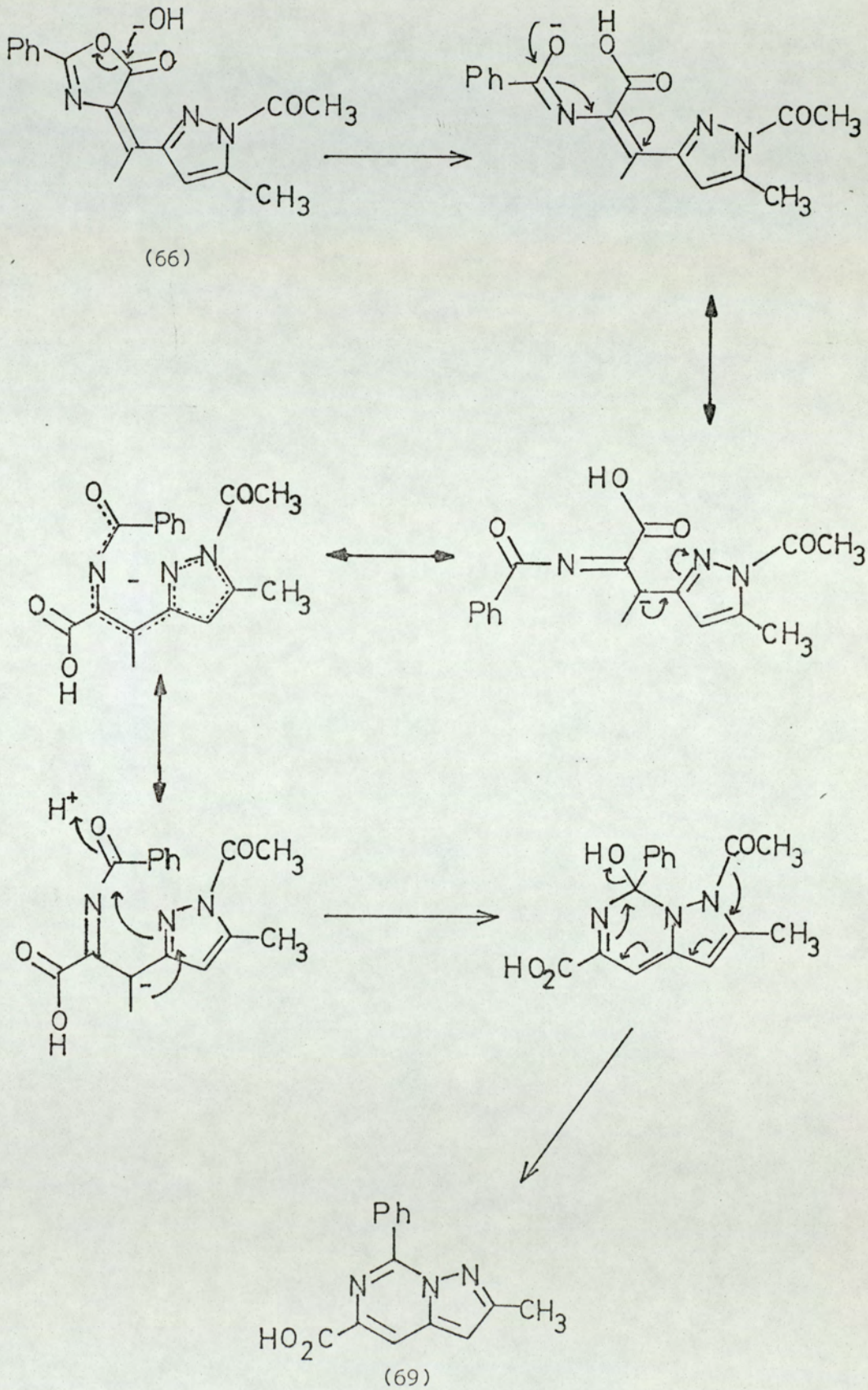
2-Methyl-7-phenylpyrazolo[1,5-c]pyrimidin -5-carboxylic acid (69)

An aqueous 10% $^{w}/_{v}$ solution of sodium hydroxide converted both oxazolone fractions to the pyrazolo[1,5-c]pyrimidine (69).

Heating the oxazolone (66) on a steam bath for 1 hour with 1% $^{w}/_{v}$ aqueous sodium hydroxide (conditions of Herz) produced starting material in quantitative yield. It is postulated that under the more vigorous conditions employed in this work (compared to those employed by Herz[98]) that polariazation of the olefinic bond, and free rotation about the resultant carbon-carbon bond occurs. A possible mechanism is illustrated below.

The infrared spectrum of the pyrazolopyrimidine (69) contains broad bands at 3150-2850cm^{-1} (bonded O-H stretch) and at 2650cm^{-1} (attributed to a quaternary amine), and peaks at 1700cm^{-1} (carboxylic acid -C=O); and 1610cm^{-1} (carboxylate ion). The compound then, appears to exist as a zwitterion.

Proton resonance evidence for the cyclisation at N-1 in the pyrazole and not at C-4 is seen. The 3 proton is observed to resonate at τ 3.31 and 4 proton at τ 1.75.

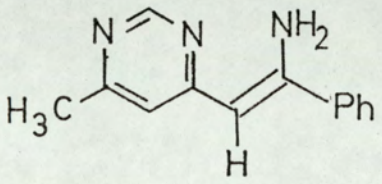


(66)

(69)

From Pyrimidines

A series of reactions was attempted in this laboratory which culminated in the production of 4-(1'-Aminostyryl)-6-methylpyrimidine (70). This product was obtained as a dark brown oil and was purified and characterised as the acetyl derivative. Phenyl lithium, prepared *in situ*, was treated



(70)

with 4,6-dimethylpyrimidine and benzonitrile under anhydrous conditions to give the product (70) described above[100]. Attempts were made to effect a cyclization of this compound by the oxidative method described by Bowers and Ramage, using potassium ferricyanide, which resulted in the isolation of starting material in quantitative yield.

This approach however, would seem to be a potentially successful route to pyrazolo[1,5-c]pyrimidines, possibly by prior reduction of the olefinic bond and subsequent use of other oxidizing agents such as manganese dioxide.

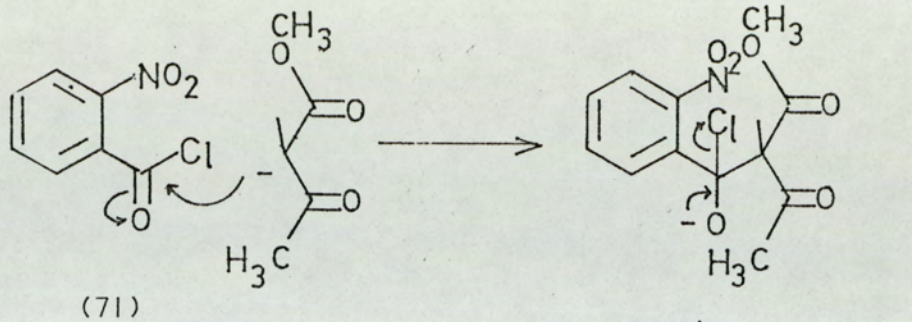
PYRAZOLO|1,5-c|QUINAZOLINES

The essential intermediate in the preparation of 2-hydroxy- and 2-methyl-pyrazolo|1,5-c|quinazolines is methyl 2-nitrobenzoylacetoacetate which was prepared by the condensation of 2-nitrobenzoylchloride with methyl acetoacetate using methods similar to those of Gabriel and Gerhard[90] and Coutts, Hooper and Wibberley[91].

The preparation of 2-nitrobenzoyl chloride is a tedious process, involving long periods of reflux to ensure complete reaction of the thionyl chloride with the 2-nitrobenzoic acid and long periods of distillation to remove hydrogen chloride and excess thionyl chloride.

Care is necessary during the heating periods to prevent hot metal parts of the water bath contacting the reaction vessel as this may cause focal points of overheating to develop, which can result in an explosion. The progress of this reaction is, however, easily monitored using infra-red techniques. The longer wavelength of the carbonyl absorption due to the acid chloride(71) denotes the completion of the reaction.

Condensation of 2-nitrobenzoylchloride with methyl acetoacetate is easily accomplished but in some experiments it was necessary to acidify the reaction mixture with hydrochloric acid to ensure complete precipitation of the acetoacetate (72) . Experiments involving the use of ethyl aceto-acetate in place of the methyl ester resulted in the isolation of an oil which could not be crystallized (see also Koenigs and Freund[92]).



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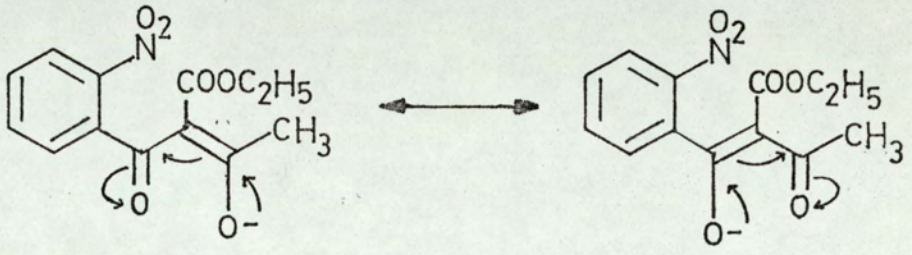
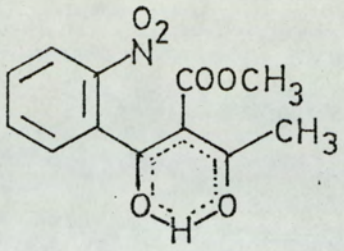


(72)

Examination of the infrared spectrum of methyl 2-nitrobenzoylaceto-acetate(72) suggests that a preponderance of the enol tautomer of this compound (≃ 99.9%) exists. No evidence of carbonyl absorption other than that due to the ester carbonyl group (1715cm^{-1}) is seen. The presence, in the τ 6.0-8.0 region of the n.m.r. spectrum of the compound, of only two signals at τ 7.4 and 6.5 due to the protons of the methyl groups, and the absence of a signal which could be attributed to the methine proton (τ 5-6) confirm this.

The great contribution to the tautomeric equilibrium of the enol form suggests that this tautomer is more stable than the keto structure and in fact a structure containing a six-membered, pseudo-aromatic ring (73) can be

envisaged.

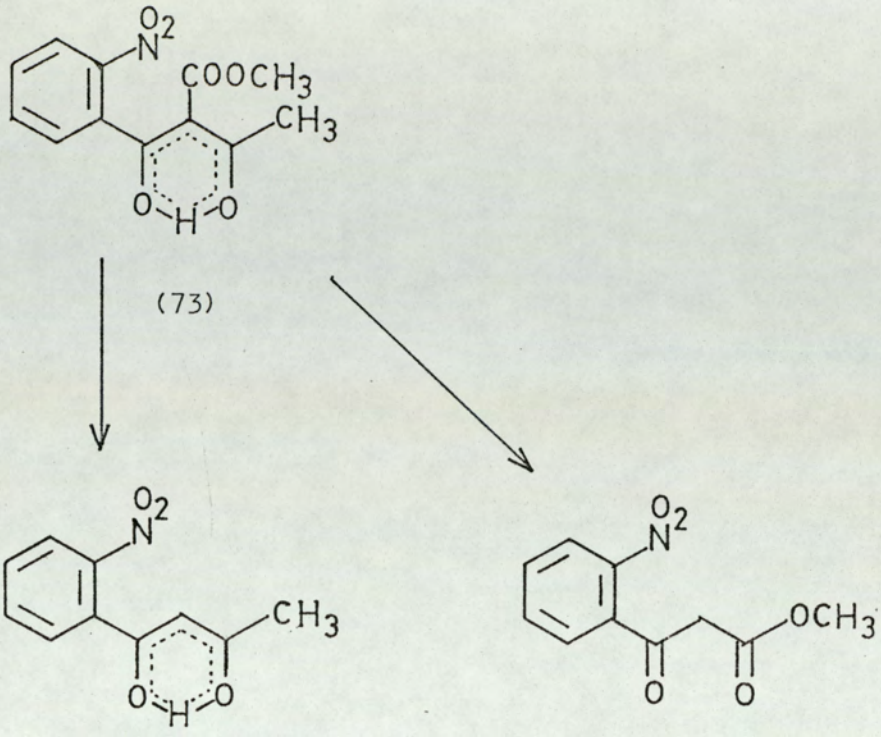


(73)

Hydrolysis of Methyl 2-Nitrobenzoylacetoacetate

It was hoped that the reaction of methyl 2-nitrobenzoyl acetoacetate with hydrazine might produce a mixture containing 4-acetyl-3-hydroxy-5-(2-nitrophenyl)pyrazole and methyl 3-methyl-5-(2'-nitrophenyl)pyrazole-4-carboxylate from which each of these compounds could be isolated separately. However, this was not possible. Instead the acetoacetate(73)was hydrolysed under acidic conditions to furnish 2-nitrobenzoylacetone(74) and under basic conditions[101] to afford methyl 2-nitrobenzoylacetate,(75) both of which were obtained in good yield. From these products 3-hydroxy-5-(2'-nitrophenyl)- and 3-methyl-5-(2'-nitrophenyl)-pyrazoles are obtainable.

2-Nitrobenzoylacetone(74) like methyl 2-nitrobenzoylacetoacetate appears to exist as the enol tautomer. Infrared spectroscopy reveals no carbonyl absorption and n.m.r. spectroscopy shows only a very small contributio from the keto tautomer. The stable six-membered chelate theoretically possible for the starting material(73) is also possible for this product.



(73)

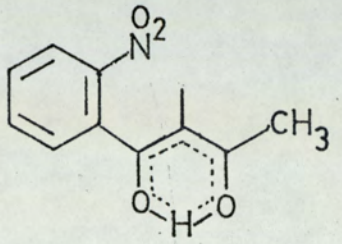
(74)

Methyl 2-Nitrobenzoylacetate(75) by contrast, appears to exist totally in the keto form as shown by infrared and n.m.r. studies. The possibility of the existence of a stable six-membered chelate as envisaged for compound(74) would seem to be less likely, due to the effect of the methoxy group. However a substantial contribution from the enol tautomer might be expected, especially in view of the reports by Smalley and others claiming a 30% enol contribution from 3-fluorobenzoylacetates. Nitro group involvement would appear to be indicated.

Pyrazole formation

The condensation of hydrazine hydrate with 2-nitrobenzoylacetone and methyl 2-nitrobenzoylacetate affords 3-methyl-5-(2'-nitrophenyl)pyrazole

(76) and 3-hydroxy-5-(2'-nitrophenyl)pyrazole(77) respectively in good yield. (See also De Stevens et al[84,85,102]).



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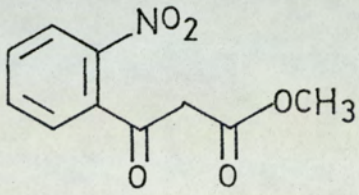

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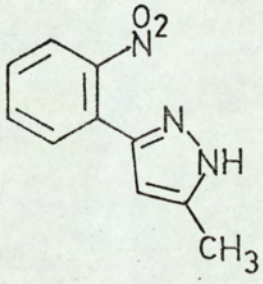

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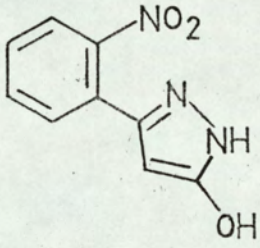


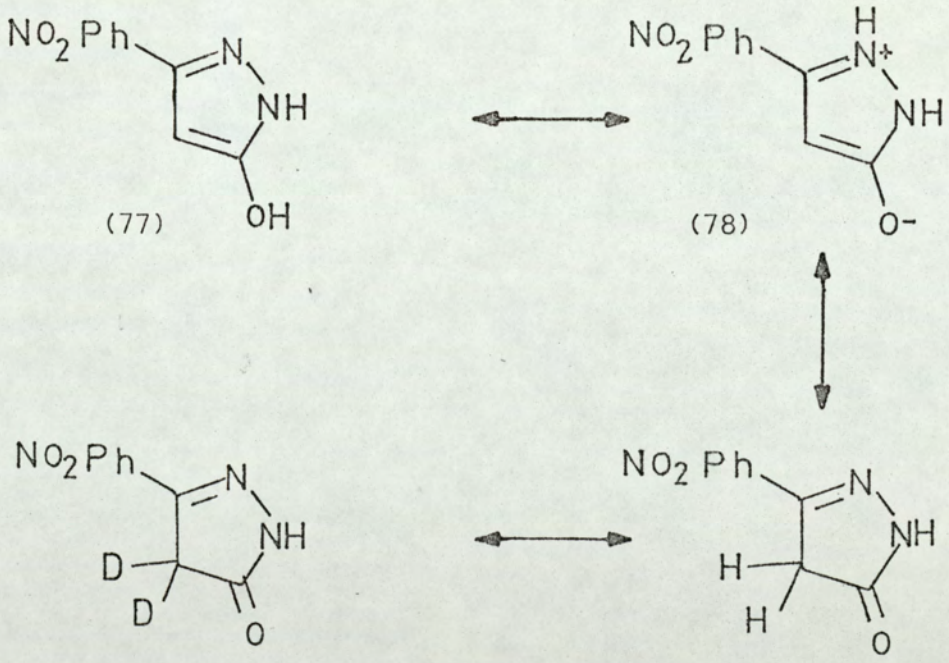
(77)

Pyrazole ring formation is confirmed in the infrared spectrum of (76) by the presence of a peak at 3350cm^{-1}, due to the N-H stretching vibration and, in the n.m.r. spectrum by the disappearance of the ethylenic proton signal (τ 4.2) and the appearance of a one proton singlet at τ3.75, attributed to the 4 proton (the 4 proton in pyrazole itself resonates at τ 3.95). A broad signal at τ -0.25 which disappears on shaking with deuterium oxide, is allocated to the secondary amine proton.

The existence of compound (77) is likewise indicated by infrared spectroscopy; no carbonyl absorption is seen, but a broad band at 2750cm^{-1}

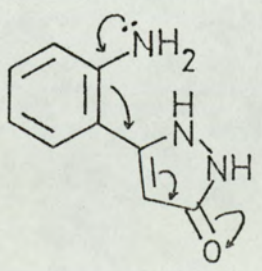
is attributed to $\overset{+}{N}$-H bend in the zwitterionic form of (77). This compound appears to exist entirely as the zwitterion (78) in the solid state.

A study of the n.m.r. spectrum of 3-hydroxy-5-(2'-nitrophenyl)pyrazole suggests the existence of at least three tautomeric forms of this compound. The 4 proton resonates at τ 4.45 (1-H) but disappears on shaking with deuterium oxide which suggests a contribution of 5-(2'-nitrophenyl)pyrazol-3(4H)-one(79) to the tautomeric equilibrium. Since this structure is not indicated in the infrared spectrum of(77) it must be assumed that this contribution is small or that in solution, a different equilibrium structure exists.

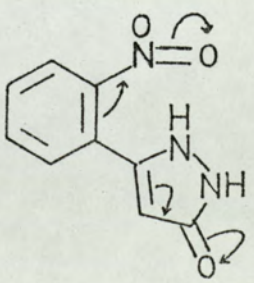


Reduction of the nitro groups of 3-methyl- and 3-hydroxy- 5- (2-nitrophenyl)pyrazole is easily accomplished with hydrogen in the presence of palladium catalyst adsorbed onto charcoal, without effecting any other change in the molecule. 3-(2'-Aminophenyl)-5-methylpyrazole(81;R=CH_3) and 3-(2'-aminophenyl)pyrazol-5(2H)-one (80) are only produced in good yield when small scale experiments are performed. However see Koenigs and Freund[92]. In the infrared spectrum of 3-(2'-aminophenyl)-5-methyl pyrazole(81; R = CH_3) the presence of peaks at 3450cm^{-1} and 3250cm^{-1} (due to primary and secondary N-H) and the absence of absorption peaks at 1540 and 1360cm^{-1} (due to the nitro groups in the starting material) indicate that reduction has occurred. Differences in the n.m.r. spectrum of the reduced product compared to that of starting material can also be seen.

The infrared spectrum of the pyrazolone (80), however, also contains an intense peak at 1780cm^{-1} which is due to the carbonyl group. The large contribution to the equilibrium structure of this ketone(80) can be understood since an elongated system of conjugation exists to confer stability on this molecule.Conjugation in the unreduced hydroxy compound (82) would tend to destabilise the keto tautomer and thus reduce its contribution to the equilibrium structure. The infrared and ultraviolet spectra of several pyrazol-5-ones have been studied in order to clarify their structure; a distinction between -5(1H)- and -5(4H)-ones was not possible[85,94,95].



(80)

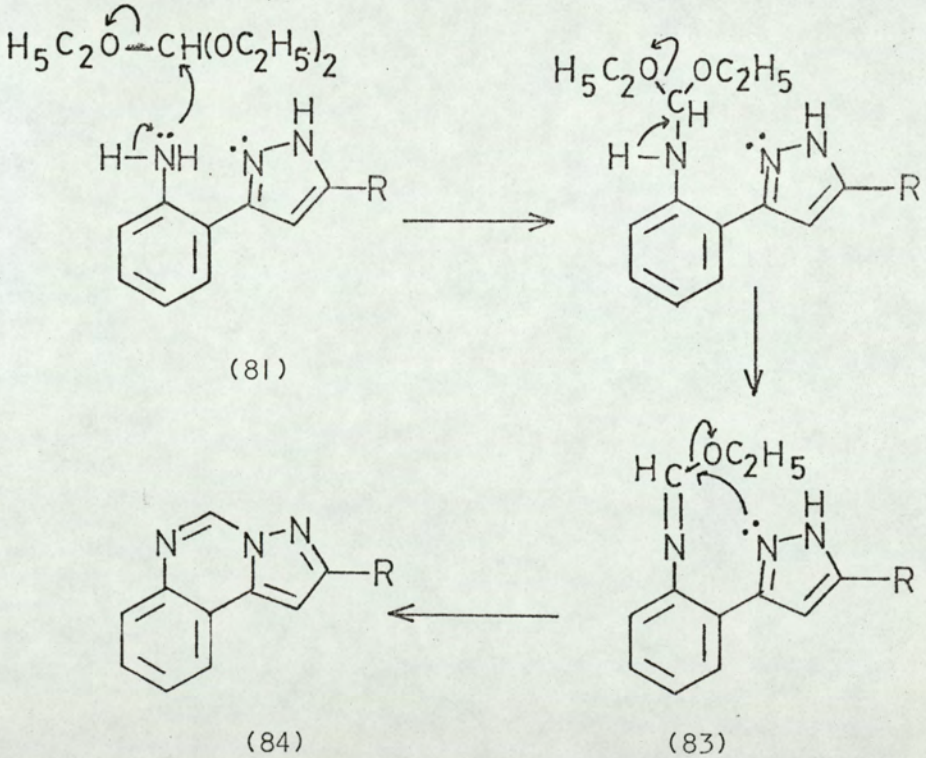


(82)

A study of the n.m.r. spectrum of 3-(2'-aminophenyl)pyrazol-5-one (80)reveals that the 4 proton is labile and exchanges readily with deuterium oxide. A small contribution from a pyrazol-5(4H)-one would explain this (see nitrophenyl compound).

Pyrazolo|1,5-c|quinazolines

The cyclisation of 3-(2'-aminophenyl)-5-methyl pyrazole(81;R=CH_3) and 3-(2'-aminophenyl)pyrazol-5-one (81;R=OH) is accomplished easily by refluxing these compounds in triethylorthoformate to afford 2-hydroxy- and 2-methylpyrazolo|2,3-c|quinazolines (84;R=OH and CH_3 respectively).



(81) (83) (84)

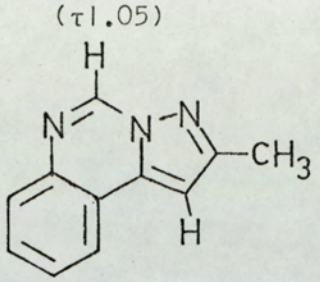
It may be that the formation of the imidate(83)is not a rate determining step, but that the loss of two molecules of ethanol and cyclisation occur simultaneously. A consideration of relative basicities of the primary and

secondary amine groups suggests that initial attack is of the primary amine lone pair of electrons at the relatively electrophilic carbon atom of the orthoformate.

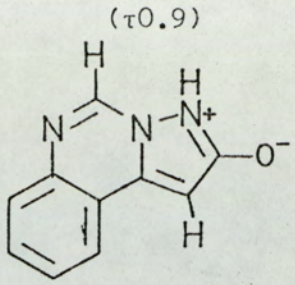
In theory, the cyclisation may occur into the pyrazole ring at position 4 to afford a pyrazolo|4,3-c|quinoline, especially with the pyrazole-5-one (80),as this compound has a more activated carbon atom at position 4 (see introduction pg.3 , reaction in base of cyanoacetylhydrazines and pyrazol-5-ones, and Ridi[95], condensation of aldehydes and ketones at carbon 4 of pyrazol-5-ones). The conditions used in this cyclisation, however (120^{o}) did not lead to the isolation of any products other than the pyrazolo|1,5-c| quinazolines (84).

The infrared spectra of these compounds (84; R =CH_3, OH) do not contain a peak which could be attributed to the N-H stretching vibration (1^{o}, 2^{o} in primary or secondary amines)but the spectrum of 2-hydroxypyrazolo |1,5-c|quinazoline contains a broad band at 2550cm^{-1} due to $\overset{+}{N}$-H bend in the zwitterion (13)in which form this compound seems to entirely exist; no carbonyl absorption is observed.

A study of the n.m.r. spectra of these compounds offers more conclusive evidence of cyclisation. The one proton singlet around τ 1.0 is attributed to the 9 proton and this shift value is typical of a 2-pyrimidinyl proton (a 2-pyridinyl proton usually resonates at τ 1.5). The 3 proton is seen to resonate at τ 3.35 which is 0.25τ downfield from the signal produced by the 4 H proton in starting material, and offers a convincing argument that cyclization has occurred at the pyrazole nitrogen atom.

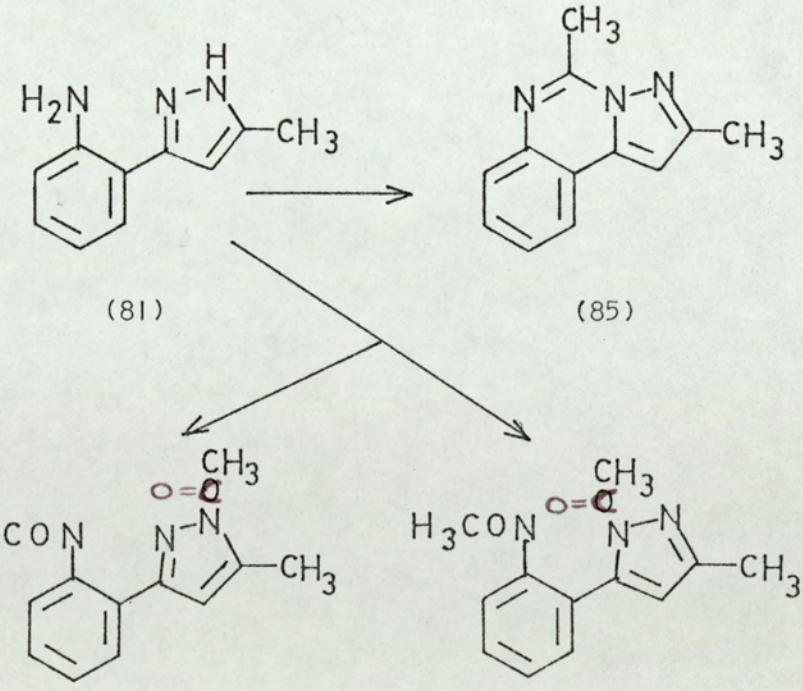


(84b)



(84a)

2,9-Dimethylpyrazolo[1,5-c]quinazoline (85) was obtained in only very small amounts from the reaction at room temperature of 3-(2'-aminophenyl)-5-methylpyrazole (81)with acetic anhydride. (De Stevens did not isolate an analagous product from the reaction of 3-(2'-aminophenyl)pyrazole with acetic anhydride[85]). The major product was 3-(2'-acetamidophenyl)-1 (2) acetyl-5-methylpyrazole(86a+b) analogous to the product isolated by De Stevens.



(81) (85)

(86a) (86b)

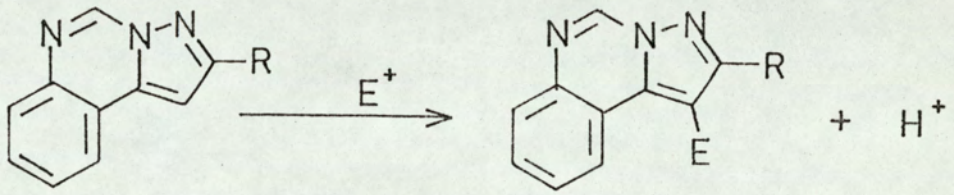
The proportion of cyclized material (85) could not be increased by using longer reaction times, higher temperatures or by adding catalysts such as acetyl chloride, sodium acetate, sodium hydroxide. Attempts to cyclise the diacetyl compound (86) met with failure.

A study of the n.m.r. spectra of the compounds (85) and(86)in conjunction with the infrared spectral data confirms the structures given.

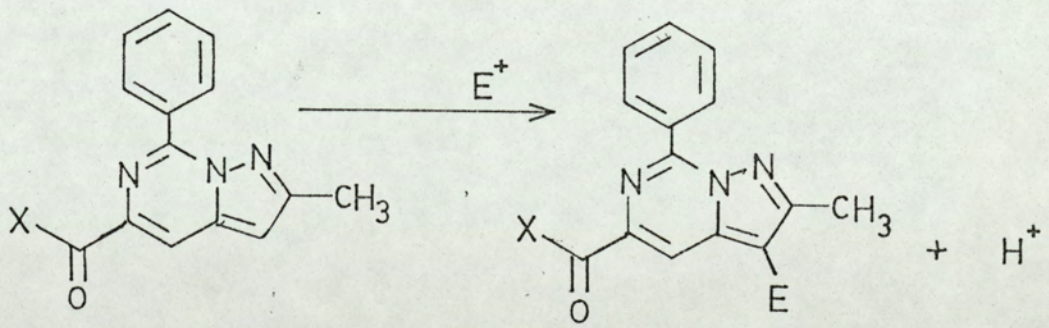
CHEMICAL PROPERTIES

ELECTROPHILIC SUBSTITUTION.

Electrophilic substitution into the nuclei of pyrazolo|1,5-c|pyrimidines and pyrazolo|1,5-c|quinazolines invariably occurs ar carbon 3, as is the case in pyrazolo|1,5-a|pyrimidines (see introduction).



(87) (88)



(89) (90)

Conclusive evidence that substitution has taken place is afforded by infrared and n.m.r. spectroscopy. Nitro and formyl groups are easily identified in the infrared spectra of the substituted products and the signal produced by the resonance of the 3 proton in the n.m.r. spectra of the starting materials is absent in the spectra of the substituted products, furthermore, the chemical shift of the signals due to 4 proton resonance is, in some cases, significantly different in the starting materials and substituted products. The chemical shifts of the 9 proton in pyrazoloquinazolines (87) and of the phenyl protons in the pyrazolopyrimidines (89) are also affected by substituents at C-3.

Bromination

Similarly, the bromination of ethyl 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate (89; X=OC_2H_5) and of 2-methylpyrazolo|1,5-c|quinazoline (87; R=CH_3) with molecular bromine in chloroform is easily accomplished to afford ethyl 3-bromo-2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate (90; E =Br, X=OC_2H_5) and 3-bromo-2-methylpyrazolo|1,5-c|quinazoline (88; R =CH_3, E =Br).

The infrared spectra of the substituted products (90) and (88; R=CH_3) are little changed but differ in the fingerprint region from those of the starting materials. The proton resonance spectra of 88 and 90 do not contain a signal that could be allocated to the 3 proton, and also the n.m.r. spectrum of the quinazoline (88) contains signals due to the 4 and 9 protons at chemical shifts significantly different from those of the 4 and 9 protons in starting material.

3-Bromo-2-hydroxypyrazolo|1,5-c|quinazoline (88; R^1=OH, E =Br) could not be isolated by the above procedure. The salt precipitated during the reaction, when heated in water, or triturated with ammonia gave the starting material in quantitative yield. (However see pg.58)

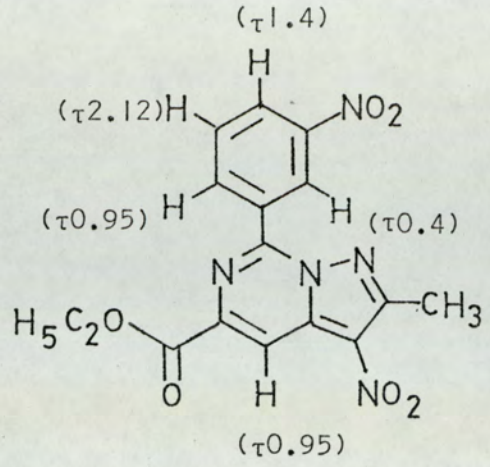
The bromination of pyrazolo|1,5-c|pyrimidines at C-4 by Kranz, is mentioned in the introduction to this work (pg.19), however bromination at C-4 of the pyrazolo|1,5-c|pyrimidine (89) was not observed, using excess bromine, probably because of the deactivating influence of the ester group at position 5.

Nitration

Pyrazoles, in general, are not nitrated easily, due to the formation of the cation which is resistant to further electrophilic attack. Nitrating mixture is necessary to effect nitration[104].

1-Phenyl- and 3-phenyl-pyrazoles, however, have scarcely any basic properties and are nitrated easily[105]. Pyrazolo|1,5-c|-pyrimidines and -quinazolines, therefore, are expected to be easily nitrated at C-3, due to the reduction in basicity of the pyrazole tertiary amine groups caused by the fused pyrimidine and quinazoline rings respectively. This is observed to be the case. Nitric acid at room temperature effects nitration of 2-methyl-pyrazolo|1,5-c|quinazoline at position 3, and a dinitration of the pyrazolo-pyrimidine (89).

Nuclear magnetic resonance data suggest that ethyl 2-methylpyrazolo|1,5-c|pyrimidine-5-carboxylate is nitrated at C-3 and in the phenyl ring at C-3' as anticipated, to afford 2-methyl-3-nitro-7-(3'-nitrophenyl)pyrazolo|1,5-c|pyrimidin -5-carboxylate (91).



(91)

A comparison of the effects of the 7-(2-methyl-3-nitropyrazolo|1,5-a|pyrimidin-5-carboxylate) group (90; X=O C_2H_5, E=NO_2) and the nitro group (nitrobenzene) on the chemical shift of the ortho-benzene protons indicates that the 6' proton resonates at lower field than the 4' proton. The 2' proton resonates at lowest field. The signals of all phenyl protons are broadened due to long range coupling. The pi-electrons of the nitro group effect a deshielding of the 4 proton of 0.8τ compared to starting material. Ethyl 2-methyl-3-nitro-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate(90;E=NO_2) is obtained in 38% yield from the reaction of the unsubstituted pyrazolopyrimidine (90; X=OC_2H_5) with nitric acid in acetic anhydride.

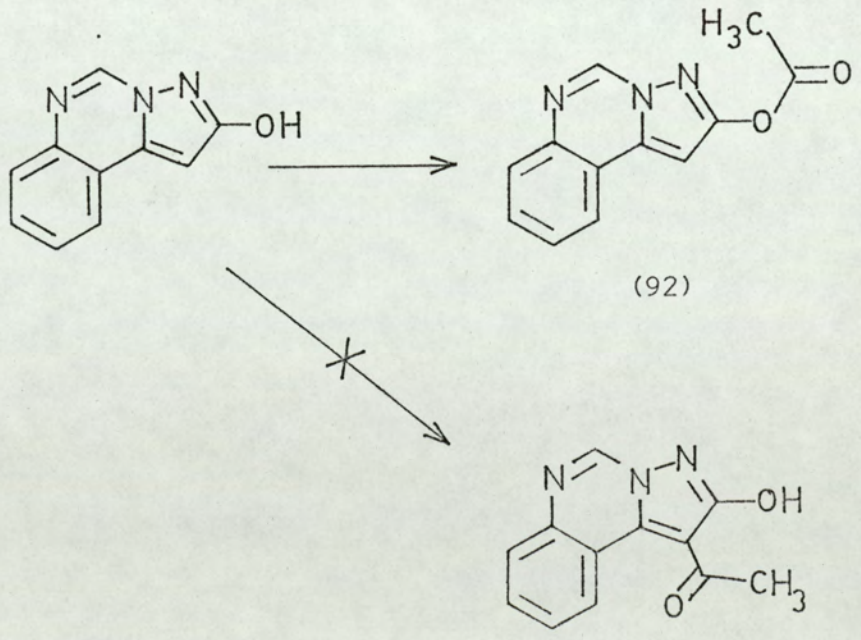
2-Hydroxypyrazolo|1,5-c|quinazoline(87;R=OH)however, upon nitrosation does not yield a product which is purely 2-hydroxy-3-nitropyrazolo|1,5-c|quinazoline (Microanalytical data do not support this structure) although infrared, n.m.r. and mass spectral data suggest that some nitration at C-3 has occurred. Possibly a ring-opened compound makes some contribution to the product (see pg.53)

Formylation of the pyrazolopyrimidine(89) and the pyrazoloquinazoline (87) at C-3 is achieved with phosphoryl chloride and dimethylformamide. Good yields of ethyl 3-formyl-2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin

-5-carboxylate (90; X=OC_2H_5,E=CHO) and 3-formyl-2-methylpyrazolo|1,5-c| quinazoline (88; E =CHO) are obtained if the complex is hydrolysed with water. (Hydrolysis with sodium hydroxide gave poor yields of the 3-formyl compounds). The carbonyl absorbtion of the formyl group, in the infrared, and the absence of the 3 proton in the nuclear magnetic resonance spectra of the product confirm structures (89,90;E=CHO). The anisotropic effect of the carbonyl pi-electrons causes a deshielding of the 4 proton by 0.8τ compared to starting material, in both compounds.

Acetylation of the nucleus of pyrazolo|1,5-c|-pyrimidines and -quinazolines (87; R =CH_3 and 89 ; X=COOH) could not be accomplished, although von Auwers[106] and Grandberg[107,108], report the acylation at C-4 of pyrazoles under extreme conditions.

Acetylation of 2-hydroxypyrazolo|1,5-c|quinazoline occurs very easily to afford 2-acetoxypyrazolo|1,5-c|quinazoline (92) in excellent yield. Further acetylation could not be accomplished.



(92)

The presence of the 3 proton signal in the n.m.r. spectrum of the product confirms that electrophilic substitution into the nucleus does not take place (see also (Weissberger[109]). A deshielding of the 3 proton by the ester group of 0.68τ is seen.

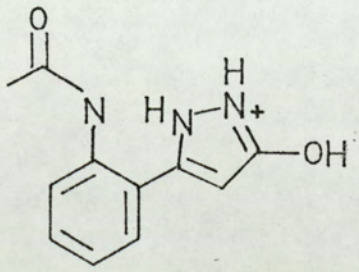
Nitrosation. Reference has been made in the introduction to this work to the nitrosation of pyrazolo|1,5-a|pyrimidines at C-3 (pg.12), however nitrosation of the pyrazolo|1,5-c|-pyrimidine (89; $X=OC_2H_5$) and -quinazolines (87; $R'=CH_3$ or OH) could not be accomplished in this laboratory. The nitrosation of the pyrazolopyrimidin -5-carboxylate was not expected to be successful due to the deactivating influence of the ester group on position 3, but the opposite effect is present in the quinazoline series, and in view of this and the easy nitrosation of 3-alkoxypyrazoles[110,111,112] the observed lack of reactivity is surprising. However, see later (pg. 58) for a discussion of the stability of the pyrazolo|1,5-c|quinazoline ring system.

Diazocoupling reactions of phenyldiazonium chloride with the pyrazolo-pyrimidine (89; $X=OC_2H_5$) and the quinazoline (87; $R'=CH_3$) were unsuccessful, starting material being recovered completely. 2-Hydroxypyrazolo|1,5-c| quinazoline (87; R'=OH) when reacted at 0° with phenyldiazonium chloride gave a coloured compound but on recrystallisation a colourless product (starting material) was recovered. Possibly a small proportion of the 3-phenylazo compound (88; R'=OH, E =Ph-N=N) is formed, the main product being 2-phenylazoxypyrazolo|1,5-c|quinazoline (87; $R=Ph-N_2$) which decomposes on neutralization of the reaction mixture with hydrochloric acid incurring the loss of the phenyldiazonium ion (see pg.13).

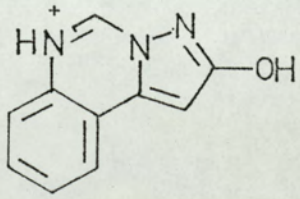
With dilute mineral acid.

The apparent lack of reactivity of 2-hydroxypyrazolo[1,5-c]quinazoline to electrophilic reagents, prompted an investigation into the stability of the ring system to acid, since the substitution reactions were attempted in mildly acidic conditions. Stirring this compound (87;R=OH) with dilute (10%) hydrochloric acid at room temperature gives rise to colourless needles which analyse as $C_{10}H_9N_3O_2.H.Cl$.

Infrared spectra of this compound contain a peak at 3350cm^{-1} (O-H or N-H), a broad band at 3000-2400cm^{-1} ($\overset{+}{N}H$ and OH) and a peak at 1650cm^{-1} which could be due to a formamido carbonyl group (93) or to $C=\overset{+}{N}$ stretch (94) . Nuclear magnetic resonance spectral data confirm that ring opening could have occurred. A signal at τ0.5 could be attributed to the aldehydic proton (93) or to the 9 proton (94) (see Bullock et al[114,115], who report that the pyrimidinyl 2-proton in purines resonates in acidic solution at τ0.4). The singlet at τ3.15 may be assigned to either the 4 proton of compound (93) (the 4 proton of 3-chloromethylpyrazole hydrochloride resonates at τ3.15) or to the 3 proton in compound (94).

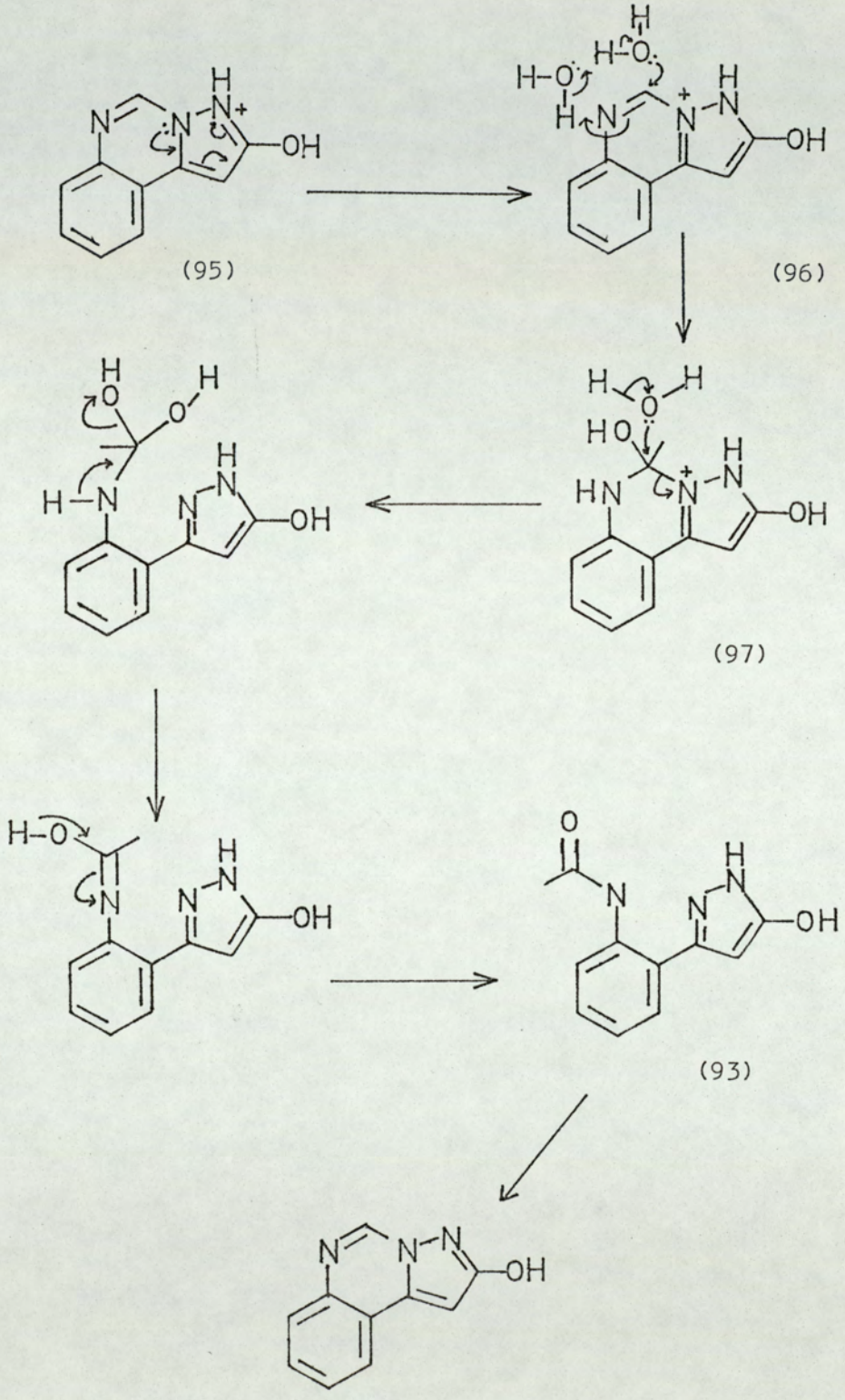


(93)



(94)

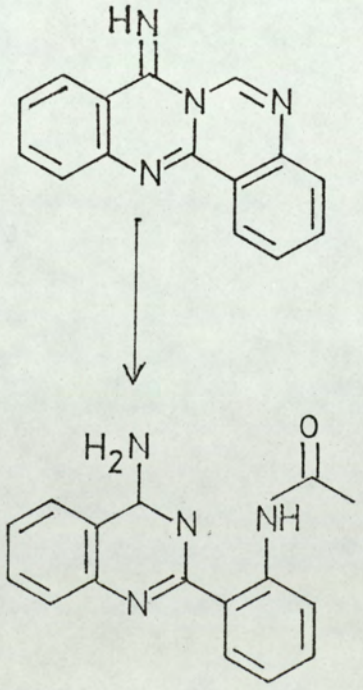
A possible mechanism for ring opening is outlined below.



(95) (96) (97) (93) (84a)

It is postulated that since 2-hydroxypyrazolo|1,5-c|quinazoline exists as a zwitterion (84a; pg.44), protonation in acidic media, occurs at the oxygen atom. Stabilisation of the resultant cation (95) is possible by delocalisation of the lone pair of electrons associated with the bridgehead nitrogen atom (N-10). The cation (96) so produced is analogous with the quinazoline cation (Albert & Armarego[121]) and might be expected to undergo covalent hydration across the N-8 - C-9 bond, to afford 8,9-dihydro-2,9-dihyroxypyrazolo|1,5-c|quinazoline hydrochloride (97) . This compound is assumed to be unstable in water and to undergo ring cleavage to the hydrochloride of 3-(2'-formamidophenyl)-5-hydroxypyrazole (93) , which cyclises to the pyrazoloquinazoline starting material when heated in water or ethanol.

The ring-opening of the fused pyrimidine (98) in acid reported by Partridge[113] may occur by a mechanism similar to that described above.



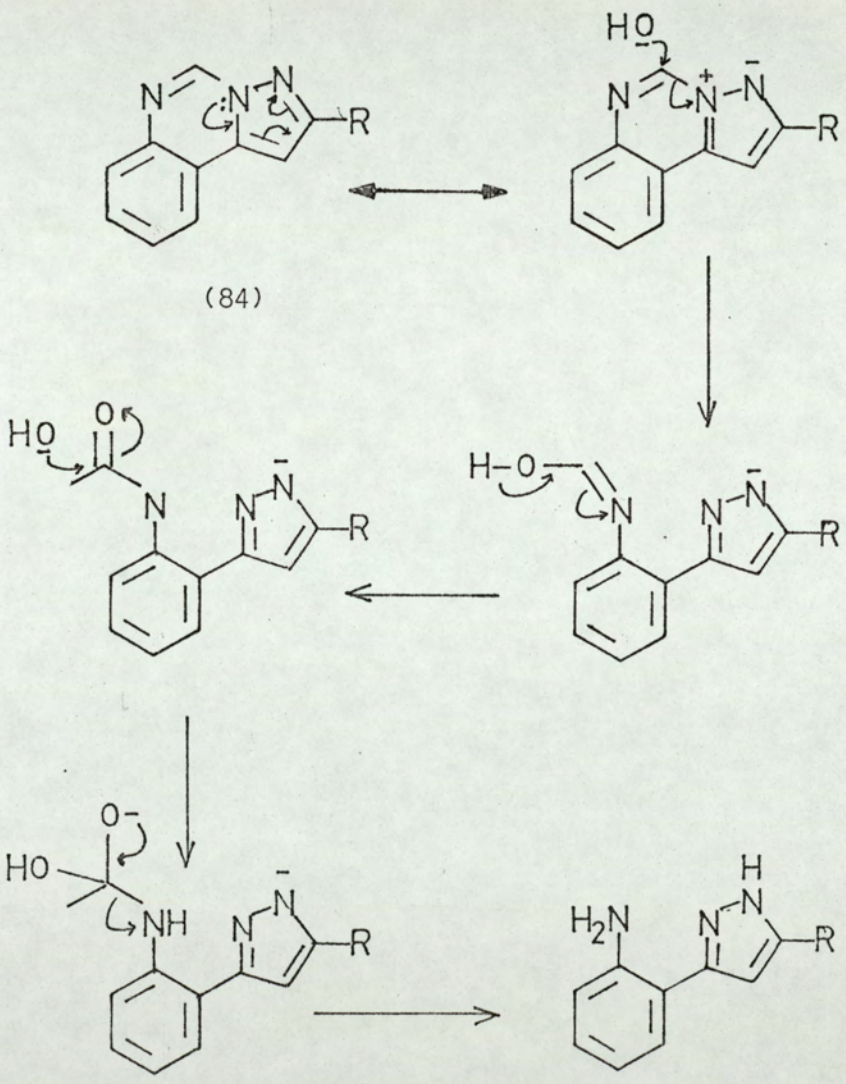
(98)

A salt is not precipitated from an acidic solution of 2-methylpyrazolo|1,5-c|quinazoline(87;R=CH_3)or 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylic acid (89). The former molecule is presumably protonated at N-8 and the cation can be stabilised by the delocalisation of the lone pair associated with the bridgehead nitrogen atom. The molecules thus produced, because of the presence of a proton at N-8, is not exactly analogous to that produced by the zwitterion and the mechanism of ring cleavage described for the zwitterion would not be expected to operate. Other mechanisms for ring cleavage can however, be envisaged but they either do not operate leaving the pyrazoloquinazoline hydrochloride in solution, or give products which are soluble in acid. An attempt to isolate any ring-opened products by methods involving the use of heat would presumably allow cyclisation to occur and result in the isolation of starting material.

The pyrazolopyrimidin-5-carboxylic acid (89) would be expected to be a much weaker base than the pyrazoloquinazoline (87) due to the ease of delocalisation of the N-6 lone pair of electrons into the phenyl ring or the carboxyl group. Consequently the site of protonation is not easily determined theoretically. However, in the eventuality of protonation occurring at N-1, the 7-phenyl group might prevent hydration by steric hindrance. The driving force for protonation at N-1, and therefore for subsequent ring cleavage, is much weaker in this molecule than in 2-hydroxypyrazolo|1,5-c|quinazoline, and ring cleavage would therefore be less likely to occur.

With hot aqueous alkali.

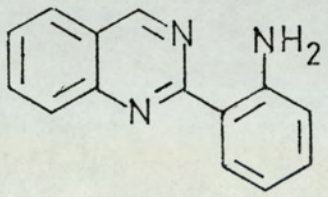
Cleavage of the pyrimidine ring in 2-hydroxy and 2-methylpyrazolo[1,5-c]quinazolines (84;R=OH,CH_3) occurs when these compounds are heated in a 10% $^{w}/_{v}$ aqueous sodium hydroxide solution for several hours to afford 3-(2'-aminophenyl)-5-methylpyrazole, characterised by m.p. and infrared and n.m.r. data. A mechanism is outlined below.



(84)

(81, 82)

The ring-opening of the fused pyrimidine[113] could also occur by a similar mechanism.



Reactions of the 5-functional group

Decarboxylation of the 5-carboxylic acid (69) was attempted. The usual methods of decarboxylation failed to produce the parent heterocycle. However an experiment involving the use of copper bronze powder produced a small amount of an oil in addition to the sublimed acid. The oil contained no carbonyl group, as shown by infrared spectroscopy. Attempts to improve the yield of this oil were unsuccessful.

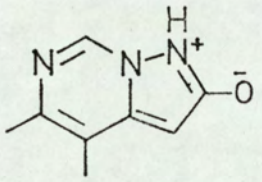
Esterification is accomplished by refluxing the acid (89 ; X=OH) in methanol containing sulphuric acid. The identity of the ester (89 ; $X=OC_2H_5$) is disclosed by a study of infrared and n.m.r. spectral data.

Ammonolysis of the ester (89 ; X=OH) is effected by stirring in ammonia (d 0.880) over a period of several hours. The amide (89 ; $X=NH_2$) is produced in good yield.

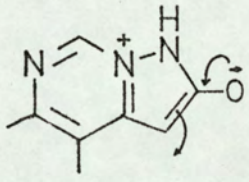
Hydrazinolysis occurs when the ester is boiled under reflux with hydrazine hydrate to give 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylic acid hydrazide (89 ; $X=NHNH_2$) in excellent yield. Ring cleavage does not occur.

An Explanation for the failure of certain electrophilic substitutions

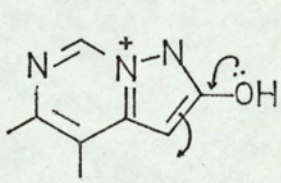
It is proposed that the observed reactivity to electrophiles of position 3 in 2-hydroxypyrazolo|1,5-c|quinazolines is the result of two opposing effects; a) the deactivation of the ring at C-3 by the contribution to the tautomeric equilibrium of a structure which is protonated at N-1, namely the zwitterion, (99) in which form this compound has been shown to exist and b) the activation of the ring by the contribution to the resonance hybrid of the 'unlikely' doubly changed connonical forms (100, 101) in which structures the oxygen lone pair is able to conjugate directly with C-3. (The double bonds in pyrazolo|1,5-c|quinazolines can be described as 'fixed' since structures (100, 101) are 'unlikely').



(99)

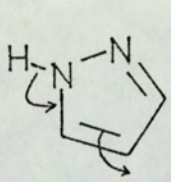


(100)

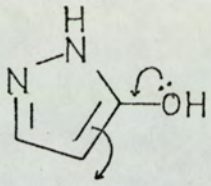


(101)

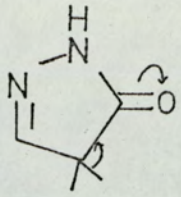
Electrophilic substitution is therefore not facilitated to the extent observed in pyrazoles (102) where the lone pair associated with the second nitrogen atom can easily conjugate with pi electrons in the ring and in 5-hydroxypyrazoles (103) or pyrazol-5-ones (104) where additional conjugation with C-4 is seen.



(102)



(103)



(104)

The substitution of 2-hydroxypyrazolo|1,5-a|pyrimidines by weak electrophiles (bromine and the nitrosonium ion) has been summarised in the introduction to this work and although the above considerations can also be applied to these compound the substituents at C-5 and C-7 (alkyl, phenyl, hydroxyl and amino groups) effect an increase in electron density at C-3. The fused benzene ring of pyrazolo|1,5-c|quinazolines effects a decrease in electron density at C-3.

The existence in acid of the protonated structures 95, 96 has been postulated to be responsible for ring cleavage and it is further suggested that the presence of hydrogen bromide in the bromine used in the attempted bromination of 2-hydroxypyrazolo|1,5-c|quinazoline effects ring cleavage of structures 96, 97 in the manner described on page 53 to precipitate from solution the ring-opened compound, as the hydrobromide, which cyclises to the starting material when heated in water. A similar explanation can be forwarded to account for the isolation of starting material from the attempted nitrosation of 2-hydroxypyrazolo|1,5-c|quinazoline.

The nitrosation of 2-methylpyrazolo|1,5-c|quinazoline presumably fails because the hydrochloride of this molecule is insufficiently reactive to the weakly electrophilic nitrosonium ion; pyrazoles containing no activating substituents cannot be nitrosated. Similarly acetylation of the pyrazolo-

pyrimidine (69) and pyrazoloquinazolines(84; R'=OH,Me) also fails.

Further work on the relative basicities of N-1 and N-8 in pyrazoloquinazolines and of N-1 and N-6 in the pyrazolopyrimidin could be undertaken to clarify the ring opening reaction and the lack of reactivity of 2-hydroxypyrazolo[1,5-c]quinazolines towards electrophiles.

Experimental

Infrared spectra were determined as potassium bromide discs (unless otherwise stated) with a Unicam S.P. 200 spectrophotometer.

Nuclear magnetic resonance spectra were determined, with tetramethylsilane as internal standard in deuterochloroform solutions and with tetramethylsilane as external standard when deuterated dimethylsulphoxide was used as solvent, on a Varian A-60 A spectrophotometer.

All peaks are assigned in terms of τ values. Abbreviations used in the interpretation of n.m.r. spectra; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; J = coupling constant; a = removed on deuteration.

Mass spectra were determined with an A.E.I. MS9 spectrophotometer operating at 50μa and 70EV. M^+ signifies the molecular ion peak observed experimentally.

Melting points are uncorrected. Reaction temperature quoted, are those of the external bath.

1,1-Diethoxypentan-2,4-dione. (63)

A method similar to that described by W. Braker et al. [116] was used. Molecular sodium (1.4 g) was suspended, by vigorous stirring in light petroleum b.p. 100-120°, (50 cm^3) and ethyl diethoxyacetate (13.5 g) was added slowly at 0°. The subsequent addition of dry acetone (4.0 g) at 0° over a period of 30 minutes followed by the isolation procedure described by Braker gave 1,1-diethoxypentan-2,4-dione (7.1 g, 50%); b.p. 2.0 mm, 80-82° (lit, 60% b.p. 3.0 mm 78-82°). [116,117,118].

$\tau(CDCl_3)$ 8.8(6H, t, J=7Hz, 1-CH_2-$C\underline{H}_3$), 7.9(3H, s, $C\underline{H}_3$),
6.4(4H, q, J=7Hz, 1-$C\underline{H}_2$-CH_3), 5.2(1H, s, $C\underline{H}_3$), 4.1(1H, s, 3-$\underline{H}$).

3(5)-Diethoxymethyl-5(3)-methylpyrazole. (64)

A method similar to that of Helmut Bredereck et al. [97] was adopted. Hydrazine hydrate (1.4 g) in ethanol (10 cm^3) was added dropwise with stirring and cooling, to a solution of 1,1-diethoxypentan-2,4-dione (3.76 g) in ethanol (20 cm^3). Bredereck's isolation gave 3(5)-diethoxymethyl-5(3)methylpyrazole (2.9 g, 73%); b.p. 0.005 99-101°, (lit, 78% b.p. 0.001 mm 94-96°) [97] as a yellow oil which was sufficiently pure for further reactions.

$\tau(CDCl_3)$ 8.9(6H, t, J=7Hz, 2-CH_2-$C\underline{H}_3$), 7.8(3H, s, $C\underline{H}_3$),
6.4(4H, q, J=7Hz, 2-$C\underline{H}_2$-CH_3), 4.4(1H, s, methine-$\underline{H}$),
3.9(1H, s, 4-$\underline{H}$), 1.9(1H, broad s, $N\underline{H}$)[a].

3(5)-Formyl-5(3)-methylpyrazole. (65)

3(5)-Diethoxymethyl-5(3)-methylpyrazole (2.9 g) was dissolved in a solution of conc. hydrochloric acid (0.65 cm^3) in water (15.5 cm^3). The solution was allowed to stand at room temperature for 10 hours. The colourless crystals were filtered washed well with water and methanol and dried, to give 3(5)-formyl-5(3)-methylpyrazole (1.4 g, 95%), m.p. 188-189°, (lit, 94%. m.p. 188-189°).[97]

(Found: M^+, 110.048010; $C_5H_6N_2O$ requires M, 110.048047).

$\nu_{max.}$ 3100 (aromatic C-H), 2900 (aliphatic C-H), 2700 (aldehydic C-H) 1690 (C=O), 1630 (C=N), 1450 (C-H), 1380 (C-H), 1060,840 800 $cm.^{-1}$

A suitable solvent for n.m.r. spectral analysis was not available.

4- 1'(2')-Acetyl-5'-methylpyrazol-3'-ylidene 2-phenyloxazol-5(4H)-one. (66)

Sodium acetate (1.0 g), benzoylglycine (1.0 g) and 3(5)-formyl-5(3)-methylpyrazole (0.5 g) were finely ground and intimately mixed. Acetic anhydride (3.0 cm^3) was added and the mixture heated under reflux on a steam bath for 1 hour, cooled until solid and triturated with water to yield a yellow solid, which was filtered, washed well with cold water and dried to give crude 4-(1'(2')-acetyl-5'-methylpyrazol-3'-ylidene)2-phenyloxazol-5(4H)-one (1.0 g) m.p. 188°.

The crude solid was extracted twice with boiling ethanol (20 cm^3) from which crystallization occurred. Concentration of the mother liquors produced a further crop of crystals. Both crops were combined and recrystallized from ethanol to give the oxazolone (66) (0.2 g, 20%) m.p. 189°. This compound and the remainder of the crude product (0.6 g) had identical infrared and n.m.r. spectra.

Alternatively, in another preparation, the whole of the crude yellow solid was dissolved in warm pyridine (10 cm^3). The solution was cooled and water (30 cm^3) was added carefully with stirring, to

give a yellow precipitate which was filtered, washed well with water and dried to give the oxazolone (66; 0.6 g, 60%) m.p. 188°, which was sufficiently pure for further reaction. An analytical sample was obtained, by several recrystallizations, (from ethanol) as pale yellow plates m.p. 190-191°.

(Found: C, 64.02; H, 4.66; N, 14.06%; $\underline{M}^+$, 295.096541. $C_{16}H_{13}N_3O_3$ requires C, 65.16; H, 4.41; N, 14.25%; $\underline{M}$, 295.09568).

$\nu_{max.}$ (Nujol) 1800 (lactone C=O), 1720 (acyl C=O), 1600 (C=C), 1320,980,960,880,720,700 $cm.^{-1}$

$\tau(CDCl_3)$ 7.5(3H, s, $C\underline{H}_3$), 7.4(3H, s, $C\underline{H}_3$), 3.0(2H, s, pyrazole 4-$\underline{H}$ and ylidene protons), 2.6-2.8(3H, m, 3',4' and 5' phenyl protons), 2.0-2.2(2H, m, 2' and 6' phenyl protons).

2-Methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylic acid. (69)

A solution of 4-1'(2')-acetyl-5'-methylpyrazol-3'-ylylidene -2-phenyloxazol-5(4H)-one (1.0 g) in aqueous 10% sodium hydroxide solution (20 cm^3) was heated under reflux for 2 hours on a steam bath. The yellow solution was allowed to cool and was filtered. The filtrate was carefully acidified to pH4 (congo-red paper) to yield a fine colourless precipitate which coagulated in 10 minutes and was filtered, washed well with water and dried to give 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylic acid as colourless needles (0.85 g, 85%) m.p. 210-211° decomp. (from ethanol).

(Found: C, 66.1; H, 4.2; N, 16.0%; $\underline{M}^+$, 253.085931. $C_{14}H_{11}N_3O_2$ requires C, 66.5; H, 4.4; N, 16.6%; $\underline{M}$, 253.085121).

$\nu_{max.}$ 3150-2850 (bonded-OH), 2650 (quaternary amine), 1700 (carboxylic-OH), 1610 (carboxylate C-O), 1540,1520,1500 (C=C), 1450,1380,1280,1220,800,740,680,660 $cm.^{-1}$

$\tau(CDCl_3)$ 7.4(3H, s, $C\underline{H}_3$), 3.3(1H, s, 3-$\underline{H}$), 2.4-2.6(3H, m, 3',4' and 5' phenyl protons), 1.8(1H, s, 4-$\underline{H}$), 1.5-1.7(2H, m, 2' and 6'

phenyl protons).

Attempted Decarboxylation of 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxlic acid. (69)

Method A.

2-methyl-7-phenylpyrazolo 1,5-c pyrimidin-5-carboxylic acid (0.1 g) was heated at 250° for 2 hours. Sublimation occurred to afford unchanged starting material (0.08 g), m.p. 200-210°. $\nu_{max.}$ identical with starting material.

Method B.

The carboxylic acid (69; 0.1 g) and copper bronze (0.02 g) were mixed well and heated at 250° for 2 hours. A pale yellow powder was collected, washed (light petroleum; b.p. 40-60°) and dried to afford unchanged starting material (0.08 g). Evaporation of the petroleum washings afforded a trace of a pale yellow oil, the infrared spectrum showed no carboxylic acid absorption. Increasing the amount of copper powder in the reaction mixture up to 60% by weight did not improve the yield of the oil.

2-Methyl-3-nitro-7-(3'-nitrophenyl)pyrazolo|1,5-c|pyrimidin-5-carboxylic acid. (91)

2-Methyl-7-phenylpyrazolo 1,5-c pyrimidin-5-carboxylic acid (0.25 g) was dissolved in conc. sulphuric acid (3.0 cm^3). A mixture of conc. sulphuric and conc. nitric acids in equal parts by volume (3.0 cm^3) was added over a period of 20 minutes, at 0°. The reaction mixture was maintained at this temperature for 10 hours then poured onto crushed ice (5.0 g). The precipitate was collected, washed well with water and dried in vacuo to give 2-methyl-3-nitro-7-(3'-nitrophenyl) pyrazolo 1,5-c pyrimidin-5-carboxylic acid (0.32 g, 93%).m.p. 267-269° (from ethanol).

(Found: C, 48.5; H, 2.6; N, 20.3%; M^+, 343.056095. $C_{14}H_9N_5O_6$ requires C, 49.0; H, 2.6; N, 20.4%; M , 343.055276).

$\nu_{max.}$ 3150-2850 (bonded-OH), 2700 (quaternary amine), 1535 (NO_2), 1460,1350 (NO_2), 1280,1210.1175,1100,940,840,720,680 $cm.^{-1}$

τ(DMSO-d_6) 7.4(3H, s, 2-CH_3), 2.3(1H, t, 5'-H), 1.7(1H, d, 4'-H), 1.6(1H, s, 4-H), 1.4(1H, d, 6'-H), 0.98(1H, broad s, 2'-H).

Attempted preparations of 2-Methyl-3-nitro-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylic acid. (90); X=OH, E=NO_2)

Method A.

2-Methyl-7-phenylpyrazolo 1,5-c pyrimidin-5-carboxylic acid (0.25 g) was dissolved in conc. sulphuric acid (3.0 cm^3) and the solution cooled to 0°. A mixture of conc. sulphuric and conc. nitric acids in equal parts by volume (3.0 cm^3) was added dropwise, over a period of 15 minutes. The reaction mixture was allowed to stand at 0° for a further 15 minutes and was then poured onto crushed ice (5.0 g). The precipitate was collected, washed well with water and dried in vacuo, to give a mixture of 2-methyl-3-nitro-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylic acid, and the dinitrated product (91) (0.2 g, 80%) m.p. 258-269°.

(Found: M^+, 298.070458, $C_{14}H_{10}N_4O_4$ requires M^+, 298.070198;
M^+, 343.055686; $C_{14}H_9N_5O_6$ requires M, 343.055276.

Method B.

A further preparation of the mononitrated product (90) was attempted by treatment of 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylic acid (0.2 g) with fuming nitric acid (4.0 cm^3) at 0° for 30 minutes. The reaction mixture was worked up as in method A above and the colourless precipitate was filtered, washed with water and dried to

give a mixture of starting material (69) and 2-methyl-3-nitro-7-phenylpyrazolo 1,5-c pyrimidin-5-carboxylic acid (0.15 g, 85%), m.p. 212-220°.

(Found: M^+, 253.085931; $C_{14}H_{11}N_3O_2$ requires M, 253.085121;

M^+, 298.070458; $C_{14}H_{10}N_4O_4$ requires M, 298.070198).

Attempted preparation of 2-Methyl-3-acetyl-7-phenylpyrazolo[1,5-c]pyrimidin-5-carboxylic acid. (90) ; X=OH, E=CH_3CO)

Method A.

2-methyl-7-phenylpyrazolo[1,5-c]pyrimidin-5-carboxylic acid (0.25 g) was dissolved with warming in a mixture of equal volumes of acetic anhydride and glacial acetic acid (10 cm^3). The solution was heated on a steam bath under reflux for 3 hours, allowed to cool and then poured into cold water (50 cm^3). The pale yellow precipitate was filtered and dried in vacuo, giving starting material, (0.2 g, 80%), m.p. 206-209°. $\nu_{max.}$ identical with starting material. The product was reprecipitated from base with dilute hydrochloride acid and used in the next reaction.

Method B.

The starting material obtained above (0.09 g) was dissolved with sodium acetate (0.2 g) in acetic anhydride (50 cm^3). The solution was heated under reflux on an oil bath (120°) for 3 hours, allowed to cool and poured into cold water (100 cm^3). The solution was evaporated to dryness in vacuo to give starting material (0.06 g) m.p. 200-204°. $\nu_{max.}$ identical with starting material.

Method C.

2-methyl-7-phenylpyrazolo[1,5-c]pyrimidin - 5-carboxylic acid (0.1 g) was mixed intimately with finely powered, dry, yellow aluminium trichloride (0.2 g, 4 mole.). Acetyl chloride (0.065 g) in nitrobenzene (20 cm^3) was

added and the mixture heated at 165° for 3 hours. The reaction mixture was cooled and acidified with hydrochloride acid (10 cm^3) and water (20 cm^3) was added.

A pale brown solid was isolated by steam distillation which was starting material (0.09 g, 90%), m.p. 204-208. $\nu_{max.}$ identical with starting material.

2-Methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxamide. (89; X=NH_2)

Ethyl 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate (; 0.26 g) was dissolved in conc. ammonia solution (d 0.88) (20 cm^3) and stirred at room temperature for 72 hours.

The colourless solid was filtered, washed and dried to give 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxamide (0.19 g, 85%) m.p. 246-247° as colourless needles (from ethanol).

(Found: C, 66.8; H, 4.8; N, 22.5%; M^+, 252.099524; $C_{14}H_{12}N_4O$ requires C, 66.7; H, 4.8; N, 22.2%; M , 252.101105).

$\nu_{max.}$ 3500 (free N-H), 3500-2900 (bonded NH and C-H), 1700 (C=O), 1620 (C=N), 1600 (C=C), 1550,1500,1420,1300,1240,900,820,690,670 cm^{-1}

τ(DMSO-d_6) 7.6(3H, s, 2-CH_3), 3.2(1H, s, 3-H), 2.4-2.5(3H, m, 3',4' and 5' phenyl protons), 1.8(1H, s, 4-H), 1.3-1.6(2H, m, 2' and 6' phenyl protons).

2-Methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylic acid Hydrazide. (89; X=$NHNH_2$)

Methyl 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate (; 0.26 g) was boiled under reflux with hydrazine hydrate (10 cm^3) for 15 minutes, by which time solution had occurred. Methanol (10 cm^3) was added and the mixture was heated under reflux for 1 hour. The mixture was evaporated under vacuum and the colourless solid collected

and dried to give 2-methyl-7-phenylpyrazolo 1,5-c pyrimidin-5-carboxylic acid hydrazide (0.2 g, 80%), m.p. 229-230° as colourless needles (from ethanol).

(Found: C, 62.7; H, 5.0; N, 26.4%; M^+, 267.11165; $C_{14}H_{13}N_5O$ requires C, 62.9; H, 4.9; N, 26.2%; M , 267.112004).

$\nu_{max.}$ 3300-2900(N-H), 1680 (C=O), 1610 (C=N), 1560 (C=C), 1500 (C=C), 1480,1100,960,780,690 $cm.^{-1}$

$\tau(CDCl_3)$ 7.5(3H, s, 2-CH_3), 5.7-6.0(2H, broad s, NH_2)[a], 3.4(1H, s, 3-H), 2.3-2.5(3H, m, 3',4' and 5' phenyl protons), 1.8(1H, s, 4-H), 1.4-1.6(2H, m, 2' and 6' phenyl protons), 0.9-1.2(1H, broad s, N-H)[a].

Ethyl 2-Methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate.(89;X=OC_2H_5) 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylic acid (69 ; 0.625 g) was dissolved in ethanol (30 cm^3). Conc. sulohuric acid (0.02 g) was added and the mixture heated under reflux for 6 hours, then evaporated to dryness in vacuo. The yellow solid was washed well with water and dried to give ethyl 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate (0.6 g, 92%) m.p. 98-99° (from ethanol) as colourless needles.

(Found: C, 67.6; H, 5.6; N, 14.7%; M^+, 281.117415; $C_{16}H_{15}N_3O_2$ requires C, 68.3; H, 5.3; N, 15.0%; M , 281.116419).

$\nu_{max.}$ 3100 (aromatic C-H), 2900 (aliphatic C-H), 1725 (C=O), 1620 (C=N), 1500,1240,1110,1040,795,775,700,660 $cm.^{-1}$

$\tau(CDCl_3)$ 8.5(3H, t, J=7Hz, CH_2CH_3), 7.4(3H, s, CH_3), 5.5(2H, q, J=7Hz, CH_2CH_3), 3.3(1H, s, 3-H), 2.3-2.5(3H, m, 3',4' and 5' phenyl protons), 1.8(1H, s, 4-H), 1.2-1.5(2H, m, 2' and 6' phenyl protons).

Ethyl 2-Methyl-3-nitro-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate.

(90; X=OC_2H_5, E=NO_2)

Ethyl 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate (89; X=OC_2H_5 ; 0.14 g) was dissolved in acetic anhydride (4.0 cm^3). A solution of fuming nitric acid (d 1.5; 0.9 g) in acetic anhydride (2.0 cm^3; 1.0 cm^3) was added at 0°. After 30 minutes at 0° the reaction mixture became blue in colour and was allowed to remain at 10° for 3 days. The dark green solid was collected, washed with acetone and dried to give ethyl 2-methyl-3-nitro-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate (0.06 g, 38%), m.p. 179-180° as yellow needles (from ethanol).

(Found: C, 57.7; H, 4.4; N, 16.8%; M^+, 326.102232; $C_{16}H_{14}N_4O_4$ requires C, 58.9; H, 4.3; N, 17.2%; M , 326.101497).

$\nu_{max.}$ 1710 (C=O), 1625 (C=N), 1545,1520,1490,1450 (NO_2), 1260,1200,1030 $cm.^{-1}$

τ($CDCl_3$) 8.5(3H, t, J=7Hz, $CH_2\underline{CH_3}$), 7.1(3H, s, 2-$\underline{CH_3}$), 5.4(2H, q, J=7Hz, $\underline{CH_2}CH_3$), 2.2-2.5(3H, m, 3',4' and 5' phenyl protons), 1.2-1.5(2H, m, 2' and 6' phenyl protons), 1.05(1H, s, 4-H).

Ethyl 2-Methyl-3-nitro-7-(3'-nitrophenyl)pyrazolo|1,5-c|pyrimidin-5-carboxylate. (91)

Ethyl 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate (89 ; 0.14 g) was dissolved in conc. sulphuric acid. A mixture of conc. nitric and conc. sulphuric acids in equal parts by volume, (2.0 cm^3) was added dropwise. The orange reaction mixture was allowed to stand at room temperature for 2 hours and was then poured onto crushed ice (1.0 g). The precipitate was collected, washed well with water and dried to give pale yellow needles of ethyl 2-methyl-3-nitro-7-(3'-nitrophenyl)

pyrazolo|1,5-c|pyrimidin-5-carboxylate (0.14 g, 87%) m.p. 166-167° (from ethanol).

(Found: C, 51.5; H, 3.4; N, 18.6%; M^+, 371.087173; $C_{16}H_{13}N_5O_6$ requires C, 51.8; H, 3.5; N, 18.9%; M , 371.086574).

$\nu_{max.}$ 1730 (C=O), 1620 (C=N), 1540 (NO_2), 1360 (NO_2), 1240,1170,1100,1020,840,730,690 $cm.^{-1}$

$\tau(CDCl_3)$ 8.5(3H, t, J=7Hz, $CH_2\underline{CH_3}$), 7.1(3H, s, 2-$\underline{CH_3}$), 5.4(2H, q, J=7Hz, $\underline{CH_2}CH_3$), 2.1(1H, broad t, 5'-H), 1.4(1H, broad d, 4'-H), 0.95(1H, broad d, 6'-H), 0.95(1H, s, 4-H) overlaooing, 0.4(1H, broad s, 2'-H).

Ethyl 3-Bromo-2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate. (90; X=OC_2H_5, E=Br.)

Bromine (0.18 g) in chloroform (1.0 cm^3) was added slowly to a stirred solution of ethyl 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate (0.28 g) in chloroform (10 cm^3). The mixture was allowed to stand at room temperature for 15 minutes and was then evaporated to dryness under reduced pressure.

The pale yellow solid was washed with water, filtered and dried to yield ethyl 3-bromo-2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate (0.32 g, 90%) m.p. 128-129° as pale yellow crystals (from ethanol).

(Found: C, 52.9; H, 3.8; N, 11.6%; M^+, 359.026649; $C_{16}H_{14}N_3O_2Br$ requires C, 53.3; H, 3.9; N, 11.7%; M , 359.026985).

$\nu_{max.}$ 1730 (C=O), 1620 (C=N), 1540 (C=C), 1225,1110,1025,780, 735,690 $cm.^{-1}$

$\tau(CDCl_3)$ 8.7(3H, t, J=7Hz, $CH_2\underline{CH_3}$), 7.6(3H, s, 2-$\underline{CH_3}$), 5.6(2H, q, J=7Hz, $\underline{CH_2}CH_3$), 2.5-2.7(3H, m, 3',4' and 5' phenyl protons), 2.0(1H, s, 4-H), 1.4-1.7(2H, m, 2' and 6'

phenyl protons).

Ethyl 3-Formyl-2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate. (90; X=OC_2H_5, E=CHO)

Phosphoryl chloride (0.19 g) was added carefully to freshly distilled, dry dimethylformamide (0.15 g), and the mixture allowed to stand at room temperature for 10 minutes, during which time ethyl 2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate (89; 0.28 g) was dissolved in warm, freshly distilled, dry dimethylformamide (2.0 cm^3). The phosphoryl chloride-dimethylformamide complex was added slowly to the solution of the ester (89) and the mixture heated at 120° for 2 hours. The reaction mixture was allowed to cool, then poured onto crushed ice (2.0 g) and the pink solid was filtered after 30 minutes, washed with water and dried to give ethyl 3-formyl-2-methyl-7-phenylpyrazolo|1,5-c|pyrimidin-5-carboxylate (0.18 g, 60%) m.p. 134-135° as pale yellow needles (from ethanol).

(Found: C, 65.3; H, 5.0; N, 13.5%; M^+, 309.111334; $C_{17}H_{15}N_3O_3$ requires C, 66.0; H, 4.9; N, 13.6%; M , 309.111681).

$\nu_{max.}$ 1720 (ester C=O), 1670 (aldehydic C=O), 1620 (C=N), 1500 (C=C), 1270,1220,1040,800,700 $cm.^{-1}$

$\tau(CDCl_3)$ 8.5(3H, t, J=7Hz, $CH_2\underline{CH_3}$), 7.2(3H, s, 2-CH_3), 5.4(2H, q, J=7Hz, $\underline{CH_2}CH_3$), 2.3-2.4(3H, m, 3',4' and 5' phenyl protons), 1.3-1.4(2H, m, 2' and 6' phenyl protons), 1.05(1H, s, 4-H), -0.5(1H, s, aldehydic-H).

2-Nitrobenzoyl Chloride. (71)

2-Nitrobenzoic acid (41.7 g) was dissolved in hot benzene (150 cm^3) on a steam bath. Thionyl chloride (40 cm^3) was added and the mixture boiled under reflux for 3 hours. Excess thionyl chloride and hydrogen chloride were distilled from the reaction mixture, and small amounts of dry benzene were added to the reaction mixture at intervals during the distillation. * When the fresh distillate did not fume in moist air, the distillation was assumed to be complete and the 2-nitrobenzoyl chloride in benzene was used for further reaction.

Methyl-2-Nitrobenzoylacetoacetate. (72)

A method similar to that of Gabriel and Gerhard[90] was used in the preparation. (See also Koeings and Freund [92])

Clean metallic sodium (8.0 g) was dissolved in ethanol (80 cm^3) at room temperature. Methyl acetoacetate (29 g) was added with stirring over 30 minutes, followed 1-nitrobenzoylchloride in benzene (from 1-nitrobenzic acid; 41.7 g) at room temperature over 30 minutes. The mixture was boiled under reflux for 2 hours, allowed to cool and diluted with water (100 cm^3). Ethanol (30 cm^3) was added, (pH adjusted to an acidic value with conc. hydrochloric acid if necessary).

Benzene (100 cm^3) was added until the emulsion separated, with the benzene layer above the aqueous layer. The benzene layer was washed with water (100 cm^3 x 3) and then with sodium carbonate solution (10%; 25 cm^3 x 4). The sodium carbonate extracts were combined and acidified with dilute sulphuric acid and the oil which separated

* Danger of explosion during heating period.

was extracted into ether (25 cm^3 x 4). The ether extracts were combined, washed with water (10 cm^3 x 3), dried (magnesium sulphate) and evaporated to dryness to give methyl-2-nitrobenzoyl acetoacetate (30.0 g, 49%) m.p. 90-92° (from ethanol), (lit, 44%, m.p. 91-92°). [91]

$\nu_{max.}$ 3100 (aromatic C-H), 2950 (aliphatic C-H), 2800-2600 (-O-H), 1715 (C=O), 1650-1580 (C=O, C=C), 1530 (NO_2), 1350 (NO_2), 1250,1140,1095,1000,880,860,800,790,760,700 $cm.^{-1}$

$\tau(CDCl_3)$ 7.4(3H, s, ketone $C\underline{H}_3$), 6.5(3H, s, ester $C\underline{H}_3$), 2.4-2.7(1H, m, phenyl protons), 2.1-2.4(2H, m, phenyl protons), 1.5-1.7(1H, broad d, phenyl protons).

2-Nitrobenzoylacetone. (74)

Methyl 2-nitrobenzoylacetoacetate (10 g) was gently boiled under reflux for 2 hours with aqueous sulphuric acid (25% w/v; 15 cm^3). The reaction mixture was cooled, and the oil extracted into ether (20 cm^3 x 2). The ether extracts were combined, washed with water (10 cm^3) and washed with aqueous sodium hydrogen carbonate (5% w/v; 15 cm^3 x 4). The ethereal solution was then extracted with aqueous sodium hydroxide (5%; 10 cm^3 x 3). The sodium hydroxide extracts were combined and carefully acidified to yield a brown oil which crystallised on standing to give 2-nitrobenzoylacetone (3.0 g, 50%) m.p. 55° (lit. 55°)[125] (from ethanol).

$\nu_{max.}$ 1610-1600 (C=O, C=C), 1540 (NO_2), 1360 (NO_2), 1310 $cm.^{-1}$

$\tau(CDCl_3)$ 7.9(3H, s, $C\underline{H}_3$), 7.6(0.35H, s, $C\underline{H}_3$), 6.0(0.23H, s, $C\underline{H}_2$), 4.2(1H, s, ethylenic-$\underline{H}$), 2.0-2.5(4H, m, phenyl protons).

3-Methyl-5-(2'-nitrophenyl)pyrazole. (76)

2-Nitrobenzoylacetone (3.0 g) was dissolved in ethanol (20 cm^3) and added dropwise at 20° to a solution of hydrazine hydrate (1.0 g) in ethanol (10 cm^3). The mixture was boiled under reflux for 2 hours and

the solvent removed in vacuo. The yellow solid was collected, washed well with water and dried to give 3(5)-methyl-5(3)-(2'-nitrophenyl) pyrazole (2.1 g, 60%) m.p. 103-104° (lit. 103-104°) [92]

$\nu_{max.}$ (Nujol) 3350 (N-H), 1540 (NO_2), 970,860,800,795,775,755,720 $cm.^{-1}$

($CHCl_3$) 3500 (N-H), 1540 (NO_2), 1360 (NO_2) $cm.^{-1}$

τ($CDCl_3$) 7.8(3H, s, CH_3), 3.8(1H, s, pyrazole 4-H),

2.2-2.7(4H, m, phenyl protons), -0.25(1H, broad s, NH)[a].

3-(2'-Aminophenyl)-5-methylpyrazole. (81; R=CH_3)

Palladium-charcoal catalyst (0.1 g) was treated with ethanol (10 cm^3) followed by 3(5)-methyl-(5)3-(2'nitrophenyl)pyrazole (1.0 g). Reduction with hydrogen at atmospheric pressure was allowed to proceed for 14 minutes intil hydrogen (330 cm^3) had been absorbed (calculated, 336 cm^3).

The reaction mixture was heated to 50°, then filtered through kieselguhr. The filtrate was evaporated to dryness in vacuo to give a yellow oil which solidified to yield 3(5)-(2'-aminophenyl)-5(3)-methylpyrazole (0.7 g, 88%) m.p. 119-120° (from ethanol) (lit. 120°) [120] (and 122°) [92]

$\nu_{max.}$ (Nujol) 3450 (N-H), 3400-3100 (NH), 1605 (C=N, C=C), 1580 (C=C), 1510 (C=C), 1140,1040,960,800,760 $cm.^{-1}$

($CHCl_3$) 3500 (N-H), 3400-3200 (NH), 3005 (aromatic C-H), 2950 (aliphatic C-H), 1620 (C=C, C=N), 1580 (C=C), 1480,1320,1160,960 $cm.^{-1}$

τ($CDCl_3$) 7.7(3H, s, CH_3), 3.6(1H, s, pyrazole 4-H),

2.3-3.4(7H, m, phenyl protons and NH x 3).

2-Methylpyrazolo[1,5-c]quinazoline. (84; R=CH_3)

3(5)-(2'Aminophenyl)-5(3)-methylpyrazole (0.7 g) was heated in triethyl orthoformate at 120° for 1 hour. The solvent was removed in vacuo

and the yellow solid collected, washed with ethanol and dried to give 2-methylpyrazolo 1,5-c quinazoline (0.55 g, 71%) m.p. 93-94° (from ethanol), (lit. 75%; m.p.93-94°) [84]

$\nu_{max.}$ 3100 (aromatic C-H), 1625 (C=N), 1540,1485,1395,900, 795,770,760 $cm.^{-1}$

$\tau(CDCl_3)$ 7.5(3H, s, $C\underline{H}_3$), 3.4(1H, s, 3-H), 2.0-2.6(4H, m, 4,5,6 and 7-H), 1.05(1H, s, 9-H).

m/e M^+, 183.

The reaction of 3(5)-(2'-Aminophenyl)-5(3)-methylpyrazole (81; R=CH_3) Acetic Anyhdride.

3(5)-(2'-Aminophenyl-5(3)-methylpyrazole (0.4 g) was stirred at room temperature in acetic anhydride for 18 hours. The solvent was removed under reduced pressure to give a white solid which was washed with water and dried, yielding (0.4 g, 100%) of a mixture m.p. 95-157°.

$\nu_{max.}$ (Nujol) 3200 (N-H), 1730 (pyrazole N acyl C=O), 1680 (amide C=O), 1615 (C=N), 1600 (C=C), 1570 (C=C), 1550 (C=C), 1480,1430,1390, 1370,1340,1300,1280,1050,1040,1000,960,780 $cm.^{-1}$

The white solid was extracted continuously with dry ether for 2 hours. Evaporation of the ether gave 2,9-dimethylpyrazolo 1,5-c quinazoline (85) (0.03 g, 8%) m.p. 87-88°

(Found: $\underline{M}^+$, 197.094173; $C_{12}H_{11}N_3$ requires M, 197.095293).

$\nu_{max.}$ (Nujol) 1620 (C=N), 1550 (C=C), 1480,1460,1390,780 $cm.^{-1}$

$\tau(CDCl_3)$ 7.5(3H, s, 2-$C\underline{H}_3$), 7.1(3H, s, 9-$C\underline{H}_3$), 3.3(1H, s, 3-H), 1.9-2.6(4H, m, 4,5,6 and 7-H).

The residual whote solid was collected to give 5-(2'-acetamidophenyl)-1(2)-acetyl-3-methylpyrazole (86) (0.3 g, 55%) m.p. 194-195° (from ethanol).

(Found: M^+, 257.115432; $C_{14}H_{15}N_3O_2$ requires M, 257.116419).

$\nu_{max.}$ (Nujol) 3200 (NH), 1730 (pyrazole N acyl C=O), 1680 (amide C=O), 1610 (C=N), 1590 (C=C), 1570 (C=C), 1540,1480,1430,1370,1340, 1300,1280,960 $cm.^{-1}$

$\tau(CDCl_3)$ 7.8(3h, s, pyrazole 3-CH_3), 7.3(3H, s, CH_3), 7.2(3H, s, CH_3), 3.4(1H, s, pyrazole 4-H), 2.1-2.7(4H, m, phenyl protons).

The method of De Stevens [85] was also used and gave a quantative yield of the diacetyl product (86).

Attempted Thermal Cyclization of 5-(2'-Acetamidophenyl-1(2)-acetyl-3-methylpyrazole. (86)

5-(2'-Acetamidophenyl)-1(2)-acetyl-3-methylpyrazole (0.2 g) was heated at 210° for 2 hours. The product was collected and recrystallised from ethanol to give starting material (0.18 g, 90%) m.p. 194-195°.

$\nu_{max.}$ and $\tau(CDCl_3)$ identical with starting material.

3-Bromo-2-methylpyrazolo|1,5-c|quinazoline. (88; R=CH_3, E=Br)

A solution of bromine (1.0 cm^3) in chloroform (10.0 cm^3; 1.1 cm^3) was added dropwise with stirring to a solution of 2-methylpyrazolo 1,5-c quinazoline (0.37 g) in chloroform (10.0 cm^3). The yellow precipitate, a salt, was filtered, washed and heated with water for 10 minutes. This precipitate was filtered, washed well, and dried to give 3-bromo-2-methylpyrazolo|1,5-c|quinazoline (0.32 g, 58%) m.p. 126-127° (from ethanol).

(Found: C, 50.5; H, 3.2; N, 16.0%; M^+, 260.989892; $C_{17}H_{12}N_3Br$ requires C, 50.4; H, 3.05; N, 16.0; M ,260.990209).

$\nu_{max.}$ 1620 (C=N), 1480,1380,1060,920,790,770 $cm.^{-1}$

$\tau(DMSO_{D6})$ 7.5(3H, s, 2-CH_3), 2.0-2.4(3H, m, 5,6, and 7-Hs), 1.2-1.5(1H, m, 4-H), 0.75(1H, s, 9-H).

2-Methyl-3-nitropyrazolo|1,5-c|quinazoline. (88; R=CH_3, E=NO_2)

2-Methylpyrazolo 1,5-c quinazoline (0.25 g) was dissolved in fuming nitric acid (d 1.5; 4.0 cm^3) and allowed to stand at room temperature for 2 hours. The reaction mixture was poured onto crushed ice (2.0 g) and the yellow precipitate collected, washed well with water and dried *in vacuo* to give 2-methyl-3-nitropyrazolo|1,5-c|quinazoline (0.26 g, 84%) m.p.188-189° (from methanol).

(Found: C, 57.3; H, 3.6; N, 24.3%; M^+, 228.063750; $C_{11}H_8N_4O_2$ requires C, 57.9; H, 3.5; N, 24.6%; M , 228.064721).

$\nu_{max.}$ 1615 (C=N), 1600 (C=C), 1535 (NO_2), 1500 (C=C), 1480,1460, 1400,1350 (NO_2), 1300,1200,940,785 $cm.^{-1}$

τ($DMSO_{D6}$) 7.2(3H, s, CH_3), 1.7-2.2(4H, m, 4,5,6 and 7-Hs), 0.43(1H, s, 9-H).

3-Formyl-2-methylpyrazolo|1,5-c|quinazoline. (88; R=CH_3, E=NO_2)

Phosphoryl chloride (0.19 g) was added carefully to freshly distilled, dry dimethylformamide (0.15 g) and the mixture allowed to stand at room temperature for 10 minutes, during which time 2-methylpyrazolo 1,5-c quinazoline (0.18 g) was dissolved in freshly distilled, dry dimethylformamide (1.0 cm^3). The phosphoryl chloride-dimethylformamide complex was added slowly to the solution of the quinazoline ( ) and the mixture heated at 110° for 1.5 hours. The reaction mixture was allowed to cool, then poured onto crushed ice (2.0 g). The precipitate was collected, washed with water and dried to give 3-formyl-2-methylpyrazolo|1,5-c|quinazoline (0.14 g; 66%) m.p. 167-168° (from ethanol).

(Found: C, 67.8; H, 4.5; N, 20.1%; M^+, 211.075359; $C_{12}H_9N_3O$ requires C, 68.3; H, 4.3; N, 19.9%; M , 211.074557).

$\nu_{max.}$ 3010 (aromatic C-H), 1675 (C=O), 1600 (C=C), 1530,1480,1400, 1370,1280,1140,1070,970,800 $cm.^{-1}$

$\tau(CDCl_3)$ 7.3(3H, s, $C\underline{H}_3$), 1.9-2.5(3H, m, 5,6, and 7-$\underline{H}$s), 0.6-0.8(1H, m, 4-$\underline{H}$), 1.0(1H, s, 9-$\underline{H}$), -0.3(1H, s, C$\underline{H}$O).

Attempted Nitrosation of 2-Methylpyrazolo|1,5-c|quinazoline.(87; R=CH_3) 2-Methylpyrazolo|1,5-c|quinazoline (0.26 g) was dissolved in glacial acetic acid and the solution cooled in ice/water. Sodium nitrite (0.07 g) in cold water (5 cm^3) was added slowly. After 15 minutes the precipitate was filtered, washed and dried to give starting material (0.25 g, 95%). m.p. 89-90° (ethanol) $\nu_{max.}$ and $\tau(CDCl_3)$ identical with starting material.

Similar preparations were attempted with dilute hydrochloric acid and conc. hydrochloric acid instead of glacial acetic acid, which also produced starting material in quantitative yield.

Attempted Acetylation of 2-Methylpyrazolo|1,5-c|quinazoline.(88; R=CH_3) 2-Methylpyrazolo|1,5-c|quinazoline (0.26 g) was heated under reflux for 24 hours with a mixture of glacial acid (25 cm^3) and acetic anhydride (25 cm^3).

The solvent was evaporated under reduced pressure and the residue triturated with water and ammonium hydroxide solution. The solid was filtered, washed with water and dried to give starting material (0.2 g) m.p. 89-91°. The oil which separated on basification of the residue, was extracted into chloroform, dried (magnesium sulphate) and evaporated to dryness to give starting material (0.3 g) m.p. 87-90° (ethanol). $\nu_{max.}$ and $\tau(CDCl_3)$ identical with starting material.

Starting material was also obtained quantitatively when the quinazoline (87) (0.26 g) was reacted with the same mixture of acetic

anhydride and glacial acetic acid containing acetyl chloride (0.08 g) at 80° for 24 hours, and sodium acetate (0.13 g) at 80° for 24 hours.

2-Methylpyrazolo[1,5-c]quinazoline (87) with sodium hydroxide.

2-Methylpyrazolo[1,5-c]quinazoline (0.1 g) was dissolved in aqueous sodium hydroxide solution (10% $^{w}/_{v}$; 25 cm^3). The solution was heated for 4 hours on a steam bath. The solid precipitate was filtered, washed with water and dried to give 3-(2'-aminophenyl)-5-methylpyrazole (0.09 g; 87%). m.p. 118-119° (ethanol) with identical i.r. and n.m.r. to the compound (81) prepared from 3-methyl-5-(2'-nitrophenyl) pyrazole (76; pg 74).

Methyl 2-Nitrobenzoylacetate. (75)

A method similar to that used by Coutts et al [101] was followed. Methyl 2-nitrobenzoylacetoacetate (10.6 g) was dissolved in a hot solution of methanol (20 cm^3) and ether (5 cm^3). To this solution was added dropwise a solution of potassium hydroxide (2.6 g) in methanol (12 cm^3).

After 5 minutes the reaction mixture was cooled and ether (20 cm^3) added. The yellow precipitate was collected, washed with methanol (10 cm^3) and ether (20 cm^3) to give the potassium salt of methyl 2-nitrobenzoylacetoacetate (10 g).

The potassium salt (73; 5.0 g) was dissolved in water (20 cm^3) and warmed on a steam bath. Ammonium chloride (2.25 g) was added and the solution heated and shaken for 10 minutes. The reaction mixture was cooled rapidly and extracted with ether (5 cm^3).

The process was repeated 6 times using ammonium chloride (0.75 g) each time. On the fifth and sixth repeat, 15 minutes heating was allowed. The ether extracted were continued, washed with aqueous sodium hydrogen carbonate solution (5% $^{w}/_{v}$, 5 cm^3 x 4), washed with

water (5 cm^3 x 2), dried (calcium chloride) and evaporated to dryness under reduced pressure, to yield a deep red oil.

The oil was dissolved in warm methanol (10 cm^3) and treated dropwise with a solution of potassium hydroxide (1.2 g) in methanol (6 cm^3). The mixture was cooled after 5 minutes and treated with ether (10 cm^3) to give a yellow solid which was filtered, washed with ether and dried. The yellow solid was dissolved in water (15 cm^3) and the solution acidified with carbon dioxide gas to give methyl 2-nitrobenzoylacetate (1.4 g, 31%) m.p. 41-42° (lit. 41-42°) [91]

$\nu_{max.}$ 3020 (aliphatic CH), 2950 (aromatic C-H), 1740 (C=O), 1710 (C=O), 1540 (NO_2), 1350 (NO_2), 1000,800,760,700 $cm.^{-1}$

$\tau(CDCl_3)$ 6.2(3H, s, $C\underline{H}_3$), 6.0(2H, s, $-C\underline{H}_2$), 2.0-2.5(4H, m, phenyl protons).

3-Hydroxy-5-(2'-nitrophenyl)pyrazole. [77]

Methyl 2-nitrobenzoylacetate (0.45 g) was dissolved in methanol (20 cm^3) and the solution was added over 15 minutes to a solution of hydrazine hydrate (0.13 g) in methanol (5 cm^3) with cooling. The mixture was heated under reflux at 80° for 1 hour after which time the solvent was removed in vacuo to give a brown oil. The oil was triturated with water to give a pale yellow solid which was collected, washed with water and dried in vacuo to give 3(5)-hydroxy-5(3)-(2'-nitrophenyl) pyrazole (0.32 g, 81%) m.p. 189-190° (from water).

(Found: C, 52.4; H, 3.2; N, 20.3%; $\underline{M}^+$, 205.048533 $C_9H_7N_3O_3$ requires C, 52.7; H, 3.4; N, 20.5%; $\underline{M}$, 205.048736).

$\nu_{max.}$ 3320 (OH), 2950 (aromatic C-H), 2700-2400 (N^+-H), 1630 (C=N), 1610 (C=C), 540 (NO_2), 1360 (NO_2), 790,760,700 $cm.^{-1}$

$\tau(DMSO_{D6})$ 6.0-7.0(2H, broad s, N-$\underline{H}$ and O-$\underline{H}$)[a], 4.5(1H, s, pyrazole 4-$\underline{H}$)[a], 2.1-2.7(4H, m, phenyl protons).

3-(2'-Aminophenyl)pyrazol-5-one. (80)

3-(2'-aminophenyl)pyrazol-5-one (0.5 g) was dissolved in ethanol (5 cm^3) and the solution added to palladium-charcoal catalyst (0.05 g) in ethanol (5 cm^3). Reduction at atmospheric pressure with hydrogen was allowed to take place until the theoretical quantity of hydrogen had been absorbed (340 cm^3, 12 minutes). The reaction mixture was heated and filtered through celite. The filtrate was evaporated to dryness to give 3-(2'-aminophenyl)pyrazol-5-one (0.4 g, 84%) m.p. 219-220° (from ethanol).

(Found: C, 61.4; H, 5.1; N, 23.7%; M^+, 175.074697 $C_9H_9N_3O$ requires C, 61.7; H, 5.1; N, 24.0%; M , 175.074557).

$\nu_{max.}$ 3400 (N=H), 3300 (NH), 3150 (NH), 2900 (C-H), 1780 (C=O), 1610 (C=C, C=N), 1500 (C=C), 1320,1260,750,720 $cm.^{-1}$

$\tau(DMSO_{D6})$ 4.3(1H, s, pyrazole 4-H)[a], 2.4-3.7(4H, m, phenyl protons), 1.4-3.0(4H, broad s, $N-H_2$, N-H and O-H)[a].

2-Hydroxypyrazolo 1,5-c quinazoline. (84; R=OH).

3-(2'-Aminophenyl)pyrazol-5-one (0.4 g) and methyl orthoformate (15 cm^3) were heated together at 120° for 15 minutes. The yellow precipitate was filtered, washed with methanol and dried to give 2-hydroxypyrazolo 1,5-c quinazoline (0.35 g, 88%) m.p.274-275° (from ethanol).

(Found: C, 64.4; H, 3.7; N, 22.9%; M^+, 185.058715 $C_{10}H_7N_3O$ requires C, 64.8; H, 3.8; N, 22.7%; M , 185.058908).

$\nu_{max.}$ 3100 (CH), 2700-2400 (N^+-H), 1625 (C=N), 1600 (C=C), 1540,1500,1380,1100,920,790,750 $cm.^{-1}$

$\tau(DMSO_{D6})$ 3.3(1H, s, 3-H), 1.8-2.4(4H, m, 4,5,6 and 7-H), 0.9(1H, s, 9-H).

Attempted Bromination of 2-Hydroxypyrazolo|1,5-c|quinazoline.(84; R=OH) 2-Hydroxypyrazolo|1,5-c|quinazoline (0.25 g) in glacial acetic acid (5.0 cm^3) was heated at room temperature with a 10% solution of bromine in glacial acetic acid (0.7 cm^3). After 1 hour the white precipitate was collected, washed and dried to afford a compound (0.31 g) m.p. 300°. $\nu_{max.}$ 1650 $cm.^{-1}$

Heating this compound with water afforded the starting material m.p.274-275. $\nu_{max.}$ identical with starting material.

2-Hydroxy-3-nitropyrazolo|1,5-c|quinazoline. (88; R=OH, E=NO_2) 2-Hydroxypyrazolo|1,5-c|quinazoline (0.2 g) was added to fuming nitric acid (3.0 cm^3) and the mixture allowed to remain at room temperature for 1 hour. The brown liquid was poured onto ice water and the precipitate collected, washed with water and dried, to give 2-hydroxy-3-nitropyrazolo 1,5-c quinazoline (0.2 g, 90%) m.p. 281° as pale yellow prisms.

(Found: C, 50.7; H, 2.8; N, 23.8%; M^+, 230.044278 $C_6H_{10}N_4O_3$ requires C, 52.2; H, 2.6; N, 24.4%; M , 230.043986).

$\nu_{max.}$ 1620,1575 (NO_2), 1480,1420,1355 (NO_2), 1150,800,780 $cm.^{-1}$

$\tau(DMSO_{D6})$ 1.9-2.3(3H, m, 5,6 and 7-Hs), 0.8-1.2(1H, m, 4-H), 0.75(1H, s, 9-H).

Attempted Nitrosation of 2-Hydroxypyrazolo|1,5-c|quinazoline. (84; R=OH) A solution of sodium nitrite (0.138 g) in water (5 cm^3) was added slowly at 1° to a solution of 2-hydroxypyrazolo 1,5-c quinazoline (0.37 g) in conc. hydrochloric acid (25 cm^3). The mixture was stirred at 0° for 45 minutes and the colourless precipitate filtered, washed with water and dried to give starting material m.p. 274-275° (from ethanol). $\nu_{max.}$ and $\tau(DMSO_{D6})$ identical with starting material.

Attempted diazocoupling of 2-Hydroxypyrazolo|1,5-c|quinazoline.(84; R=OH) Aniline (0.24 g) was dissolved in dilute hydrochloric acid (10%, 2.0 cm^3) and heated with an aqueous solution of sodium nitrite (3.5 cm^3; 0.2 g) at 0°. The resulting solution was added at 0° to a solution of 2-hydroxypyrazolo 1,5-c quinazoline (0.45 g) in aqueous sodium hydroxide (10%; 6.0 cm^3) also at 0°.

The red coloured solution produced was stirred for 15 minutes at 0° and neutralised (dilute hydrochloric acid). The white precipitate was filtered, washed and dried to afford starting material (84; 0.43 g) m.p. 274-275°. $\nu_{max.}$ identical with starting material.

2-Acetoxypyrazolo|1,5-c|quinazoline. (92)

2-Hydroxypyrazolo|1,5-c|quinazoline (0.5 g) was heated at 100° for 2 hours in acetic anhydride. The reaction mixture was evaporated to dryness in vacuo to give a pale yellow oil. The oil was triturated with water to give a buff coloured solid which was filtered, dried and extracted continuously with ether. Evaporation of the ether gave 2-acetoxypyrazolo 1, 5-c quinazoline (0.38 g, 74%) m.p. 99-100° (from ether).

(Found: C, 63.0; H, 4.2; N, 18.7%; M^+, 227.069578 $C_{12}H_9N_3O_2$ requires C, 63.4; H, 4.0; N, 18.5%; M , 227.069472).

$\nu_{max.}$ 2950 (CH), 1760 (C=O), 1620 (C=N, C+C), 1450,1380,1200 (C-O), 900,790,720 $cm.^{-1}$

$\tau(DMSO_{D6})$ 7.5(3H, s, CH_3), 2.7(1H, s, 3-H), 1.4-2.4(4H, m, 4,5,6 and 7-H), 0.66(1H, s, 9-H).

Further reaction of the quinazoline ( ) with acetic anhydride for 36 hours at 120° produced the starting material m.p. 99-100° in quantitative yield. $\nu_{max.}$ and $\tau(DMSO_{D6})$ identical with starting material.

2-Acetoxypyrazolo|1,5-c|quinazoline (92) with acetyl chloride.

2-Acetoxypyrazolo|1,5-c|quinazoline (0.2 g) was heated in acetic anhydride containing acetyl chloride (0.15 g) at 120° for 2 hours. Evaporation of the solvent afforded starting material (0.19 g, 92%) m.p. 98-99° (ethanol) $\nu_{max.}$ and $\tau(DMSO_{D6})$ identical with starting material.

2-Acetoxypyrazolo|1,5-c|quinazoline (92) with Acetic acid.

2-Acetoxypyrazolo 1,5-c quinazoline (0.2 g), sodium acetate (0.13 g), and glacial acetic acid (25 cm^3) were heated together at 120° for 2 hours, the solvent was removed in vacuo and the residue triturated with water, filtered and dried to give starting material in quantitative yield (ethanol) $\nu_{max.}$ and $\tau(DMSO_{D6})$ identical with starting material.

2-Hydroxypyrazolo|1,5-c|quinazoline (84;R=OH) with dilute mineral acid

2-Hydroxypyrazolo| 1,5-c |quinazoline (0.19 g) was dissolved slowly with stirring at room temperature in hydrochloric acid (2N, 5 cm^3) and was allowed to stir at room temperature for 6 hours.

The colourless needles were filtered, washed with ethanol and dried in vacuo to give 3(5)-(2'-Formamidophenyl)-5(3)-hydroxypyrazole (93) hydrochloride (0.15 g, 58%) m.p. 275-276°.

(Found: C, 50.6; H, 4.3; N, 17.6%; M^+, 185.058715 $C_{10}H_9N_3O_2HCl$ requires C, 50.1; H, 4.2; N, 17.6%; M ,).

$\nu_{max.}$ 3350 (NH), 3000-2400 (N^+H and OH), 1650 (C=O), 1600 (C=C), 1540,1480,1400,1300,1220,980,770 $cm.^{-1}$

τ(DMSO) 3.2(1H, s, pyrazole 4-H), 1.5-2.4(8H, m, NH, N^+H, and phenyl protons), 0.5(1H, s, formyl-H).

2-Hydroxypyrazolo|1,5-c|quinazoline with sodium hydroxide.

2-Hydroxypyrazolo|1,5-c|quinazoline (0.2 g) was dissolved in sodium hydroxide solution (10% $^{w}/_{v}$; 50 cm^3) and heated on a steam bath for 4 hours. The solution was cooled, acidified with conc. hydrochloric acid until slightly acidic (litmus), and allowed to stand at room temperature for 2 hours. The yellow solid was filtered, washed with water and dried, to give 3-(2'-amniophenyl)pyrazol-5-one (0.16 g, 78%) m.p. 218-219° (ethanol), i.r. and n.m.r. spectra were identical with compound (80).

(Found: $\underline{M}^+$, 175.074697; $C_9H_9N_3O$ requires $\underline{M}$, 175.074557).

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