UNIVERSITY OF GLASGOW

THESIS

submitted for the degree of

DOCTOR OF PHILOSOPHY

by

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Financial assistance was generously donated by the Department of Scientific and Industrial Research in the form of a Maintenance Allowance over a period of three years.

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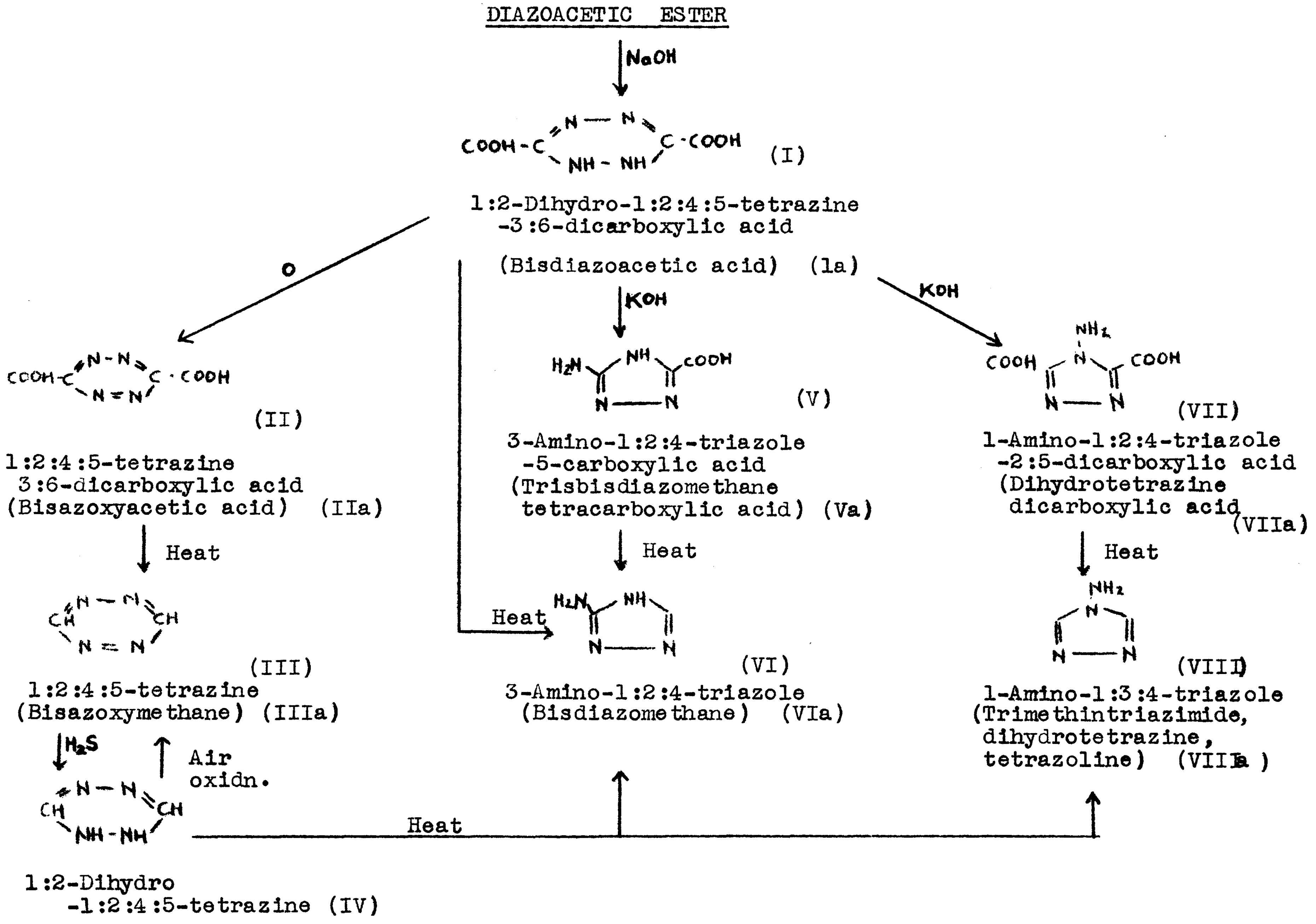
PART I.

"Tricyclic derivatives of 1:2:4-triazole and tetrazole."


DIAZOACETIC ESTER
NaOH
(I)
1:2-Dihydro-1:2:4:5-tetrazine -3:6-dicarboxylic acid
(Bisdiazoacetic acid) (1a)
O
KOH
KOH
(II)
1:2:4:5-tetrazine 3:6-dicarboxylic acid
(Bisazoxyacetic acid) (IIa)
(V)
3-Amino-1:2:4-triazole -5-carboxylic acid
(Trisbisdiazomethane tetracarboxylic acid) (Va)
(VII)
1-Amino-1:2:4-triazole -2:5-dicarboxylic acid
(Dihydrotetrazine dicarboxylic acid (VIIa)
Heat
Heat
Heat
Heat
(III)
1:2:4:5-tetrazine
(Bisazoxymethane) (IIIa)
(VI)
3-Amino-1:2:4-triazole
(Bisdiazomethane) (VIa)
(VIII)
1-Amino-1:3:4-triazole
(Trimethintriazimide, dihydrotetrazine, tetrazoline) (VIIIa)
H2S
Air oxidn.
Heat
1:2-Dihydro -1:2:4:5-tetrazine (IV)

INTRODUCTION.

In 1883 Curtius[1] discovered the first aliphatic diazo compounds by diazotising the esters of amino acids such as glycine, alanine, tyrosine, leucine, aminomalonic, aspartic, and glutamic. In working with diazoacetic ester he soon found that it was converted by alkali into an extremely interesting compound which he named triazoacetic acid[2]. It was by hydrolysis of this acid that hydrazine[3] rather unexpectedly made its first appearance. Several years later, however, Hantzsch and Silberrad[4] showed that triazoacetic acid was really derived from two molecules of diazoacetic ester and renamed it bisdiazoacetic acid (Ia).

This acid gave rise to the following three series of compounds about which there was controversy for nearly twenty years:-

(a) Mild oxidation of the acid produced a new deep red coloured acid, bisazoxyacetic acid[2a,5] (IIa), which was easily decarboxylated to bisazoxymethane (IIIa). Curtius, Darapsky and Müller[6] found the key to this series when they isolated the colourless dihydro-derivative of bisazoxymethane, easily reoxidised to the deep red bisazoxymethane. This was the first time that true dihydrotetrazine (IV), ($C_2H_4N_4$), as they named it, had been isolated and it established this series, as well as the parent bisdiazoacetic acid, as

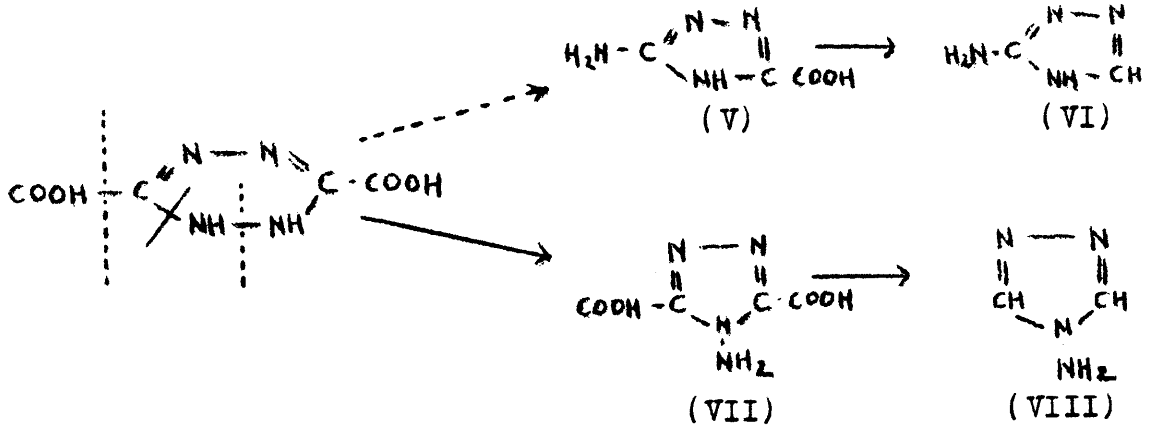
1:2:4:5-tetrazine derivatives.

(b) On boiling potassium "bisdiazoacetate" with aqueous potash it was partially decarboxylated to the salt of a new acid which Hantzsch and Silberrad[4a] interpreted as being a complicated trisbisdiazomethane tetracarboxylic acid (Va) which on heating lost carbon dioxide to give bisdiazomethane ($C_2H_4N_4$) (VIa). Again, Curtius, Darapsky and Müller[6a] supplied the correct interpretation when they noticed that the above compounds (VIa) and (Va) were identical with 3-amino-1:2:4:-triazole (VI) and its 5-carboxylic acid (V) respectively which had previously been synthesised by Thiele and Manchot[7] by a method which left their structures unambiguous.

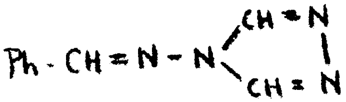
(c) Along with the acid (V) obtained under (b) was also obtained another acid, in smaller yield, called dihydrotetrazine dicarboxylic acid (VIIa) which could be decarboxylated to give a compound $C_2H_4N_4$ (VIIIa). The same substance could be obtained directly by heating "bisdiazoacetic acid" and was given by various workers at different times the names tetramethintriazimide[2b], isodihydrotetrazine[8], tetrazoline[9], symmetrical dihydrotetrazine[10], and N-dihydrotetrazine[4b]. It can thus be imagined that when Bulow[11], in 1906, suggested that this compound was not a tetrazine at all but a triazole derivative, namely 1-amino-1:3:4-triazole (VIII), there was some reluctance shown in accepting it.

The main causes of uncertainty about the structures of the compounds obtained under (a), (b) and (c) were that so many of the substances were isomeric, and had similar properties (the hydrochlorides of both amines (VI) and (VIII) have the same melting point), that dihydrotetrazine changed readily into both amines (VI) and (VIII), and dihydrotetrazine dicarboxylic acid into both acids (V) and (VII), that the same substance written in different tautomeric forms was given different names, and that an apparently simple synthesis[4c,9] of dihydrotetrazine from two molecules of formylhydrazine really gave 1-amino-1:3:4-triazole (VIII).

Bülow contended that the formation of (VI) and (VIII) could be explained by disruption of dihydrotetrazine dicarboxylic acid in the following way:-



In addition the N-aminotriazole structure gave a much simpler formulation of the benzylidene derivative (IX) than



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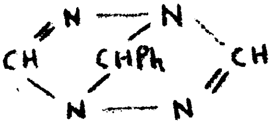
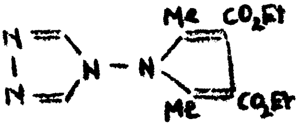


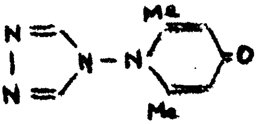
(IXa)

that postulated by Stollé[10] on the basis of a "dihydrotetrazine" structure.

Bülow obtained the condensation products (X) and (XI) with diacetyl succinic ester and acetonylacetone respectively[11], which Stollé claimed[12] could equally well be formulated as



(X)



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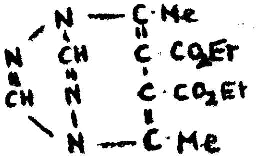
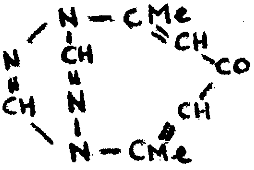
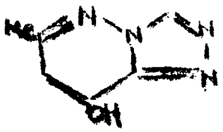


(Xa)

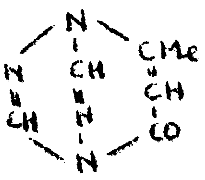


(XIa)

(Xa) and (XIa). Thus it appeared that a position of stalemate had been reached until Bülow, in 1909, synthesised the first of his "heterohydroxylic acids", (XII) by condensing N-aminotriazole with acetoacetic ester[13]. According to the



(XII)

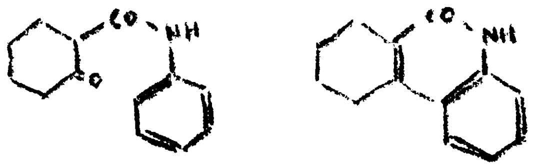


(XIIa)

"dihydrotetrazine" structure the product would be (XIIa) which would offer no explanation for its strongly acidic nature. Thus Bülow's formulation of 1-amino-1:3:4-triazole was finally accepted and all the isomerisation products from diazoacetic ester established.

Bülow, now engrossed in "heterohydroxylic acid" syntheses condensed several β-ketoesters with N-aminotriazole and other amines capable of giving cyclic condensation, e.g., 5-aminotetrazole[14], 3-amino-1:2:4-triazole[15] and 1-phenyl-3-methyl-5-aminopyrazole[16]. The last reaction was taken as disproving Walther's imino structure[17] for the cyclisation product from acetoacetonitrile phenylhydrazone.

It should be noted that on condensation of β-ketoesters with amines in general, reaction temperatures above 120° favour anilide formation while lower temperatures favour anil (or β-aminoacrylate) formation[18]. Where cyclisation takes place the position of substituents will, of course, depend on which intermediate was formed, e.g., in the condensation of ethyl cyclohexanone-2-carboxylate with aniline[19] either an angular compound, tetrahydrophenanthridone (XIII) or a



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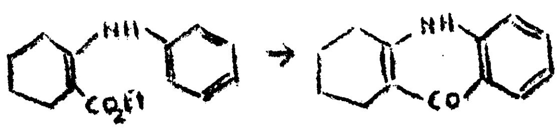
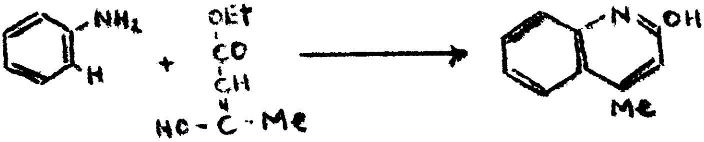


(XIV)

linear one, tetrahydroacridone (XIV) can be formed.

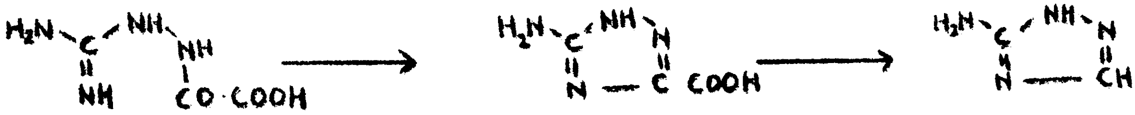
It is curious that Bülow[13], when explaining the condensation of β-ketoesters with 1-amino-1:3:4-triazole to give derivatives of (XII), describes its similarity to Knorr's synthesis[20] of 4-methyl-2-carbostyril (XV) formulating the reaction as shown, and yet he gives his own con-



(XV)

densation products a structure which involves an anil (or β-aminoacrylate) intermediate.

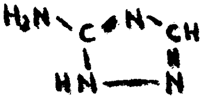
Although at this time ideas on tautomerism were not well defined, examples had been recognised, as in Knorr's pyrazole series[21], in the triazole series[4d,6b], and in the 3-amino-1:2:4-triazole series where it was noted[6c] that Thiele and Manchot's preparations from oxalylaminoguanidine (XVI) should give different tautomeric forms from those



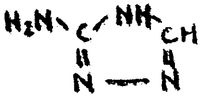
(XVI)

obtained by rearrangement of dihydrotetrazine dicarboxylic acid (see p.3) while in fact they were identical.

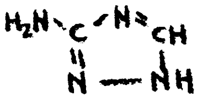
It is now known that several tautomeric structures may be written for 3-amino-1:2:4-triazole, namely:-



(XVII)



(XVIIa)

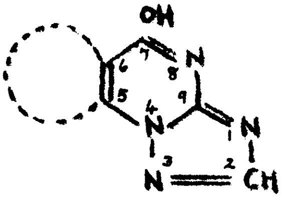


(XVIIb)

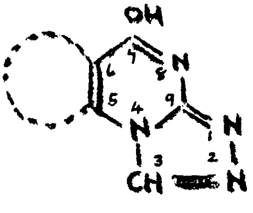
(XVIIc)

as well as three other 3-imino forms. Of the above forms only (XVII) and (XVIIa) are capable of cyclic condensation with β-ketoesters (these forms have an imino group adjacent to the amino-bearing carbon atom), but once condensation has taken place the products are no longer tautomeric modifications of the one substance but two quite distinct compounds.

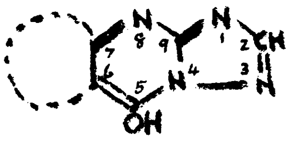
Thus, taking into account the possibilities of anilide or anil formation and the tautomerism of 3-amino-1:2:4-triazole, the latter may condense with cyclic β-ketoesters to give the following products:-



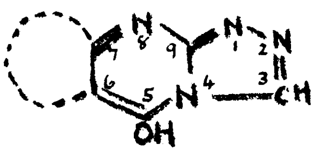
(XVIII)



(XVIIIa)

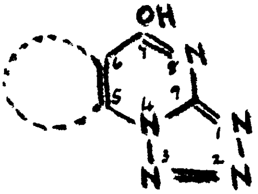


(XIX)

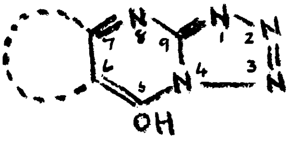


(XIXa)

which are described herein as triazaindolizines with the above numbering[22]. With 5-aminotetrazole the configuration of the azole ring is unambiguous, the derivatives obtained being called tetrazaindolizines.



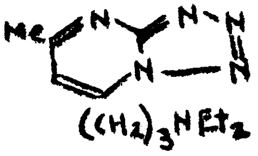
(XX)



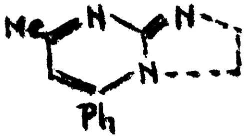
(XXI)

It is of interest to note that Dewar[23], on condensing the β -diketone 7-diethylaminoheptane-2:4-dione $CH_3COCH_2CO(CH_2)_3NEt_2$, with 5-aminotetrazole, isolated two isomeric tetrazaindolizines (in the form of picrates) having, presumably, the structures (XXII) and (XXIII).

(XXII)



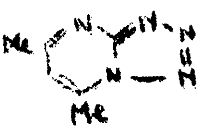
(XXIII)



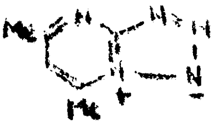
(XXIV)

When the unsymmetrical β -diketone benzoylacetone is condensed with amines capable of giving cyclic condensation only one product is isolated. Bülow gives reasons for supposing that in such condensations benzoylacetone reacts as if only the keto group adjacent to the phenyl group were enolic. Thus on condensation with 1-amino-1:3:4-triazole the product is (XII, OH becoming Ph)[24], so the analogous product with 5-aminotetrazole and 3-amino-1:2:4-triazole should have the structure (XXIV) though for some reason Bülow interchanges the positions of the methyl and phenyl groups[14a,15a], while with 1-phenyl-3-methyl-5-aminopyrazole they are back in their original positions[16a].

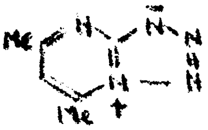
On examination of the absorption spectra of 5:7-dimethyl-1:2:3:8-tetrazaindolizine (XXV), Nachod and Steck[25] found evidence that zwitterions contribute to the structure of the molecule in acid, and to a lesser extent, in neutral solution, namely (XXVa to d).



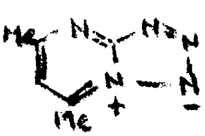
(XXV)



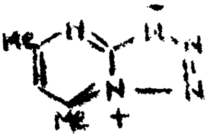
(XXVa}



(XXVb)



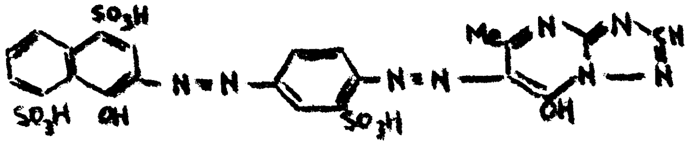
(XXVc)



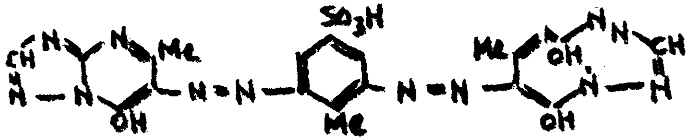
(XXVc)

The spectra in acid solution showed a similarity to styrene, indole, benzotriazole and even benzoxazole. In alkaline solution the tendency for addition of protons at positions 1 and 3 disappears and only the unionised structure (XXV) remains which has an absorption spectra resembling that of 1:3:5:7-octatetraene indicating its conjugated system.

Recently Heimbach[26] discovered that certain triazaindolizine derivatives are of use in photography where coloured, insoluble, silver salts are used in filter interlayers in multilayered colour film and in antihalation layers to prevent fogging. The mercury salts have been found to be of use in pharmaceutical preparations. Some triazaindolizine derivatives may be used to dye textiles and exhibit excellent heat and light stability. These dyes are obtained by coupling a diazotised amine with a β-ketoester and then condensing the azo-ketoester with aminotriazole, e.g., by coupling diazotised 2-amino-5-nitrobenzenesulphonic acid with acetoacetic ester, condensing the product with 3-amino-1:2:4-triazole, reducing the nitro group to amino, diazotising, and coupling with 1-naphthol-4:8-disulphonic acid the green dye (XXVI) is obtained, while on coupling tetrazotised 2:6-diamino-4-toluenesulphonic with acetoacetic ester and condensing the product with 3-amino-1:2:4-triazole the red dye (XXVII) is obtained.

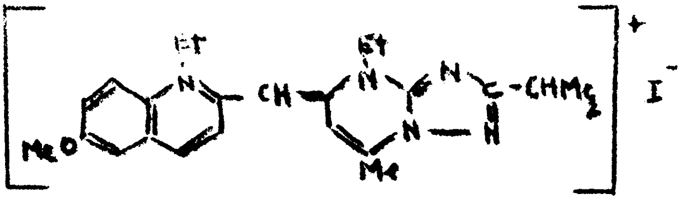


(XXVI)

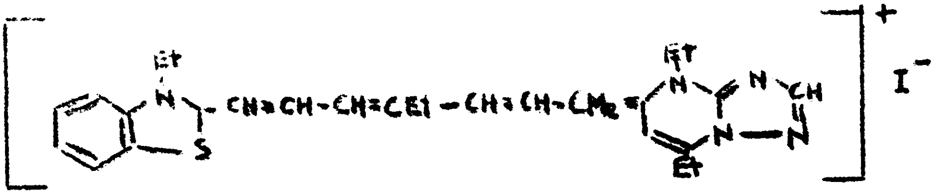


(XXVII)

Several asymmetric cyanine dyes[27] containing a triazaindolizine nucleus have been found to be excellent photosensitising dyes, increasing the sensitivity of emulsions and, being water soluble, are easily removed from the exposed emulsion layer during processing. They are prepared by condensing quaternary triazaindolizine salts with cyclammonium quaternary cyanine dye salt intermediates containing a reactive group, e.g., 2-isopropyl-5:7-dimethyl-1:3:8-triazaindolizine ethiodide reacts with 2-methylmercapto-6-methoxyquinaldine ethiodide to give (XXVIII), presumably



(XXVIII)



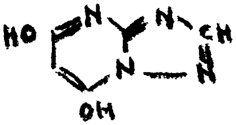
(XXIX)

by elimination of thio-ether, a more complex dye (XXIX) being obtained by condensation of 5:7-diethyl-1:3:8-triazaindolizine ethiodide with 2-(4-ethyl-6-anilino-1:3:5-hexatrienyl) benzthiazole ethiodide.

In the above condensations it should be noted (a) that the 7-alkyl group shows reactivity akin to that of the

2-alkylquinolines, and (b) that although it has been assumed that on alkylation of the triazaindolizine nucleus the alkyl group enters the 8-position it seems more likely, in view of the evidence based on the absorption spectra of 5:7-dimethyl-1:2:3:8-tetrazaindolizine, that it enters the 1 or 3 position.

The condensation of 3-amino-1:2:4-triazole with β -diketones and β -ketoesters has been extended by Heimbach[28] to include other difunctional compounds, e.g. (XXX) is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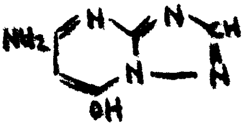
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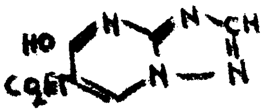
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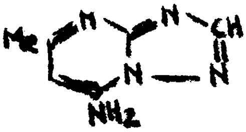
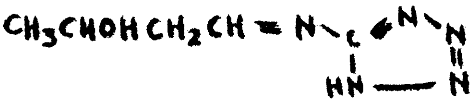
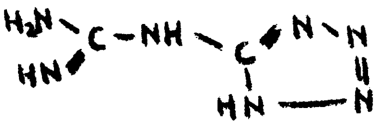

(XXXIII)

obtained with ethyl hydrogen malonate, (XXXI) with cyanoacetic ester, (XXXII) with diethyl methoxymethylenemalonate, and (XXXIII) with β -iminobutyronitrile or acetoacetonitrile.

A rather puzzling paper was published by Bures and Barsi[29] on the condensation of 5-aminotetrazole with acetaldehyde and with benzaldehyde, the products later being shown by Stollé[30] to be the Schiff's base derived from 5-aminotetrazole and aldol, and 5-guanidinotetrazole respectively.


A Schiff's Base

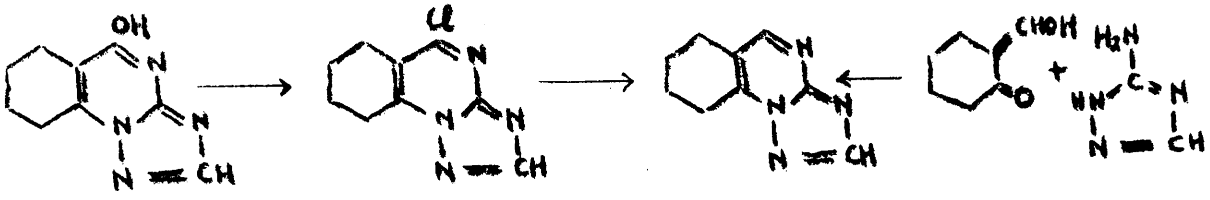

5-Guanidinotetrazole.

An extensive review on the chemistry of tetrazoles has been prepared by Benson[31].

DISCUSSION.

The present commercial availability of aminoguanidine has prompted further exploration of its use in heterocyclic syntheses, of which many examples are already recorded and have been reviewed by Lieber and Smith[32]. The two amines used in this work, 3-amino-1:2:4-triazole[7,33] and 5-aminotetrazole[34], are easily obtained from aminoguanidine. Fused ring systems containing several nitrogen atoms may have chemotherapeutic potentialities and two such compounds have been prepared and tested for trypanocidal action. The use of certain tetrazolium salts for demonstrating the presence of reducing enzyme systems in living tissues[35] adds interest to this class of compound.

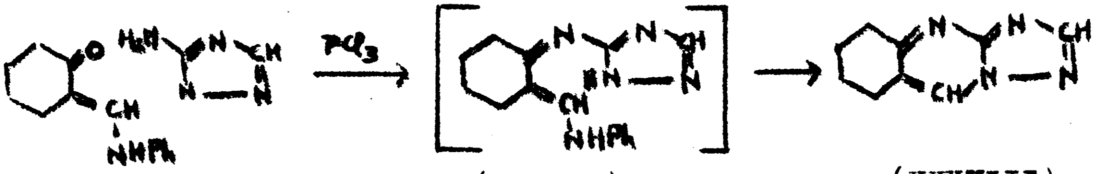
In the condensation of cyclic β-ketoesters with aminotriazole it has been shown (p.7) that theoretically four products are possible. Actually when ethyl cyclohexanone-2-carboxylate was condensed with the above amine only one product was isolated no matter whether the reaction was carried out at a high or a low temperature. Since the configuration of the azole ring of this compound has not been elucidated, Bülow's original formulation has been provisionally adopted. That this compound has the structure (XXXIV) is shown by converting it with phosphoryl chloride into the



(XXXIV) (XXXV) (XXXVI)

chloro compound (XXXV) and dechlorinating catalytically to the parent 5:6-tetramethylene-1:3:8-triazaindolizine (XXXVI) which was also obtained directly by interaction of 2-hydroxymethylenecyclohexanone and aminotriazole. This latter method would be expected to involve condensation of the primary amino group with the more reactive hydroxymethylene group rather than the cyclic carbonyl group, thus leading to the angular structure (XXXVI). The fact that the compound (XXXIV) could not be acetylated or benzoylated and did not give a ferric chloride test is an indication that it really exists mainly in the amide form. Similar resistance to acylation is shown by the α - and γ -pyridones while (XII) where the nitrogen atom is not adjacent to the hydroxyl-bearing carbon atom behaves as an enolic substance giving a ferric chloride test.

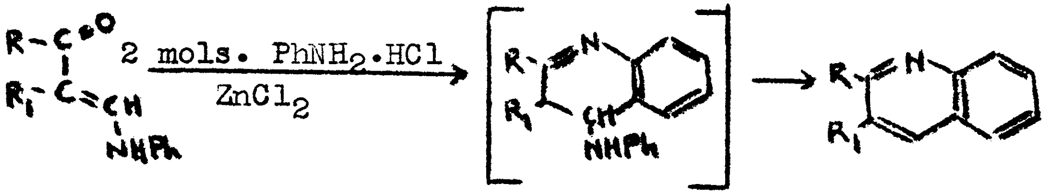
The linear isomer (XXXVIII) corresponding to (XIX, OH becoming H) was prepared by applying the amidine synthesis



(XXXVII) (XXXVIII)

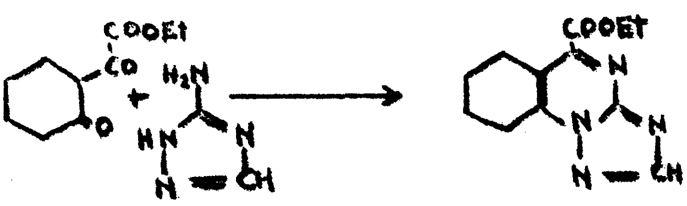
of Sen and Rây^{36} to aminotriazole and 2-anilinomethylenecyclohexanone which can be considered as the vinylogue of an amide. The expected amidine vinylogue (XXXVII) was not isolated however, cyclisation having taken place.

This cyclisation is similar to that used by Petrow to synthesise 2:3-disubstituted quinolines (XXXIX)^{37}

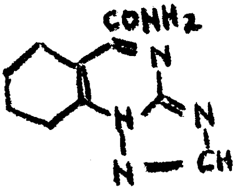


(XXXIX)

Additional evidence that compound (XXXVI) had an angular structure was provided by condensing ethyl cyclohexanone-2-glyoxylate with aminotriazole. The exocyclic keto group, being the more reactive of the two, should condense with the primary amino group to give the ester (XL).



(XL)

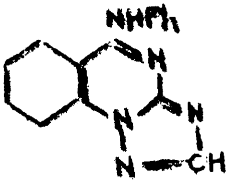


(XLI)

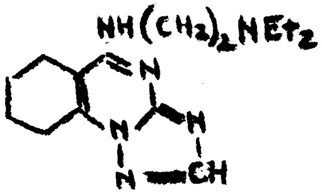
After hydrolysis of this ester, the intermediate acid was easily decarboxylated during vacuum distillation, yielding (XXXVI). Even prolonged boiling of an acetic acid solution of the ester (XL) caused decomposition to (XXXVI). The ease of decarboxylation of this acid is characteristic of heterocyclic acids where the carboxyl group is in the α-position to a nitrogen atom.

The ester (XL) was converted to the amide (XLI) with ammonia solution but Hofmann reactions, as described by Adams[38], were unsusecessful. On treating the ester (XL) with alcoholic hydrazine hydrate, two different crystalline compounds were obtained, one of which was partly converted to the other oncrystallisation, but as neither could be obtained pure and an analysis was not informative, the investigation was discontinued.

The activity of the chlorine atom in the chloro compound (XXXV) can be judged by the fact that it can be replaced by an hydroxyl group merely by boiling it in alcoholic solution containing a little water, and even without the presence of alkali. An anilino derivative (XLII) was prepared by heating



(XLII)

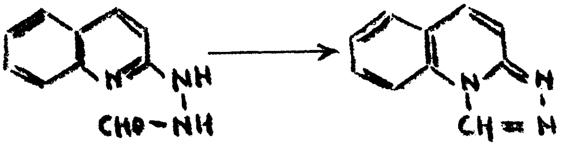


(XLIII)

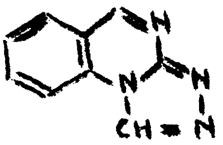
an alcoholic solution of the chloro compound (XXXV) with two equivalents of aniline. When one equivalent of

N:N-diethylethylenediamine was similarly treated the base hydrochloride (XLIII) was obtained. This compound was tested by Professor C.H. Browning, F.R.S. for trypanocidal activity on mice infected with *T.congolense* and *T. brucei* but was found to be lethal for mice in doses of 4 mg. per 20 g. body weight, while in sub-lethal doses it had no therapeutic effect.

When Marckwald and Meyer treated 2-chloroquinoline with hydrazine they obtained the hydrazino derivative which on formylation cyclised to give naphtriazole[39] or 5:6-benz-1:2-diazaindolizine (XLIV). There is no reason to doubt that 2-chloroquinazoline[40] would undergo a similar



(XLIV)

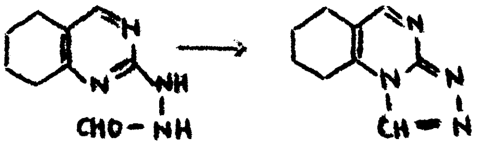


(XLV)

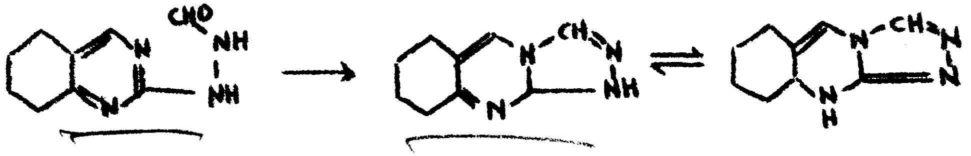
series of reactions to yield the as yet unknown 5:6-benz-1:2:8-triazaindolizine (XLV). Thus if (XXXVI) could be dehydrogenated there was a possible way of determining the azole ring structure for if the dehydrogenated product were identical with (XLV) the original condensation product (XXXIV) would be established as having the structure (XVIIIa), while if it were different from (XLV) the structure now adopted (XVIII) would be correct.

Dehydrogenation of (XXXVI) was attempted using palladium black or palladised charcoal, with or without α-methylnaphthalene as solvent, sulphur, chloranil in xylene[41], N-bromosuccinimide in carbon tetrachloride[42], and aqueous potassium ferricyanide solution[43], but in each case without success.

It was later realised, though time did not permit of experiment, that a similar series of reactions applied to 2-chloro-5;6;7;8-tetrahydroquinazoline might also provide information about the azole ring structure of the triazaindolizines. Such a condensation could give rise to a product with an angular (XLVI) or a linear structure (XLVII) depending on whether cyclisation occurred at position 1 or 3.



(XLVI)

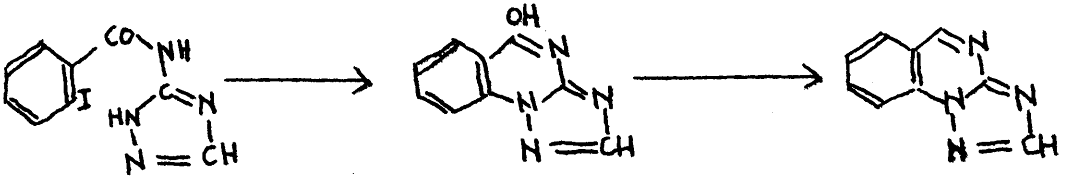


(XLVII)

If the product proved identical with (XXXVI) the azole ring structure is at once established. If it is different from

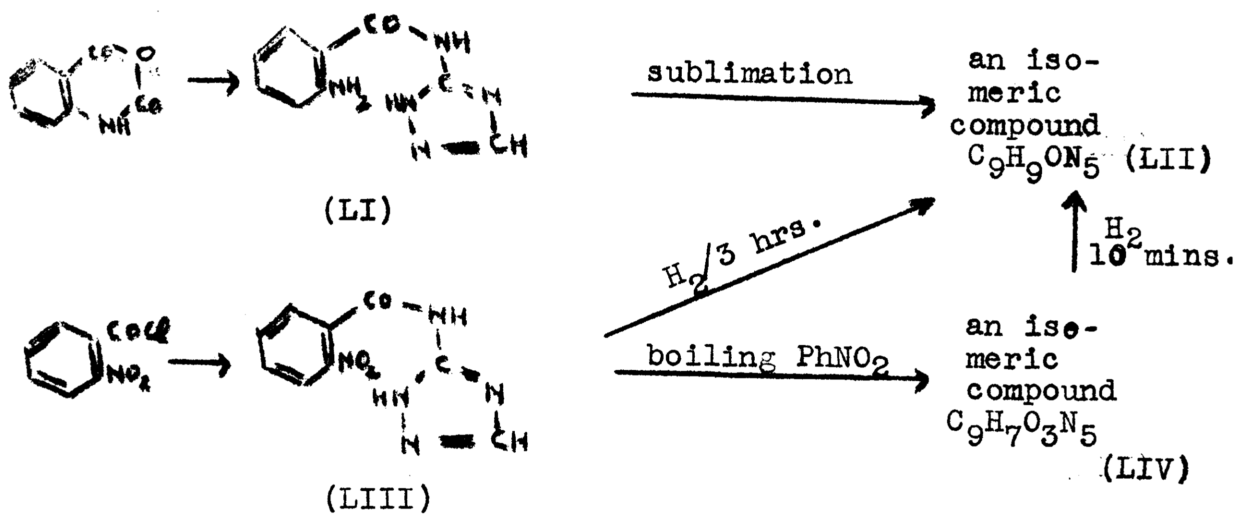
(XXXVI), before it can be used as evidence it must be shown that it does not have the linear structure (XLVII). The latter would necessarily contain an imino group and so be capable of nitrosation. Thus if the product of the above reaction depressed the melting point of (XXXVI) and did not form a nitroso derivative the structure of (XXXVI) as such would be established.

Since dehydrogenation of (XXXVI) had proved unsuccessful, synthetic approaches to the desired structure were now investigated. Suitably o-substituted benzoylaminotriazoles were prepared which if cyclised could be converted to the parent compound (XLIX) by the standard method of chlorination followed by dechlorination. o-Iodobenzoylaminotriazole (XLVIII), prepared from o-iodobenzoyl chloride



(XLVIII) (XLIX) (L)

and aminotriazole, was treated, in an effort to remove hydriodic acid, with copper bronze and heated with (a) potassium carbonate, (b) quinoline, (c) pyridine, or was heated in a sealed tube with triethylamine and nitromethane[44]. In no case was cyclised material isolated.



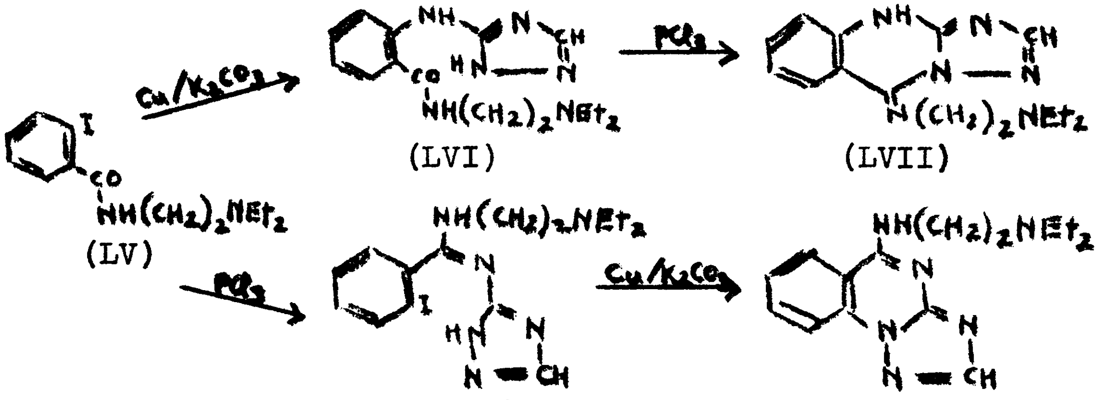
The reaction of isatoic anhydride with amines is a well known method of preparing amido-substituted anthranilamides so, with aminotriazole, o-aminobenzoylaminotriazole would be expected. On attempting to purify this material by sublimation a much higher melting isomeric substance (LII) was obtained. It was at first thought that (LII) had the anthranilamide structure, now assigned to (LI), because it was found that o-nitrobenzoylaminotriazole (LIII) on catalytic hydrogenation yielded a substance identical with (LII). Later however it was found that under the influence of boiling nitrobenzene, which was being used in an attempt to effect cyclisation[45], isomerisation of (LIII) also occurred giving (LIV). This latter compound was hydrogenated much more readily than (LIII) but gave however the same product (LII).

The above interpretation of these results, while not explaining why (LIII) does not reduce to (LI), is consistent with both (LI) and (LIII) being the anthranilamides expected by synthesis, with both isomerisation products having higher melting points than the corresponding anthranilamides, and with the fact that the change from (LIII) to (LII) which must involve isomerisation takes longer than that from (LIV) to (LII).

The structure of the isomerisation products remains an unsolved problem. Although the mildness of the reaction converting (LIII) to (LII) renders wandering of the aroyl group from the primary amino group to one of the cyclic imino groups unlikely, it may be that ring opening occurs followed by reclosure on to the acylated nitrogen atom. A change, though in the reverse direction from the ring to the amino group, has been observed in the case of 1-phenyl-5-amino-1:2:3-triazole which can be isomerised to 5-anilino-1:2:3-triazole[46], a similar mechanism being involved.

Treatment of (LI) and (LII) with acetic anhydride in an attempt to estimate amino groups by acetylation merely converted the former to the latter which then resisted the reagent, whilst diazotisation led to tarry products.

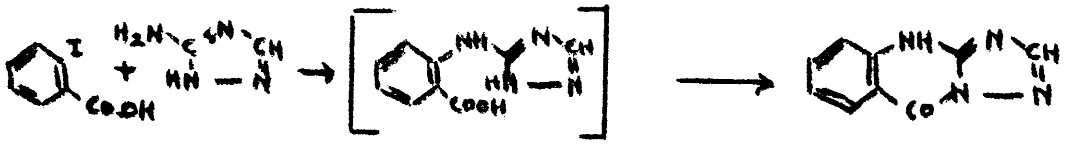
Another synthesis of the "aromatic" structure, this time with a basic side chain in position, was attempted starting from N-(N':N'-β-diethylaminoethyl)-o-iodobenzamide (LV). By treatment with copper bronze and



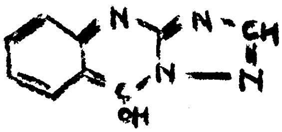
(LV) (LVI) (LVII) (LVIII) (LIX)

potassium carbonate (LVI) should be obtained which with phosphorus trichloride might cyclise to (LVII). By carrying out the reactions in the reverse order an attempt was made to obtain (LVIII) and thence (LIX). Neither synthesis was successful and the project was abandoned.

A benzindolizine derivative was obtained however by applying Bachman and Picha's synthesis of N-arylanthranilic acids[47] to potassium iodobenzoate and aminotriazole. The



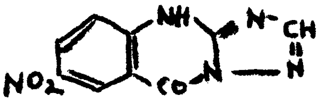
(LX) (LXI)



(LXIa)

intermediate N-triazolylanthranilic acid (LX) was not isolated but at once cyclised to 6:7-benz-1:3:8-triaza-indoliz-5-one (LXI). Attempts to chlorinate (LXI) with phosphorus oxy- or penta-chloride even in a sealed tube at elevated temperatures resulted either in complete decomposition or isolation of unchanged material. The probable explanation of this resistance to chlorination is that the intermediate enolic form (LXIa) would necessarily fix the benzenoid ring in an orthoquinonoid form and thus destroy the aromatic resonance.

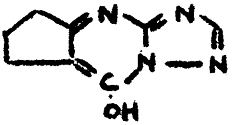
Nitration of (LXI) took place smoothly and in good yield by merely dissolving in cold fuming nitric acid and leaving for several days. A pale yellow mononitro compound m.p. 357-359° was obtained, probably (LXII) by analogy with the nitration of acridone[48] which gives 85% of the 2-nitro form. The high melting point is also analogous to that of the nitro acridones unmelted at 370° (except 4-nitro acridone m.p. 259°). In an attempt to confirm this suggestion potassium 2-chloro-5-nitrobenzoate was condensed with aminotriazole in boiling nitrobenzene. The product was an orange yellow powder which darkened above 300°, melting indefinitely between 340° and 350°. A mixed



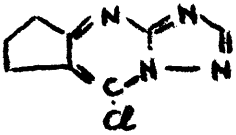
(LXII)

melting point with (LXII) was inconclusive.

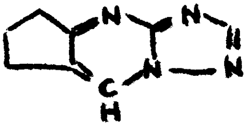
Now that the structure of the condensation product of ethyl cyclohexanone-2-carboxylate with aminotriazole had been established as having the angular structure (XXXVI), the corresponding product (LXIII) from ethyl cyclopentanone-2-carboxylate was investigated. Since the substance (LXIV) obtained by chlorination on subsequent dechlorination gave (LXV) which was different from the condensation product (LXVI) obtained from 2-hydroxymethylenecyclopentanone[66] and aminotriazole, the initial product (LXIII) must be given a linear structure, namely 5-hydroxy-6:7-trimethylene-1:3:8-triazaindolizine corresponding to (XIX).



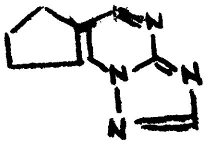
(LXIII)



(LXIV)

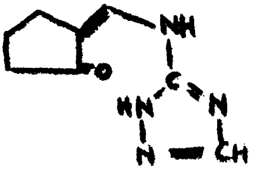


(LXV)



(LXVI)

When 2-hydroxymethylenecyclohexanone was condensed with aminotriazole the triazaindolizine was formed directly without any intermediate product being isolated but with 2-hydroxymethylenecyclopentanone, the intermediate triazolylaminomethylenecyclopentanone (LXVII) was isolated being less easily cyclised than the analogous hexane compound. A parallel to this behaviour is observed in Tiedtke's reaction. This

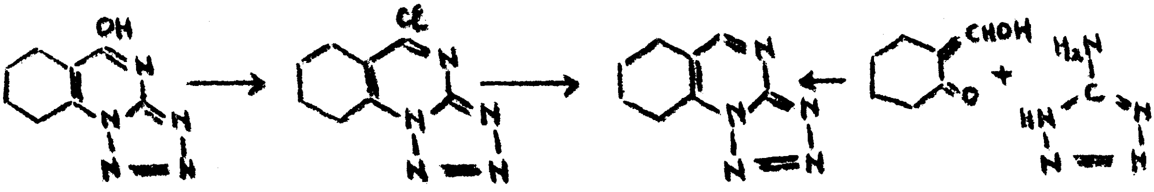


(LXVII)

involves condensation of anthranilic acid with cyclic ketones and proceeds smoothly with cyclohexanone[49], but fails entirely with cyclopentanone[19]. Cyclisation of the anilinomethylene derivative of either ketone has not been accomplished[50,19a].

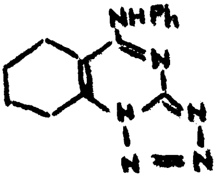
In an attempt to prepare (LXV) by a method analogous to that employed for (XXXVIII), 2-anilinomethylenecyclopentanone[19b] was prepared, but in contact with phosphorus trichloride it immediately gave black tarry material. It might be possible to carry out this condensation by Petrow's method previously described, using two equivalents of aminotriazole hydrochloride with zinc chloride.

Attention was now turned to condensations involving 5-aminotetrazole. An improvement on the preparation of this amine as described by Thiele[34] was devised in which isolation of the intermediate guanyl azide was avoided. This amine was condensed with ethyl cyclohexanone-2-carboxylate to give the hydroxy compound (LXVIII) which was converted easily to

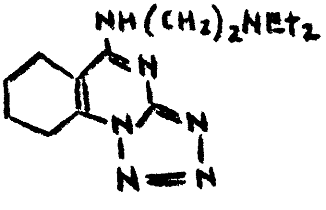


(LXVIII) (LXIX) (LXX)

the chloro compound (LXIX). Difficulty was encountered at this point in converting this compound, by the usual method of catalytic hydrogenation in alcohol solution, to the parent compound (LXX). As Bülow's method[51] of dechlorinating the chloro compound (XII; OH becoming Cl) by boiling with zinc dust and water was not effective in this case, another method used for converting 5-chloroacridine to acridine by the use of toluene-p-sulphonylhydrazine[52] was employed, without success. Finally it was found that in acetone solution hydrogenation proceeded normally to give (LXX). These compounds are given the angular structure because the product of reduction (LXX) was found to be identical with that obtained directly by condensing 2-hydroxymethylenecyclohexanone with 5-aminotetrazole. By the



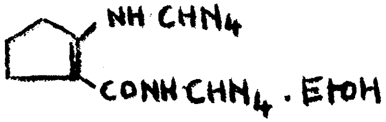
(LXXI)



(LXXII)

action of an alcoholic solution of two equivalents of aniline to one of the chloro compound (LXIX) the anilino derivative (LXXI) was obtained while with one equivalent of N:N-diethylethylenediamine the base hydrochloride (LXXII) was isolated. The latter, like the corresponding heterologue (XLIII), proved inactive as a trypanocidal agent on mice infected with *T. congolense* and *T. brucei*, being lethal in doses of 10 mg. per 20 g. body weight.

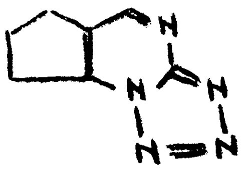
A divergency was noted in the behaviour of 5-aminotetrazole as compared with aminotriazole in regard to its condensation with ethyl cyclopentanone-2-carboxylate. On boiling the two substances in alcohol solution a product was obtained which analysed as $C_{10}H_{16}O_2N_{10}$ corresponding to condensation of one equivalent of ketoester with two equivalents of 5-aminotetrazole. This compound may have the structure (LXXIII) though no alcohol was lost on drying the material in a steam oven. In one case Bülow, on condensing 1-amino-1:3:4-triazole with benzoylacetic ester in acetic acid solution, isolated in addition to the expected triazaindolizine, another compound which analysed as $C_{15}H_{14}O_2N_8$ while an analogous reaction to that described above would require $C_{15}H_{18}O_2N_8$. Bülow suggested that it was a molecular compound of one molecule of the triazaindolizine (4-hydroxy-6-phenyl-2:3-triazo-7:0-pyridazine) with one of 1-acetylamino-1:3:4-triazole[13a]. However, as he stated that boiling with alcohol converted it to the triazaindolizine, that would seem to rule out any analogy to (LXXIII) which is quite stable under such conditions.



(LXXIII)

When the above reaction was carried out in acetic acid solution 5-acetylaminotetrazole was isolated, the ester remaining intact. On heating the two reactants in the absence of a solvent charring took place and some 5-aminotetrazole was recovered.

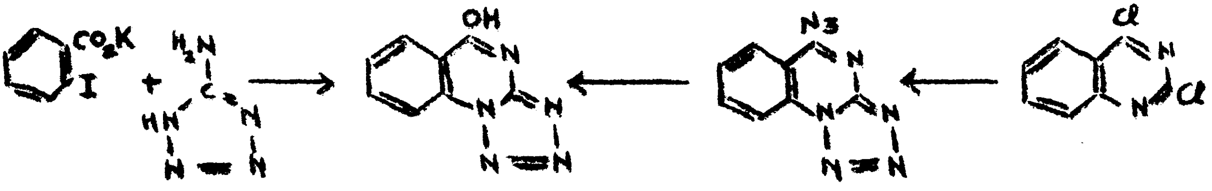
As a previous condensation of 2-hydroxymethylenecyclopentanone with aminotriazole in alcohol had yielded only a partially condensed product, the corresponding reaction with 5-aminotetrazole was carried out in acetic acid. On mixing the solutions of the two reactants an initial precipitate was formed (probably the tetrazolylaminomethylene derivative) which redissolved to give the angular 5:6-trimethylene-1:2:3:8-tetrazaindolizine (LXXIV).



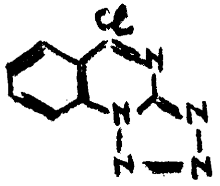
(LXXIV)

Another divergency in the behaviour of 5-aminotetrazole as compared with aminotriazole was shown in its condensation with potassium o-iodobenzoate. When these two reactants were heated with copper bronze and potassium carbonate in amyl alcohol the main product was diphenylamine-2:2'-dicarboxylic acid. It is curious that the first time this acid was prepared it was also by accident as a by-product in the preparation of anthranilic acid from o-chlorobenzoic acid and ammonia[53], while Ullmann[54] prepared it from anthranilic and o-chlorobenzoic acids under exactly similar conditions to those employed above.

The other product of the above reaction proved to be identical with the 1:2-tetrazolo-4-hydroxy-quinazoline-1:2-dihydride (LXXVI) prepared by Stollé and Hanusch[55]. Their


(LXXVI) (LXXV)

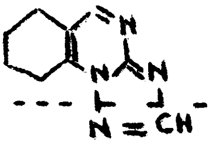
synthesis consisted of treating 2:4-dichloroquinazoline with sodium azide when one of the azido groups forms a tetrazole ring to give rise to (LXXV) followed by hydrolysis of the azide group to give (LXXVI). That it is the 2-azido, and not the 4-azido group, which forms the tetrazole ring is proved by an alternative synthesis from the known 2-chloro-4-ethoxyquinazoline[56], so there is no ambiguity about the structure of the 7-hydroxy-5:6-benz-1:2:3-tetrazaindolizine (LXXVI) produced from the potassium iodobenzoate and 5-aminotetrazole condensation.

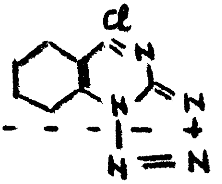

(LXXVII)

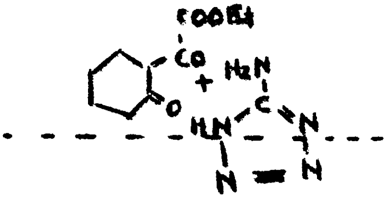
In contrast to the linear triazaindolizone (LXI), the angular tetrazaindolizine (LXXVI) was readily converted to the chloro compound (LXXVII) by the action of phosphoryl chloride. Mixed melting point of the chloro compounds derived from (LXXVI), prepared by either method, showed no depression.

An unexpected degradation product of both triaza- and tetraza-indolizine derivatives has been identified as 2-amino-5:6:7:8-tetrahydroquinazoline[57] (LXXVIII). Such a decomposition is surprising because azole rings, especially


(LXXVIII)


(a) pyrolysis


(b) hydrogenation


(c) attempted condensation

triazole and tetrazole rings, are exceeding stable, and degradation of these systems would be expected to begin at the pyrimidine ring which is in a dihydro state.

(a) Mother liquors from a crystallisation of (XXXVI) were being concentrated over a small flame and were accidentally allowed to char, some sublimation taking place. The residue and sublimate on extraction yielded a small amount of material with a much higher melting point than the original material, which analysed as shown under (a).

(b) As previously mentioned, difficulties were met on hydrogenation of (LXIX). At first a compound was isolated, the melting point of which gradually rose on repeated crystallisation to 218°, and which a molecular weight determination showed was not a di-indolizyl type of compound. No reasonable empirical formula could be deduced from the analysis results. Other hydrogenations, however, yielded material melting sharply at 210-211° which analysed as shown under (b}.

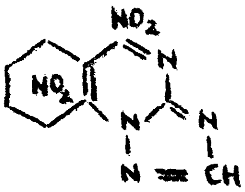
(c) In an attempt to obtain the tetrazaindolizine corresponding to (XL), ethyl cyclohexanone-2-glyoxylate was condensed with 5-aminotetrazole. The gummy product on purification yielded a small amount of material, m.p. 205-207°, which analysed as shown under (c).

As each of these quite isolated experiments (a), (b), and (c) was carried out, no suspicion as to the nature of the product was aroused (as the analyses results were rather poor due to the small amount of material obtained and the difficulty in purifying it) until the cumulative evidence of all three experiments was obtained. Mixed melting points showed that the same substance had been formed in each case, and each analysis approximated to that required by (LXXVIII) which has been prepared by Benary[57] by a condensation of guanidine carbonate with 2-hydroxymethylenecyclohexanone. A modification of this method was used to prepare an authentic sample of 2-amino-5:6:7:8-tetrahydroquinazoline which proved identical (mixed m.p.) with the material obtained under (a), (b), and (c). Further confirmation was supplied by preparing a picrate from sample (c) which did not depress the melting point of a picrate from an authentic sample of (LXXVIII).

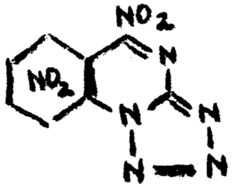
Some miscellaneous reactions were now carried out on (XXXVI) and (LXX) to compare their properties. It was found that on oxidising an aqueous solution of either substance with neutral potassium permanganate complete disruption of the heterocyclic system occurred and in each case adipic acid and ammonia (isolated as ammonium chloride) were the only products isolated. In general, azole rings are very resistant to oxidation, e.g., the phenyl and methyl groups of 1-phenyl-3-methyl-1:2:4-triazole can be oxidised leaving the azole ring intact[58], while 1:2:3-triazaindolizine is oxidised to tetrazole-5-carboxylic acid[39a]. The previous degradations to 2-amino-5:6:7:8-tetrahydroquinazoline is an indication, however, that the azole rings in this series of compounds are less stable than usual.

Treatment of (XXXVI) and (LXX) with alcoholic methyl iodide surprisingly did not lead to methiodide formation, no reaction at all taking place, though, when (LXX) was heated at 100° with methyl iodide in a stoppered bottle, decomposition took place, a black resinous material being obtained while free iodine was also present. Heimbach used triazaindolizine ethiodides in the preparation of the cyanine dyes described on p.12, but no details are given in the abstracts of how they were prepared.

Cold fuming nitric acid dissolved (XXXVI) and (LXX) immediately and after standing several days dinitro-derivatives (LXXIX) and (LXXX) respectively were obtained. That a nitro group has entered the 2-position of the triazaindolizine is rendered unlikely by the fact that the tetrazaindolizine which forms a similar dinitro derivative does not have a hydrogen atom in that position to be substituted. As both compounds have a hydrogen atom at the 7-position this may be the position of a nitro group in the nitrated products. This suggestion is supported by the fact that when the 7-hydroxy- or 7-carbethoxytriazaindolizines are similarly treated with nitric acid the products are red sticky gums in contrast to the almost colourless well crystallised dinitro compounds obtained above.



(LXXIX)



(LXXX)

The only places left for the second nitro group are in the carbocyclic ring of which the carbon atom attached to position 5 is perhaps the most likely being adjacent to the double bond and less sterically hindered than the other adjacent position. Such theorising is highly speculative so the question has been left open by formulating the compounds as (LXXIX) and (LXXX).

The results of this research have been incorporated in two communications, "Derivatives of Triaza-Indolizine", and "Derivatives of Tetraza-Indolizines" which are awaiting publication in Rec.Trav.chim.

EXPERIMENTAL.

3-Amino-1:2:4-triazole.

Aminoguanidine bicarbonate was converted to the nitrate, formylated, and the resulting formylaminoguanidine nitrate cyclised as described by Thiele and Manchot[7].

This preparation can also be effected from aminoguanidine bicarbonate without isolating intermediate compounds[33].

Ethyl cyclohexanone-2-carboxylate.

This ester was prepared by Claisen condensation of diethyl oxalate and cyclohexanone as described by Kötz and Michels[59], decarbonylisation of the glyoxylic ester being accomplished by heating with glass wool at 140° till evolution of carbon monoxide ceased (c. 3 hours). See also Org.Synth.[60].

7-Hydroxy-5:6-tetramethylene-1:3:8-triazaindolizine (XXXIV, p.14).

The condensation of 3-amino-1:2:4-triazole (8.4 g.) with ethyl cyclohexanone-2-carboxylate (17 g.) was carried out by dissolving the amine in glacial acetic acid (50 cc.), adding the ester, and boiling gently under reflux for 10 hours. When cold the solid was filtered, dissolved in

boiling water (2.5 l.), and on cooling long white needles crystallised out. By boiling the combined mother liquors with charcoal, filtering, and concentrating the filtrate additional material may be obtained. m.p. 279-281° with sublimation and decomposition. Yield, 15 g., 79%.
(Found: C, 57.0; H, 5.3; N, 29.5. $C_9H_{10}ON_4$ requires C, 56.8; H, 5.3; N, 29.5%).

When a solution of the amine (1 g.) in alcohol (10 cc.) or in glacial acetic acid (10 cc.) was added to the keto-ester (2 g.) and the mixture allowed to stand at room temperature for several weeks the same material gradually separated out in about the same yield.

The substance is quite acidic and can be titrated with alkali, e.g., 126.8 mg. in alcohol required 11.25 cc. of 0.0578$\bar{N}$ NaOH for neutralisation using phenolphthalein as indicator giving an equivalent of 195.

It is sparingly soluble in hydrocarbon solvents, slightly soluble in water or alcohol and extremely soluble in pyridine.

No acylation took place either under Schotten Baumann conditions or after 15 hours' boiling of its solution in acetic anhydride with or without pyridine, starting material being recovered.

No colour test was given with ferric chloride solution.

7-Chloro-5:6-tetramethylene-1:3:8-triazaindolizine (XXXV, p.14).

A solution of the hydroxy compound (XXXIV) (10 g.) in freshly distilled phosphoryl chloride (50 cc.) was refluxed until hydrogen chloride ceased to be evolved (c. 3 hours) and excess of the reagent was distilled off on the water bath under reduced pressure. Ice was added to the residue which gradually dissolved giving a brown solution, which in the presence of ice was made just neutral with ammonia solution, the mixture becoming pink. The precipitate was filtered, washed with water, dried in a desiccator, dissolved in benzene and boiled with charcoal. To the hot filtered solution light petroleum (b.p. 80-100°) was added till turbidity appeared and on cooling long colourless needles were obtained, m.p. 123-124°. Yield, 7.7 g., 70%. (Found: C, 51.9; H, 4.4; N, 26.8. $C_9H_9N_4Cl$ requires C, 51.8; H, 4.3; N, 26.9%).

It is soluble in most organic solvents and prolonged boiling of a slightly aqueous alcoholic solution, even in the absence of alkali, reconverts it to the hydroxy compound as does concentrated ammonia solution (S.G. 0.88).

5:6-Tetramethylene-1:3:8-triazaindolizine (XXXVI, p.14).

(a) A solution of the chloro compound (XXXV) (0.5 g.) in absolute alcohol (10 cc.) was dehalogenated by shaking with hydrogen and 2% palladised strontium carbonate[61] (absorption 53 cc.). The mixture was heated on a steam bath under reflux for 15 minutes to allow the strontium carbonate to decompose completely the base hydrochloride, then the catalyst was filtered. The filtrate was evaporated to dryness and the residue extracted with benzene leaving behind the strontium chloride. Concentration of the benzene extract and dilution with hot petroleum (b.p. 80-100°) yielded on cooling colourless needles which, after repeated crystallisation from the above petroleum had m.p. 125-126°. Yield, 0.26 g., 62%.

(Found: C, 62.1; H, 5.8; N, 31.9. $C_9H_{10}N_4$ requires
C, 62.1; H, 5.7; N, 32.2%).

Attempts to carry out reduction with zinc dust[24] or with hydriodic acid followed by zinc dust treatment[illegible] were unsuccessful.

(b) To a solution of 3-amino-1:2:4-triazole (0.5 g.) in acetic acid (5 cc.) was added* 2-hydroxymethylenecyclohexanone[50a] (0.75 g.) and the mixture heated on a steam bath for 1 hour. As no crystallisation occurred after standing

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* Freshly distilled 2-hydroxymethylenecyclohexanone resinifies in a few days, but if diluted with about ten volumes of ether it may be stored in the dark almost indefinitely.

for a day or after concentration the solution was evaporated to dryness under reduced pressure and the residual gum sublimed at 160° under 2 mm. pressure. The pale yellow powdery sublimate crystallised from benzene/hexane in colourless needles, m.p. 122-124°, which was not depressed by admixture with material prepared as under (a).

Yield, 0.2 g., 19%.

(Found: C, 62.1; H, 5.8; N, 32.2. $C_9H_{10}N_4$ requires
C, 62.1; H, 5.7; N, 32.2%).

<u>6:7-Tetramethylene-1:3:8-triazaindolizine (XXXVIII), p.14.).</u>

A solution of 3-amino-1:2:4-triazole (0.5 g.) and 2-anilinomethylenecyclohexanone[50b] (1.2 g.) in phosphorus trichloride (10 cc.) was boiled under reflux for 2 hours. Distillation of the excess phosphorus trichloride under reduced pressure left a dark gummy residue which was sublimed at 200° under 2 mm. pressure giving a powdery yellow sublimate which after crystallisation from hexane formed colourless needles, m.p. 113-118°. Yield, 0.35 g., 34%. A mixed m.p. with the isomer obtained above showed a decided depression, m.p. 90-95°.

(Found: C, 62.2; H, 5.6. $C_9H_{10}N_4$ requires
C, 62.1; H, 5.7%).

7-Carbethoxy-5:6-tetramethylene-1:3:8-triazaindolizine (XL, p.15).

3-Amino-1:2:4-triazole (4.2 g.) was dissolved in alcohol (40 cc.), ethyl cyclohexanone-2-glyoxylate (9.9 g.) added, and the resulting solution heated gently under reflux for 5 hours. During reaction some 7-hydroxy compound (XXXIV) (2 g.) was formed due presumably to the presence of ethyl cyclohexanone-2-carboxylate in the glyoxylic ester or to its formation by partial decomposition of the glyoxylic ester during reaction. The hydroxy compound was filtered from the cold reaction mixture and the filtrate after concentration gave material (1.5 g.) m.p. 95-100°, an additional quantity (3.5 g.) m.p. 90-100° being obtained on diluting the mother liquors with ether. The combined yield crystallised from benzene/light petroleum (b.p. 80-100°) in fine colourless needles of the above ester (XL), m.p. 113-115°. Yield, 4 g., 32%.

(Found: C, 58.3; H, 5.6; N, 22.8. $C_{12}H_{14}O_2N_4$ requires C, 58.5; H, 5.7; N, 22.8%).

This ester forms supersaturated solutions when dissolved in boiling water and the solution allowed to cool. Only after much scratching and standing in the refrigerator is the substance recovered in a white powdery form. It crystallises from petroleum in flocculent micro-needles.

When the above condensation was carried out in acetic acid, ~~acid~~ solution (XXXVI) was isolated.

Hydrolysis of the ester (XL) (1 g.) was effected by boiling its solution in concentrated hydrochloric acid. After evaporation to dryness the brown hygroscopic residue was vacuum distilled, the partially solid, pale yellow distillate on extraction with light petroleum (80-100°) yielding colourless needles of 5:6-tetramethylene-1:3:8-triazaindolizine (XXXVI) m.p. 123-124° undepressed by admixture with the two samples prepared by other routes. Yield, 0.4 g., 53%.

(Found: C, 62.2; H, 5.6; N, 31.9. $C_9H_{10}N_4$ requires
C, 62.1; H, 5.7; N, 32.2%).

7-Carboxamido-5:6-tetramethylene-1:3:8-triazaindolizine (XLI, p.15).

The ester (XL) (1 g.) was dissolved in alcohol (10 cc.) and concentrated ammonia solution (S.G. 0.88) (15 cc.) added. After standing overnight the amide was filtered, washed with water, dried, and crystallised from alcohol in small colourless prisms, m.p. 264-266°. Yield, 0.6 g., 65%.

(Found: C, 55.5; H, 4.9; N, 32.3. $C_{10}H_{11}ON_5$ requires
C, 55.3; H, 5.1; N, 32.3%).

A solution of sodium hypobromite was prepared by adding bromine (0.6 cc.) to an ice cold solution of sodium hydroxide

(2.4 g.) in water (20 cc.). Into one tenth of this solution was stirred the finely powdered amide (0.22 g.). The mixture turned pink at the surface so stirring was continued by bubbling in nitrogen. The mixture was left for 2½ hours in an ice bath then filtered from unchanged amide giving a red solution.

1 cc. of this filtrate was evaporated to dryness and the residue subjected to vacuum sublimation at 240° and 10 mm. pressure but only a film of colourless gum was obtained which did not form a picrate. The rest of the solution yielded no amine on chloroform extraction.

In a modified Hofmann reaction designed to isolate urethanes from amides[38a] the amide (XLI) (0.22 g.) was dissolved in methyl alcohol (30 cc.), a solution of sodium methoxide, from sodium (50 mg.) and alcohol (2.5 cc.), added, then one drop of bromine and the mixture heated on a water bath for 10 minutes. On cooling the solution was neutralised with acetic acid, evaporated to dryness, and continuously extracted with benzene, to yield however only unchanged amide in 50% yield.

Action of hydrazine hydrate on the ester (XL).

To the ester (XL) (0.2 g.) dissolved in alcohol (10 cc.) was added four drops of 90% hydrazine hydrate and the solution boiled for 4 hours. The yellow solution was boiled with charcoal for a further 2 hours, filtered, and left to crystallise. Stout orange prisms (a) formed in the midst of a pale yellow mass of microcrystals (b) and were picked out by hand. m.p. (a) 180-183°; m.p. (b) 170-171°, mixed m.p. 160-165°. The orange prisms, on recrystallisation from alcohol, gave some (b) and since the analysis of a sample m.p. 184-185° gave no information, the investigation was discontinued. (Found: C, 52.4; H, 4.5; N, 35.5%).

7-Anilino-5:6-tetramethylene-1:3:8-triazaindolizine (XLII, p.16).

A solution of the chloro compound (XXXV) (1 g.) in alcohol (5 cc.) was heated under reflux for 2 hours with freshly distilled aniline (1 g.). On cooling the product was filtered, washed with water, and crystallised from alcohol in colourless needles, m.p. 212-213°. Yield, 0.8 g., 61%. (Found: C, 69.0; H, 6.0; N, 25.8. $C_{15}H_{15}N_5$ requires C, 69.9; H, 5.7; N, 26.4%).

Hydrochloride of 7-(β-diethylaminoethylamino)-5:6-tetramethylene-1:3:8-triazaindolizine (XLIII, p.16).

A solution of the chloro compound (XXXV) (2.5 g.) and N:N-diethylethylenediamine (2.1 g.) in alcohol (25 cc.) was boiled under reflux for 3 hours. The alcohol was distilled off on the water bath and the pressure then reduced to 2 mm. to remove any unreacted diamine. The residue was dissolved in the minimum volume of hot alcohol, cooled slightly and an equal volume of ether added. On standing fine pale brown needles were deposited. By dissolving these crystals in alcohol, boiling with charcoal, filtering, adding sufficient hot dioxan to the hot filtrate to just cause a faint turbidity, and allowing to cool, large tabular crystals were obtained which were quite soluble in water and moderately so in alcohol, m.p. 204-206°. Yield, 2.5 g., 61%. (Found: C, 55.6; H, 7.6; N, 25.7; Cl, 11.0. $C_{15}H_{24}N_6\cdot HCl$ requires C, 55.5; H, 7.7; N, 25.9; Cl, 10.9%).

Attempted dehydrogenation of 5:6-tetramethylene-1:3:8-triazaindolizine (XXXVI).

(a). The above compound was heated with palladium black[62] and with palladised charcoal[63,64] in a slow stream of carbon dioxide which was then passed through 50% potassium hydroxide solution to allow measurement of hydrogen. At temperatures a little above the melting point only slow sublimation occurred, between 250° and 300° there was rapid sublimation accompanied by some decomposition. When α-methylnaphthalene was used as solvent complete decomposition took place.

In each case the gas collected did not burn so was probably nitrogen.

(b). On heating the substance (0.17 g.) with sulphur (60 mg.) vigorous decomposition occurred with evolution of hydrogen sulphide, but nothing could be extracted from the residue.

(c). Solutions of the above compound and chloranil in xylene[41] were mixed and boiled for 5 hours. The mixture became black and an intractable tar was obtained.

(d). On boiling with N-bromosuccinimide in carbon tetrachloride[42] solution fumes of hydrogen bromide were evolved. Succinimide, but no other homogeneous product, was isolated from the reaction.

(e). Treatment with potassium ferricyanide[43] in aqueous solution resulted in the formation of some potassium ferrocyanide, but no other material was isolated.

Attempted preparation of 7-hydroxy-5:6-benz-1:3:8-triaza-indolizine (XLIX).

(a). 3-o-iodobenzoylamino-1:2:4-triazole (XLVIII, p.19).

Anthranilic acid was converted to o-iodobenzoic acid, refluxed with thionyl chloride, the reagent removed, and the acid chloride distilled in vacuo.

3-Amino-1:2:4-triazole (2.8 g.) was dissolved in pyridine (10 cc.) and o-iodobenzoyl chloride (9 g.) melted and dropped into the solution which became warm. After standing for several hours the solution was poured into water (100 cc.) and the fine white precipitate filtered, washed with water, and crystallised from alcohol in rosettes of microcrystalline needles, m.p. 285-315°. Yield, 7.5 g., 72%.

(Found: C, 34.6; H, 2.3; N, 18.0. $C_9H_7ON_4I$ requires
C, 34.4; H, 2.2; N, 17.8%).

(1). On heating (XLVIII) (0.1 g.) with dry potassium carbonate (1 g.) and a trace of copper bronze to 300° the iodo-compound sublimed unchanged from the mixture.

(2). A solution of (XLVIII) (0.1 g.) in quinoline (5 cc.) with a trace of copper bronze was refluxed for 3 hours. The quinoline was removed by steam distillation but, after evaporating the residual solution to dryness, no sublimate was obtained on heating the residue to 300° under 2 mm. pressure. Without copper bronze unchanged material was isolated on cooling the quinoline solution.

(3). A solution of (XLVIII) (0.1 g.) in pyridine (10 cc.) with copper bronze was refluxed for 3 hours. The mixture quickly became green, then cloudy, and a green solid was filtered which decomposed without melting and was insoluble in solvents, being a copper salt of some kind.

(4). A mixture of (XLVIII) (0.1 g.) with triethylamine (2 cc.) and nitromethane (5 cc.) was heated to 150-160° in a sealed tube for 3 hours[44]. When the mixture was filtered a black solid and very dark filtrate were obtained, some of the colour being due to free iodine. No product could be isolated from the reaction which seemed to have completely charred.

(b). <u>3-o-aminobenzoylamino-1:2:4-triazole (LI, p.20).</u>

Isatin was oxidised in glacial acetic acid with chromic oxide, as described by Kolbe[65], the product being crystallised from dioxan.

Isatoic anhydride (8.2 g.) and 3-amino-1:2:4-triazole (4.2 g.) were dissolved in dioxan (150 cc.) and the solution refluxed for 5 hours. On cooling a small amount (0.3 g.) of unidentified material, m.p. 365-370°, was deposited. After evaporation of the solution to one third bulk and cooling, more solid (LII) (0.5 g.) separated, m.p. 270-275°. The filtrate on standing a few days yielded orange-yellow crystals (50 mg.), m.p. 200-202°, probably anthranoylanthranilic acid. As much dioxan as possible was distilled from the mother liquors on a water bath under reduced pressure and the residual gum dissolved in a small amount of alcohol. From this solution pale yellow needles (LI) (1.2 g.), m.p. 180-185°, were deposited.

In an attempt to purify (LI) by sublimation, first a yellow oil, then a white solid were obtained. The latter, m.p. 290-292°, did not depress the m.p. of (LII) which on purification also had m.p. 290-292°.

(Found: LI ; C, 53.3; H, 4.5; N, 34.4.
LII; C, 53.5; H, 4.3; N, 34.6. $C_9H_9ON_5$ requires
C, 53.2; H, 4.4; N, 34.5%).

Treatment of (LI) with acetic anhydride merely converted it to (LII) while a solution of (LII) in dilute hydrochloric acid, on the addition of sodium nitrite, gave a brown solution from which nothing could be isolated.

(c) 3-o-nitrobenzoylamino-1:2:4-triazole (LIII, p.20).

By neutral potassium permanganate oxidation of o-nitrotoluene o-nitrobenzoic acid was prepared and converted to the acid chloride by treatment with thionyl chloride followed by vacuum distillation.

To a solution of 3-amino-1:2:4-triazole (4 g., 2 mols.) in dioxan (40 cc.) was added a solution of o-nitrobenzoyl chloride (3.6 g., 1 mol.) in dioxan (10 cc.). The product separated out as an oil which gradually solidified. The solid was triturated with water and the aminotriazole hydrochloride recovered, the insoluble residue being dried and crystallised from dioxan in pale yellow prisms, m.p. 238-243°. Yield, 3.7 g., 82%.

(Found: C, 46.5; H, 3.0; N, 30.4. $C_9H_7O_3N_5$ requires
C, 46.3; H, 3.0; N, 30.0%).

A suspension of the nitro compound (LIII) (0.233 g.) in alcohol (25 cc.) was shaken with hydrogen and 2% palladised strontium carbonate (0.2 g.) till the theoretical volume of hydrogen (67 cc.) for reduction of the nitro group to amino had been absorbed (3 hours). The reduced material and catalyst were boiled with more alcohol (100 cc.), filtered, and extracted again with alcohol (100 cc.) and the combined extracts concentrated. The faintly fluorescent solution deposited white micro crystals, m.p. 290°, identical with (LII) (Mixed m.p.). Yield, 0.18 g., 89%.

The nitro compound (LIII) (2.5 g.) was dissolved in nitrobenzene (50 cc.) and the solution gently boiled for 3 hours. On cooling, brown crystalline plates separated, were collected, washed with ether, dissolved in boiling water (1 l.), filtered, charcoal added, and the mixture slowly boiled down to about 700 cc., thus steam distilling off any residual nitrobenzene. The filtered solution on cooling deposited small white prisms which after repeated crystallisation from water and then from nitromethane had m.p. 271-272°. Yield, 1.86 g., 74%.

(Found: C, 46.4; H, 3.1; N, 29.8. $C_9H_7O_3N_5$ requires C, 46.3; H, 3.0; N, 30.0%).

This isomerised material (LIV) (0.233 g.) in alcohol (25 cc.) was reduced in the same manner as the nitro compound (LIII) above, taking however only 10 minutes. The product was isolated as before in similar yield, m.p. 290°, and proved to be identical with (LII).

A mixture of (LIII) and (LIV) had m.p. 230-235°.

(d) 3-o-Nitrobenzylideneamino-1:2:4-triazole.

o-Nitrobenzaldehyde (1 g.) and 3-amino-1:2:4-triazole (1 g.) in alcohol (20 cc.) was refluxed for 3 hours. The yellow amorphous solid which separated out, m.p. 185-190° (dec.), was rather insoluble in organic solvents and difficult to purify.

N-(β-Diethylaminoethyl)-o-iodobenzamide hydrochloride (LV, p.22).

o-Iodobenzoyl chloride (5 g.) in benzene (10 cc.) was added gradually to N:N-diethylethylenediamine (2.4 g.) in benzene (5 cc.) with cooling. The mixture became hot and pasty. The benzene was distilled off and the residue crystallised from dioxan in long flat prisms, m.p. 165-168°. Yield, 7.4 g., ca. 100%.

(Found: C, 40.8; H, 5.1; N, 7.4. $C_{13}H_{19}ON_2I.HCl$ requires C, 40.8; H, 5.2; N, 7.3%).

A solution of the amide (5 g.) in water (10 cc.) was made strongly alkaline, extracted with xylene, and the extract dried with potassium carbonate.

To the dry xylene extract (40 cc.) 3-amino-1:2:4-triazole (0.6 g.), potassium carbonate (0.5 g.), and copper bronze (50 mg.) were added, the mixture being stirred for 8 hours under reflux. After adding concentrated sodium hydroxide solution to the mixture and shaking, the xylene layer was separated, washed, and dried. On evaporation a gum was obtained which was boiled with phosphorus trichloride (15 cc.) for 3 hours, excess reagent removed, the residue made alkaline, extracted with chloroform, and the chloroform extract evaporated to dryness. The residue, heated in a bath at 220° under 2 mm., gave a pale yellow oily distillate which could not be obtained solid nor as a solid picrate.

The other half of the xylene extract treated with the previous reagents in the reverse order gave no product.

6:7-Benz-1:3:8-triaza-5-indolizone (LXI, p.22).

3-Amino-1:2:4-triazole (2.5 g.), potassium carbonate (2.5 g.), potassium o-iodobenzoate (8.5 g.), copper bronze (0.13 g.) and amyl alcohol (8 cc.) were stirred under reflux on an oil bath for 8 hours. When cold the solid was filtered, washed with ether, dissolved in dilute potassium hydroxide solution, filtered from copper bronze, and poured into a slight excess of dilute hydrochloric acid. The precipitate was washed with dilute sulphurous acid, dried, and purified by sublimation at 180-200° under 2 mm. pressure, followed by crystallisation from dioxan in stout transparent needles which became white on drying, m.p. 232-237° with sublimation. Yield, 1.7 g., 31%.

(Found: C, 58.5; H, 3.1; N, 29.7. $C_9H_6ON_4$ requires
C, 58.1; H, 3.2; N, 30.1%).

Attempted chlorination of 5:6-benz-1:3:8-triaza-5-indolizone (LXI).

Using 0.2 g. in each case, this compound resisted chlorination under the following conditions:-

(a). Refluxing with a large excess of phosphoryl chloride for 3 up to 24 hours, removing excess reagent and pouring on to ice.

(b). Avoiding contact with water by extracting the dry residue with benzene followed by sublimation of residue and evaporated extract.

(c). Carrying out the reaction with a mixture of phosphorus oxy- and pentachloride (with and without dimethylaniline) at 150° for 3 hours and at 300° for 48 hours. A dark insoluble powder was obtained at 150° with dimethylaniline and at 300° without it.

What was apparently a hydrochloride was once isolated under (a) m.p. 235°, mixed m.p. with (LXI) showing no depression.

(Found: N, 25.45. $C_9H_6ON_4 \cdot HCl$ requires N, 25.2%).

Nitration of 5:6-benz-1:3:8-triaza-5-indolizone (LXI).

The above compound (LXI) (0.1 g.) was added to cold fuming nitric acid (5 cc.) in which it at once dissolved. On standing for several days, removing the acid under reduced pressure, and adding water to the residue a pale yellow powder was obtained. It was difficultly soluble in the usual solvents crystallising from ethylene glycol in pale yellow microprisms (LXII) m.p. 357-359° (dec.). Yield, 0.1 g. 80%.

(Found: C, 47.5; H, 2.5; N, 30.1. $C_9H_5O_3N_5$ requires
C, 46.8; H, 2.2; N, 30.3%).

Attempted synthesis of (LXII).

3-Amino-1:2:4-triazole (0.8 g.), potassium 2-chloro-5-nitrobenzoate (2.4 g.), potassium carbonate (0.8 g.), copper bronze (50 mg.), and nitrobenzene (10 cc.) were stirred at

200° for 5 hours. The product was isolated by filtering, washing with ether, dissolving in dilute alkali, filtering, and adding the solution to a slight excess of dilute hydrochloric acid. Being much less volatile than (LXI) during vacuum sublimation this method was inconvenient. It separated from ethylene glycol or nitrobenzene as an orange yellow powder, m.p. 340-350° with darkening above 300°. Yield, 1.2 g. Owing to the darkening and diffuse m.p., mixing with (LXII) showed no conclusive effect on the m.p.

5-Hydroxy-6:7-trimethylene-1:3:8-triazaindolizine (LXIII, p.24).

A solution of 3-amino-1:2:4-triazole (4 g.) and ethyl cyclopentanone-2-carboxylate (8 g.) in alcohol (50 cc.) was gently refluxed for 24 hours. On cooling the hydroxy compound was filtered, the filtrate concentrated to small bulk and the rest of the material which separated was filtered and the combined yield crystallised from boiling water (300 cc.), m.p. 290° (dec.). Yield, 5 g., 60%. (Found: C, 54.7; H, 4.7; N, 31.5. $C_8H_8ON_4$ requires
C, 54.5; H, 4.8; N, 31.8%).

5-Chloro-6:7-trimethylene-1:3:8-triazaindolizine (LXIV, p.24).

When a solution of the hydroxy compound (LXIII) (2.5 g.) in phosphoryl chloride (40 cc.) was boiled under reflux for 5 hours, excess reagent removed under reduced pressure, and ice added to the residue, a deep red solution was obtained. Concentrated ammonia solution (S.G. 0.88) was now added to almost neutralise the solution which was kept cold by adding pieces of ice. A pink precipitate was filtered and the filtrate extracted with benzene. The precipitate and extract were dried, combined, boiled with charcoal, filtered, concentrated, and diluted with light petroleum. Colourless needles were obtained after several recrystallisations from light petroleum, m.p. 168-169°. Yield, 1.1 g., 40%.

(Found: C, 49.5; H, 3.5; N, 28.5. $C_8H_7N_4Cl$ requires
C, 49.4; H, 3.6; N, 28.8%).

6:7-Trimethylene-1:3:8-triazaindolizine (LXV, p.24).

A solution of the chloro compound (LXIV) (0.194 g.) in alcohol (20 cc.) was shaken with hydrogen and 15% palladised barium sulphate[63a] (0.2 g.) till 22.4 cc. of hydrogen had been absorbed. After filtering and washing the catalyst with a little alcohol the filtrate and washings were concentrated to small bulk and concentrated ammonia solution (2 drops) added. The precipitate was filtered, washed with water, dried, and crystallised from ligroin (b.p. 100-120°) in clusters of short needles, m.p. 207-208°d. Yield, 0.12 g., 75%.

(Found: C, 59.9; H, 5.1; N, 34.8. $C_8H_8N_4$ requires
C, 60.0; H, 5.0; N, 35.0%).

In a Rast molecular weight determination this material (2.1mg. in camphor (34.9 mg.) depressed the m.p. from 177° to 158°, giving a molecular weight about 130, thus eliminating the possibility of its being a di-triazaindolizyl.

5:6-Trimethylene-1:3:8-triazaindolizine (LXVI, p.24).

Solutions of 3-amino-1:2:4-triazole (0.9 g.) and 2-hydroxymethylenecyclopentanone[66] (1.2 g.) each in alcohol

(10 cc.) were mixed and kept at 40° for several days. A white amorphous solid (0.9 g.) m.p. 180-185° separated and a further quantity (0.3 g.) was obtained by concentration of the mother liquors. On dissolving the solid in boiling alcohol and allowing to cool, solid slowly deposited on the walls of the flask with a melting point lower than before, m.p. 178-182°. Finally it was crystallised from benzene/acetic acid mixture in pinkish microprisms which lost their colour on drying in a vacuum pistol, m.p. 175-180°, which analysis showed to consist of 2-(3'-triazolylaminomethylene)-cyclopentanone (LXVII).

(Found: C, 53.9; H, 5.6; N, 31.3. $C_8H_{10}ON_4$ requires
C, 53.9; H, 5.7; N, 31.4%).

When a solution of this compound or of the above reactants in glacial acetic acid was boiled under reflux for several hours and the acetic acid removed under reduced pressure from a water bath a dark gummy residue was obtained. Several extractions of this gum with boiling ligroin (b.p. 100-120°) yielded, on treatment with charcoal and concentrating, colourless flat prisms, m.p. 133-134°. Yield, 1.1 g., 64%.

(Found: C, 60.3; H, 5.0; N, 34.8. $C_8H_8N_4$ requires
C, 60.0; H, 5.0; N, 35.0%).

2-Anilinomethylenecyclopentanone[56].

When aniline (0·93 g.) was added to a solution of 2-hydroxymethylenecyclopentanone (1·12 g.) in alcohol (10 cc.) and the mixture gently boiled under reflux for 10 minutes and then allowed to cool, bright yellow crystals were deposited, m.p. 178-179°. (Perkin et al[19b] quote m.p. 174° and give no analysis). Yield, 1·6 g., 86%.
(Found: C, 77·2; H, 7·0; N, 7·5. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0; N, 7·5%).

On addition of phosphorus trichloride to this compound, in preparation for condensation with 3-amino-1:2:4-triazole, the mixture at once went black and appeared to have completely decomposed.

5-Aminotetrazole.

The following modification of Thiele's method[34] was used:- To aminoguanidine bicarbonate (100 g.) was slowly added 10$\bar{N}$ nitric acid (150 cc.) and a solution of sodium nitrite (50 g.) in water (150 cc.) slowly dropped into the solution with stirring till all the aminoguanidine had reacted as shown by the presence of free nitrous acid. During the reaction the temperature was kept at 40° by cooling the reaction mixture in a water bath to which pieces of ice were periodically added. The solution was chilled, almost neutralised with concentrated ammonia solution, anhydrous sodium acetate (50 g.) added, and the mixture taken quickly to boiling point and kept boiling for 10 minutes, during which the solution became dark green. After standing overnight the pale green crystals were filtered and dissolved in boiling water (200 cc.).

The crystals which separated this time were bright yellow but after boiling in a fresh volume of water (200 cc.) with charcoal for 2 hours and filtering the cooled solution deposited colourless crystals of 5-aminotetrazole monohydrate. By treating the filtrate plus previous mother liquors with charcoal and concentrating a further yield (2.5 g.) was obtained. M.p. 200-201° (dec.). Yield, 52.5 g., 69%.

7-Hydroxy-5:6-tetramethylene-1:2:3:8-tetrazaindolizine (LXVIII, p.25)

5-Aminotetrazole (10 g.) was dissolved in glacial acetic acid (50 cc.), ethyl cyclohexanone-2-carboxylate (17 g.) added, and the solution boiled gently under reflux for 3 hours. The solvent was distilled off from a water bath under reduced pressure and the residue, dissolved in water, was boiled with charcoal for 1 hour. On filtering and allowing to cool, colourless needles were obtained, m.p. 200° (dec.). Yield, 16 g., 84%.
(Found: C, 50.5; H, 4.9; N, 36.7. $C_8H_9ON_5$ requires
C, 50.3; H, 4.7; N, 36.7%).

7-Chloro-5:6-tetramethylene-1:2:3:8-tetrazaindolizine (LXIX, p.25).

The hydroxy compound (LXVIII) (5 g.) was heated under reflux with phosphoryl chloride (20 cc.) for 4 hours and the excess reagent then distilled off under reduced pressure from a water bath. The residue, mixed with ice, was almost neutralised with concentrated ammonia solution, triturating the mixture till the gummy material solidified to a brown powder. The solid was then filtered, washed with water, dried in a desiccator, and sublimed at 110-120° under 3 mm. pressure as fine colourless needles. The sublimate

was crystallised from light petroleum (b.p. 80-100°) in needles, m.p. 97-99°. Yield, 3 g., 54%.
(Found: C, 46.0; H, 4.0; N, 33.2. $C_8H_8N_5Cl$ requires C, 45.8; H, 3.9; N, 33.4%).

5:6-Tetramethylene-1:2:3:8-tetrazaindolizine (LXX, p.25).

(a). A solution of the chloro-compound (LXIX) (0.2 g.) in acetone (15 cc.) was dehalogenated by shaking with hydrogen and 2% palladised strontium carbonate (0.2 g.) till an absorption of 22.4 cc. had been effected. The mixture was heated with acetone (20 cc.), filtered, and the filtrate evaporated to dryness. The residue was extracted with benzene, the extract concentrated to small bulk, and hot ligroin (b.p. 100-120°) added. On cooling colourless acicular prisms were obtained which after repeated crystallisation from ligroin had m.p. 122-123°. Yield, 0.08 g., 44%.
(Found: C, 54.9; H, 5.2; N, 40.1. $C_8H_9N_5$ requires C, 54.8; H, 5.2; N, 40.0%).

(b). 5-Aminotetrazole (10 g.) was dissolved in alcohol (100 cc.) and 2-hydroxymethylenecyclohexanone (12.6 g.) added, the mixture being boiled under reflux for several hours. The product crystallised on cooling in colourless plates, m.p. 122-123° alone or mixed with a sample prepared as under (a). Concentration of the filtrate afforded additional material. Yield, 14 g., 80%.

(Found: C, 54.9; H, 5.3; N, 40.1. $C_8H_9N_5$ requires C, 54.8; H, 5.2; N, 40.0%).

7-Anilino-5:6-tetramethylene-1:2:3:8-tetrazaindolizine (LXXI, p.26).

The above compound was obtained by heating a solution of the chloro compound (LXIX) (1 g.) in alcohol (5 cc.) with aniline (1 g.) on a steam bath under reflux for 2 hours. When cold the solid was filtered and washed with water to remove aniline hydrochloride. Crystallisation from alcohol afforded colourless short needles, m.p. 192-194°. Yield, 0.7 g., 55%.

(Found: C, 63.0; H, 5.3; N, 31.4. $C_{14}H_{14}N_6$ requires C, 63.1; H, 5.3; N, 31.6%).

Hydrochloride of 7-(β-diethylaminoethylamino)-5:6-tetramethylene-1:2:3:8-tetrazaindolizine (LXXII, p.26).

A solution of the chloro compound (LXIX) (1 g.) and N:N-diethylethylenediamine (1 cc.) in alcohol (10 cc.) was heated on a steam bath under reflux for 3 hours. The solvent was then distilled off and the pressure then reduced to 2 mm. to remove unreacted diamine. The residue was dissolved in alcohol, boiled with charcoal then filtered.

To the heated filtrate was added hot dioxan till turbidity appeared and on leaving to cool colourless prisms of the hydrochloride (LXXII) were obtained which were readily soluble in water. Yield, 1.3 g., 84%.

(Found: C, 52.0; H, 7.2. $C_{14}H_{23}N_7 \cdot HCl$ requires
C, 51.6; H, 7.4%).

Condensation of 5-aminotetrazole with ethyl cyclopentanone-2-carboxylate.

To 5-aminotetrazole (5 g.) dissolved in alcohol (50 cc.) was added ethyl cyclopentanone-2-carboxylate (7.8 g.) and the solution refluxed for 24 hours. When cold the product (LXXIII, p.27) was filtered from the mother liquor which gave more material on concentration. The combined yield was recrystallised from alcohol yielding tiny rectangular prisms. If crystallisation occurred very slowly over several days transparent needle-like prisms were formed. M.p. 162° (frothing) with previous softening at 158°. Yield, 6.2 g.

(Found: C, 38.9; H, 5.0; N, 45.4. $C_{10}H_{16}O_2$ requires
C, 39.0; H, 5.2; N, 45.4%).

When the reaction was carried out in boiling acetic acid over several hours there was isolated 5-acetylaminotetrazole, m.p. 273° (frothing). Thiele and Ingle[67] quote 269°.

(Found: C, 28.4; H, 3.9; N, 55.2. $C_3H_5ON_5$ requires C, 28.3; H, 4.0; N, 55.1%).

When no solvent was used charring took place and some aminotetrazole was recovered.

5:6-Trimethylene-1:2:3:8-tetrazaindolizine (LXXIV, p.28).

To a solution of 5-aminotetrazole (2 g.) in acetic acid (10 cc.) was added a solution of 2-hydroxymethylene-cyclopentanone (2 g.) in acetic acid (10 cc.) and the mixture boiled under reflux for several hours during which the initial precipitate, presumably 2-(5'-tetrazolylaminomethylene)-cyclopentanone, redissolved. The solvent was removed on a water bath under reduced pressure and the dark gummy residue extracted thrice with boiling ligroin (b.p. 100-120°) in 10 cc. portions. The combined extracts, on concentrating and cooling yielded crystals which after repeated crystallisation from this solvent formed short colourless needles, m.p. 152-153°. Yield, 1.9 g., 60%.

(Found: C, 52.2; H, 4.5; N, 43.5. $C_7H_7N_5$ requires C, 52.2; H, 4.4; N, 43.5%).

7-Hydroxy-5:6-benz-1:2:3:8-tetrazaindolizine (LXXVI, p.29).

Anhydrous 5-aminotetrazole (4.3 g.), potassium o-iodobenzoate (14.3 g.), potassium carbonate (3.5 g.), copper bronze (0.1 g.), and amyl alcohol (15 cc.) were stirred under reflux in an oil bath for 12 hours. The solid was filtered, washed with ether, dissolved in water (50 cc.), and the solution, filtered free from copper bronze, was acidified with hydrochloric acid. Extraction of the precipitate with boiling water left a residue which after crystallisation from ethylene glycol and then from glacial acetic acid yielded pale yellow prisms of diphenylamine-2:2'-dicarboxylic acid[53,54], m.p. 290-295° (dec.). Yield, 0.6 g. (Found: C, 65.75; H, 4.5; N, 5.6. $C_{14}H_{11}O_4N$ requires C, 65.4; H, 4.3; N, 5.45%).

The aqueous extract above, after treatment with charcoal and fractional crystallisation from water to remove unchanged iodobenzoic acid, gave colourless prismatic crystals of 7-hydroxy-5:6-benz-1:2:3:8-tetrazaindolizine or 4-hydroxy-1:2-tetrazoloquinazoline-1:2-dihydride[55] (LXXVI), m.p. 243° (dec.). Yield, 0.2 g.
(Found: C, 51.5; H, 2.9; N, 37.4. $C_8H_5ON_5$ requires C, 51.3; H, 2.7; N, 37.6%).

4-Hydroxy-1:2-tetrazoloquinazoline-1:2-dihydride (LXXVI).

Benzoylene urea[68], prepared by treating anthranilic acid with potassium cyanate, was chlorinated with a phosphorus oxychloride/pentachloride mixture and the uncrystallised dichloroquinazoline[56,69] at once converted to 4-azido-1:2-

tetrazoloquinazoline-1:2-dihydride (LXXV) with sodium azide in acetone. Hydrolysis of the azido group with sodium ethoxide yielded 4-hydroxy-1:2-tetrazoloquinazoline-1:2-dihydride which proved to be identical (mixed m.p.) with 7-hydroxy-5:6-benz-1:2:3:8-tetrazaindolizine (LXXVI). Overall yield from benzoylene urea, 5.3 g., 31%.

7-Chloro-5:6-benz-1:2:3:8-tetrazaindolizine (LXXVII, p.29).

The hydroxy compound (LXXVI) (0.15 g.) was heated with phosphoryl chloride (5 cc.) under reflux for 2 hours. The excess reagent was distilled off under reduced pressure from a water bath, powdered ice added to the residue and the pale yellow precipitate quickly washed with water, filtered, dried, and crystallised from benzene after charcoal treatment to remove the yellow colour. Colourless acicular prisms were deposited, m.p. 184-185°. A sample was also prepared from the 4-hydroxy-1:2-tetrazoloquinazoline-1:2-dihydride above and admixture with the original caused no depression of m.p. Yield, 0.14 g., 84%.

(Found: C, 46.7; H, 2.2; N, 34.5. $C_8H_4N_5Cl$ requires
C, 46.7; H, 2.0; N, 34.1%).

Formation of 2-amino-5:6:7:8-tetrahydroquinazoline (LXXVIII, p.30).

(a). 5:6-Tetramethylene-1:3:8-triazaindolizine (XXXVI)

(0.1 g.) in light petroleum solution (10 cc.) was distilled to dryness over a small flame and allowed to char. The residue and sublimate were extracted with benzene and the extract evaporated to dryness. Fractional vacuum sublimation of the residue yielded along with some unchanged (XXXVI) a small amount of white crystals, m.p. 208-210°.

(b). 7-Chloro-5:6-tetramethylene-1:2:3:8-tetrazaindolizine (LXIX) (0.2 g.) in alcohol solution (25 cc.) was shaken with hydrogen and 2% palladised strontium carbonate (0.2 g.). The catalyst was filtered and the filtrate evaporated to dryness. Vacuum sublimation of the residue followed by crystallisation from benzene/light petroleum yielded small prisms, m.p. 210-211°. On crystallising the hydrogenation product from light petroleum without previous sublimation a compound was obtained, the m.p. of which gradually rose during numerous recrystallisations to about 218°. Molecular weight determination showed it was not of the di-indolizyl type while no empirical formula could be deduced from the analyses. (Found: C, 52.4; 52.5; H, 5.5; 5.4: N, 35.3). Hydrogenation in acetic acid solution with 15% palladised barium sulphate also led to high melting dechlorinated material.

(c). A solution of 5-aminotetrazole (2.5 g.) in alcohol (20 cc.) was added to ethyl cyclohexanone-2-glyoxylate (5 g.)

and the mixture heated under reflux for 5 hours. The solvent was distilled off and the gummy residue heated in an oil bath at 140° under 2 mm. pressure to remove unchanged ketoester. The residue was then extracted several times with boiling benzene and the combined extracts passed through a short alumina column. The solution was then concentrated and the solid which separated was sublimed in vacuo. M.p. 205-207°.

(Found: (a) C, 64.3; H, 6.9; N, 29.0.
(b) C, 65.2; H, 7.2; N, 27.7.
(c) C, 65.1; H, 7.4; N, 27.3. $C_8H_{11}N_3$ requires
C, 64.4; H, 7.4; N, 28.2%).

To a solution of guanidine hydrochloride (3 g.) in alcohol (25 cc.) was added 2-hydroxymethylenecyclohexanone (4 g.) and sodium ethoxide solution (1 g. sodium in 25 cc. alcohol) and the mixture heated gently on a steam bath under reflux (bumping occurs). On cooling the solid was washed with a little alcohol, then water to remove sodium chloride, and crystallised from alcohol, m.p. 210°. Benary[57] gives 206-210°. Yield, 3 g., 63%.

(Found: C, 64.8; H, 7.4; N, 28.4. $C_8H_{11}N_3$ requires
C, 64.4; H, 7.4; N, 28.2%).

Mixed m.ps. among (a), (b), and (c), and of each in turn with the authentic sample of 2-amino-5:6:7:8-

tetrahydroquinazoline showed no depression below the lower melting point in each case.

2-Amino-5:6:7:8-tetrahydroquinazoline picrate.

A picrate was prepared from material obtained under (c) and also from the authentic sample of 2-amino-5:6:7:8-tetrahydroquinazoline, crystallising from much alcohol in tiny yellow prisms, softening 220°, m.p. 232°. No depression of m.p. occurred on mixing the two samples.
(Found: C, 44.65; H, 3.9; N, 22.1. $C_{14}H_{14}O_7N_6$ requires C, 44.4; H, 3.7; N, 22.2%).

Miscellaneous reactions.

Neutral potassium permanganate oxidations.

(a) 5:6-Tetramethylene-1:3:8-triazaindolizine (XXXVI).

A solution of this substance (1.7 g.) in water (100 cc.) was treated with a solution of potassium permanganate (3.2 g.) in water (100 cc.) which was quickly decolourised. More permanganate (3.2 g.) was added and after 1½ hours' reflux the manganese dioxide was filtered and the colourless filtrate acidified with concentrated hydrochloric acid, then concentrated to small bulk. Adipic acid crystallised on standing overnight, identified after several recrystallisations from water by its m.p. 149-151° and by mixed m.p. with an authentic specimen. From the mother liquors after vacuum sublimation, to remove potassium salts, a substance which sublimed without melting about 300° was isolated and identified as ammonium chloride.

(b). 5:6-Tetramethylene-1:2:3:8-tetrazaindolizine (LXX).

This material on similar oxidation also gave adipic acid and ammonium chloride.

Attempted methylation.

(a). 5:6-Tetramethylene-1:3:8-triazaindolizine (XXXVI).

To a solution of this substance (0.4 g.) in alcohol (10 cc.) was added methyl iodide (0.4 g.). After standing 1 hour or refluxing for 1 hour unreacted material was recovered on removing the solvent.

(b). 5:6-Tetramethylene-1:2:3:8-tetrazaindolizine (LXX).

No reaction being observed under the above conditions, (LXX) (0.4 g.) was heated in a steam bath with methyl iodide (5 cc.) in a securely stoppered bottle for 2 hours. When cold the bottle was found to contain a black resinous material along with free iodine.

Nitrations.

(a). 5:6-Tetramethylene-1:3:8-triazaindolizine (XXXVI).

When this compound (1 g.) was added to cold fuming nitric acid (10 cc.) it at once dissolved. After leaving for several days at room temperature the acid was distilled off from a water bath under reduced pressure. If the acid became too hot the product became red, sticky and less easily purified. On triturating with water the residue gradually formed a pale yellow powder which could be crystallised from much boiling water or from alcohol in pale yellow leaflets of (LXXIX), m.p. 180°. Yield, 1 g., 67%.

(Found: C, 41.0; H, 3.2; N, 31.6. $C_9H_4O_4N_6$ requires C, 40.9; H, 3.1; N, 31.8%).

(b). 5:6-Tetramethylene-1:2:3:8-tetrazaindolizine (LXX).

This compound (1 g.) treated and purified in the same way yielded almost white leaflets of (LXX). M.p. 120-123°. Yield, 0.7 g., 47%.

(Found: C, 36.9; H, 3.2; N, 36.6. $C_8H_3O_4N_7$ requires C, 36.2; H, 2.7; N, 37.0%).

(c). 7-Hydroxy-5:6-tetramethylene-1:3:8-triazaindolizine (XXIV).

A solution of the hydroxy compound (XXIV) (0.5 g.) in fuming nitric acid (5 cc.) on evaporation yielded a reddish gum which dissolved in water, reverting to the gummy condition on concentration.

(d). 7-Carbethoxy-5:6-tetramethylene-1:3:8-triazaindolizine (XL).

Similar treatment of this compound(0.5 g.) yielded an oily red gum which was only sparingly soluble in water.

SUMMARY.

The 2-carbethoxy, hydroxymethylene, glyoxylic ester, and anilinomethylene derivatives of cyclohexanone and the 2-carbethoxy and hydroxymethylene derivatives of cyclopentanone have been condensed with 3-amino-1:2:4-triazole and 5-aminotetrazole. The configuration of the products has been investigated and attempted dehydrogenations described.

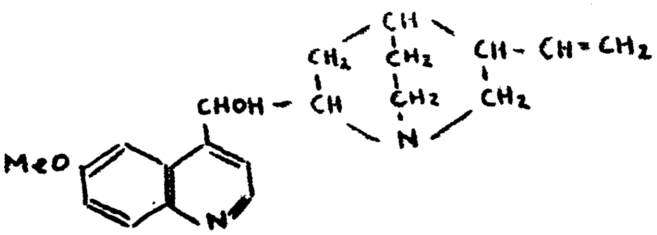
Two potential trypanocides were prepared but found to be toxic.

Cyclisation of o-substituted benzoylaminotriazoles failed, but a linear benztriazaindolizine was synthesised from potassium o-iodobenzoate and aminotriazole, in contrast to the angular benztetrazaindolizine resulting from an analogous reaction with aminotetrazole.

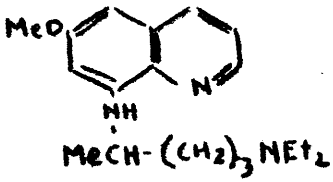
The action is described of oxidising, methylating, and nitrating agents on the 1:3:8-triaza- and 1:2:3:8-tetraza derivatives of 5:6-tetramethyleneindolizine, both of which give rise to a degradation product identified as 2-amino-5,6,7,8-tetrahydroquinazoline.

PART II.

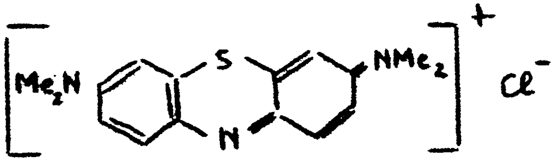
"Synthesis of Diazacarbazoles."



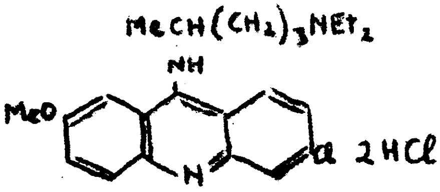
QUININE (I)



PAMAQUIN (III)



METHYLENE BLUE (II)



MEPACRINE (IV)

INTRODUCTION.

The therapeutic value of cinchona bark in the treatment of malaria has long been recognised and in 1820 the alkaloid mainly responsible for this activity, quinine (I) was isolated by Pelletier and Caventou.

Ehrlich, in 1891, when using methylene blue (II) as a biological stain, noticed that it possessed a similar, but much weaker, antimalarial activity.

Equipped with this knowledge I.G. Farbenindustrie investigators prepared numerous quinoline and acridine derivatives in a search for synthetic antimalarials culminating in the discovery of the drugs Pamaquin (III) by Schulemann in 1926 and Mepacrine (IV) by Mauss and Mietzsch in 1930 (known in America as Plasmoquine and Atebrin respectively).

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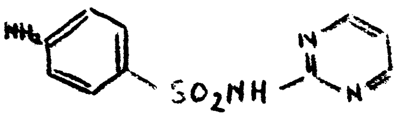
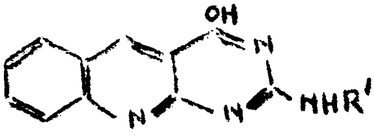
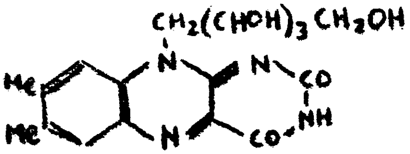
Several theories as to their mode of action were propounded. Magidson[70] and others suggested that the basic side chain of the molecule was the factor controlling its distribution in the host and aiding its penetration into the paraside (the pharmacological factor) whereas the substituted quinoline or acridine nucleus was the function which exerted a toxic action on the parasite (bacteriocidal factor). Schönhöffer[71] suggested that the activity of acridine derivatives was due to an equilibrium with the



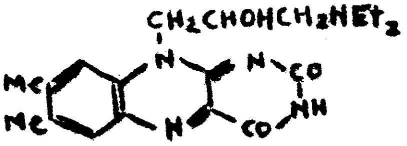
SULPHADIAZINE (V)



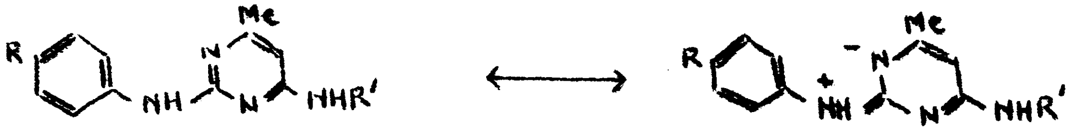
(VII)



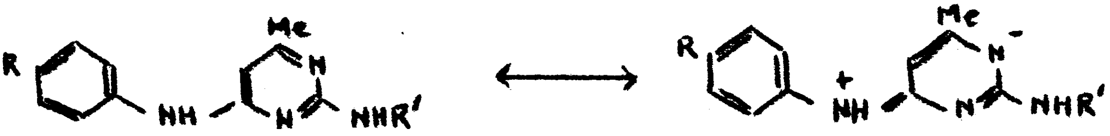
RIBOFLAVIN (VI)



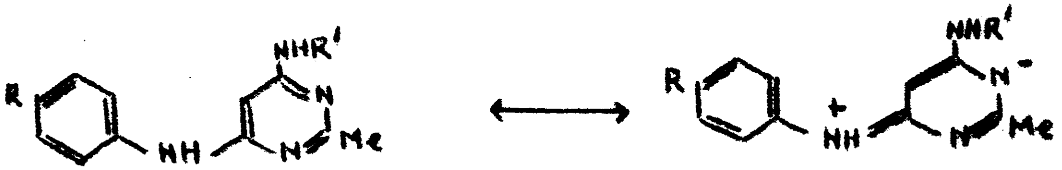
(VIII)



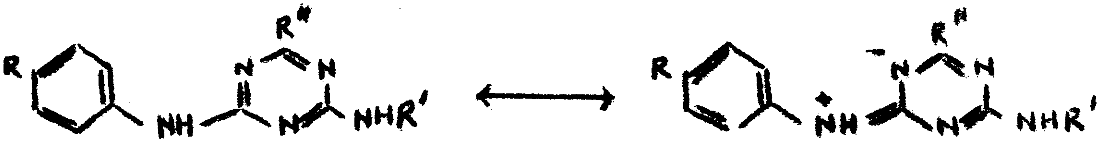
(IX) (IXa)



(X) (Xa)



(XI) (XIa)



(XII) (XIIa)

R = Cl, OMe

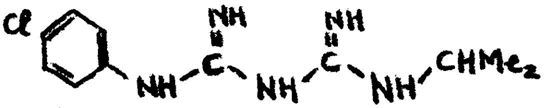
R' = $-(CH_2)_nNEt_2$

R'' = Cl, NH_2, Me.

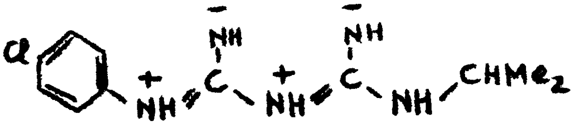
form having the central ring in a paraquinonoid form.

Subsequent attempts to synthesise new drugs were all moulded on the lines of the quinine, pamaquin, and mepacrine structures and guided by the above theories until Curd and Rose[72], departing from convention, obtained some entirely new types of drug. They had noted that some sulphonamides had a slight antimalarial activity which, like their antibacterial activity, was inhibited by p-aminobenzoic acid and which might therefore be due to a similar mechanism. They thus viewed sulphonamides, e.g., sulphadiazine (V), as aniline derivatives in which the sulphonamide group acted as the pharmacological factor. They reasoned that the quinoline and acridine nuclei of previous antimalarials were heterocyclic systems foreign to the body and so less toxic compounds might be obtained on the basis of a nucleus of biological importance for which the body would have more tolerance. Pyrimidine derivatives appeared specially suitable for investigation as being more native to the body and as very little work[73], apart from sulphonamide pyrimidines, had been done on the therapeutic properties of pyrimidines. The fact that some of these compounds bore a similarity in structure to riboflavin (VI), and that the antimalarial effect of mepacrine had been attributed by some workers[74] to a competitive effect of mepacrine in riboflavin metabolism, the bacteriostatic effect of mepacrine being antagonised by riboflavin, added interest to the work. It should be noted however that King[75] had found some diaza-acridines (VII) of little therapeutic value and that a compound (VIII) closely resembling riboflavin had been synthesised by Mosher and co-workers[76] and showed no antimalarial activity nor any tendency to behave as a riboflavin antagonist.

From the results of tests on the compounds (IX), (X), (XI), and (XII), of which only (IX) and (X) showed any antimalarial activity, a theory was developed by Curd, Landquist, and Rose[77] in which activity was related to the contributions made to the resonance hybrid by certain polarised forms in which there is conjugation, through alternate carbon and nitrogen atoms, between the aryl groups and the terminal alkyl group R'. Thus (IXa) and (Xa) satisfy these conditions while (XIa) does not, and reasons are given for assuming that (XII) does not give rise to asymmetric ionic structures like (XIIa). If, however, the triazine ring is left incomplete a biguanide structure results which will allow the conjugation deemed necessary and, indeed, this type of compound gave rise to the most suitable antimalarial discovered by Curd and co-workers, namely Paludrine (XIII).

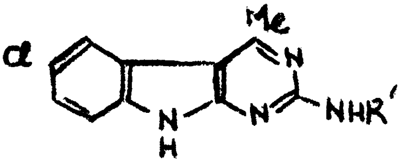


(XIII)



(XIIIa)

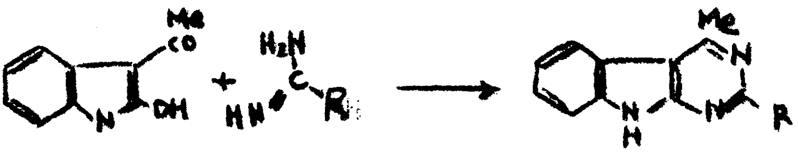
It seemed that an interesting variation would be to study a type of compound of the other extreme in which cyclisation was as complete as possible and the structure chosen was that which would result if a five-membered ring were completed in compound (X), namely the 1:3-diazacarbazole (XIV).



(XIV)

The following methods of synthesis were investigated by Ellis[78]:-

(a) Attempts were made to condense guanyl derivatives with 3-acetyloxindole[79,78a] (XV), but only one molecule of water was eliminated without cyclisation. 1-Methyl-3-acetyloxindole[80] gave what was probably 1-methyl-2-indolylurea, while 1-methyl-2-methoxy (or hydroxy)-3-formylindole and 1-methyl-3-chloromethyleneoxindole gave

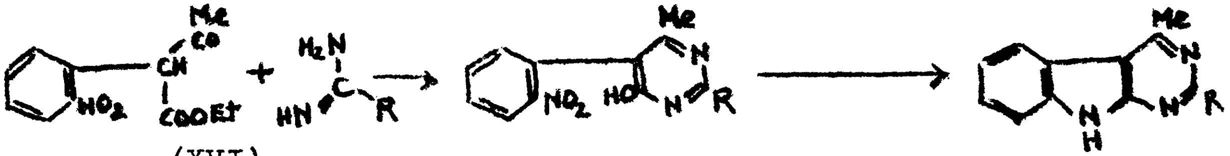


(XV)

R = OH, SH, SMe, NH_2

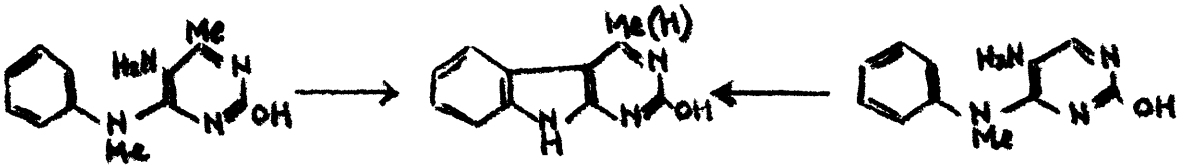
coloured compounds of indefinite constitution on treatment with the above guanyl derivatives.

(b). o-Nitrophenylacetoacetic ester (XVI) could not be prepared while 2:4-dinitrophenylacetoacetic ester[81] and

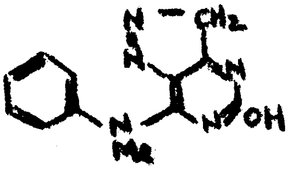

(XVI)

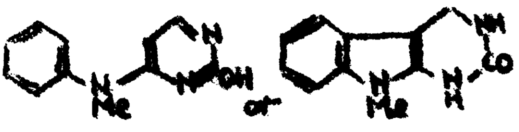
2:4-dinitrophenylmalonic ester[82] failed to condense with guanyl derivatives.

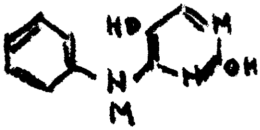
(c). Pschorr type cyclisation of the diazotised amines (XVII) and (XVIII) led, in the former case, to cyclisation


(XVII) (XVIII)

of the azo group on to the methyl group on the pyrimidine ring giving (XIX), and in the latter case to compounds of

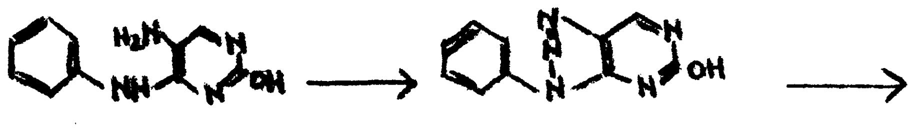

(XIX)


(XX)


(XXI)

variable melting point for which the structures (XX) and (XXI) were suggested.

(d). The Graebe-Ullmann carbazole synthesis[83] from phenyl benztriazoles was unsuccessfully applied to the triazolopyrimidine (XXIII) obtained by diazotising (XXII).

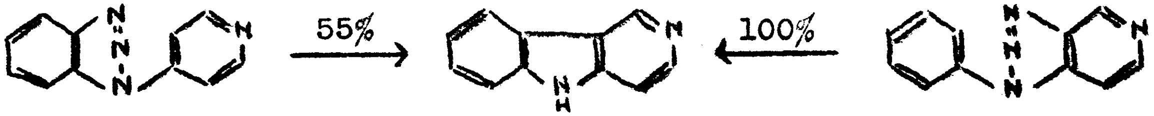


tar formation.

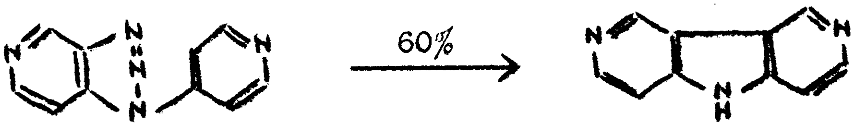
(XXII) (XXIII)

In connection with these triazolopyrimidines it has been suggested[84] that, if mepacrine and some pyrimidine antimalarials are active because of an inhibiting action on some riboflavin-containing-enzyme essential to the metabolism of the parasite, it should then be possible by means of suitably constituted reagents to arrest the growth of malaria parasites by interfering with the synthesis or utilisation of other co-enzyme constituents, e.g., the purines adenine and guanine. Thus there was reason to believe that compounds which resembled the purine bases in structure might be active therapeutically and in fact triazolopyrimidines related to (XXIII) have been found to have antibacterial properties[85].

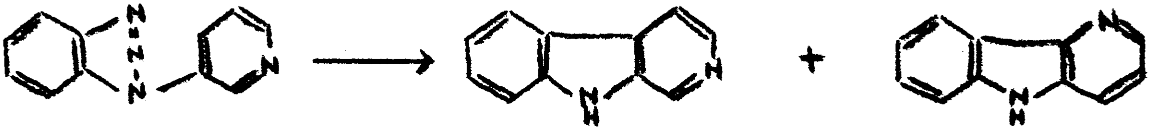
Of the previous work described the Pschorr type cyclisation of (XVIII) seemed the most promising while the triazole decomposition method had not been very extensively investigated so the work described herein consists of a



(XXIV) (XXV) (XXVI)



(XXVII) (XXVIII)



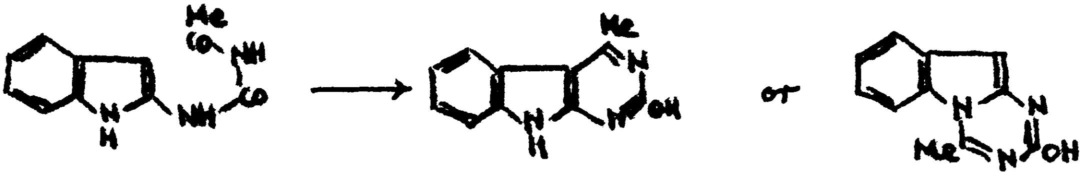
(XXIX) (XXX) (XXXI)

repetition of Ellis' synthesis of (XVIII) and renewed cyclisation attempts together with an extension of method (d) to several other triazolopyrimidines.

Besides being more easily available, the triazolopyrimidines are, from comparisons with carboline syntheses, more likely to give better yields than the corresponding pyrimidyl benztriazoles. E.g., Robinson[86] reports that γ-pyridylbenztriazole (XXIV) gives a 55% yield of γ-carboline (XXV), while Bremer[87] converted the phenyltriazolopyridine (XXVI) to γ-carboline quantitatively. Koenigs[88] obtained 3:6-diazacarbozole in fair yield from the γ-pyridyltriazolopyridine (XXVII), but very low yields were obtained of norharman (XXX) and δ-carboline (XXXI) when Späth[89] cyclised β-pyridylbenztriazole (XXIX), the main product being β-anilinopyridine.

Other methods of synthesising the required 1:3-diazacarbazole which have been suggested are:-

(a) treatment of 2-aminoindole[90] with acetyl isocyanate to give (XXXII) which might however give the indoletriazine

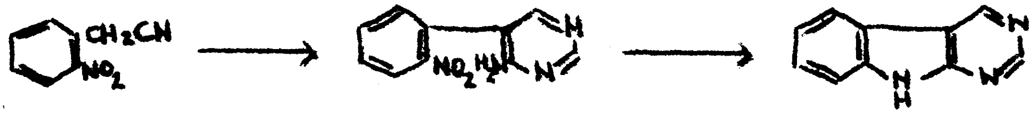


(XXXII)

(XXXIII)

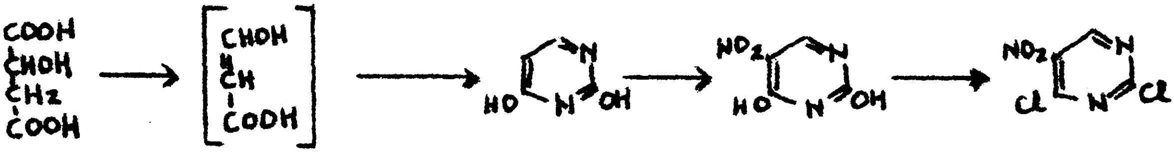
(diazaindolizine) (XXXIII) unless the indole nitrogen is blocked by a methyl group.

(b). Application of the 4-amino-5-arylpyrimidine synthesis of Davies and Piggott[91] to o-nitrobenzyl cyanide may be successful though p-nitrobenzyl cyanide only gives a 4.5% yield of 4-amino-5-(o-nitrophenyl)-pyrimidine. See, however, the footnote to the reference.



DISCUSSION.

Uracil (XXXIV) was prepared by adding malic acid to a mixture of urea in oleum. It was found that to obtain the best yields it was necessary, in preparing the urea-oleum mixture, to add the urea gradually or else the temperature of the mixture rose rapidly and poor yields were obtained.

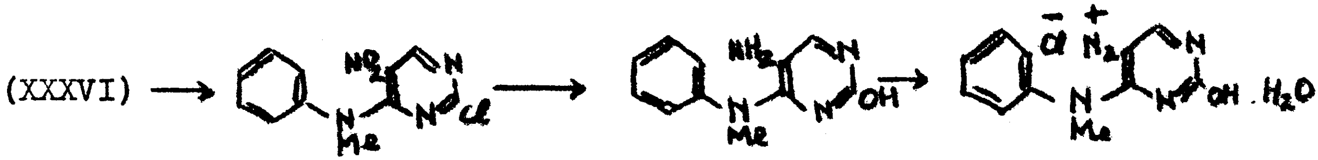


(XXXIV) (XXXV) (XXXVI)

Nitration of the uracil was found to be only partially effective as described in the literature[92] and resulted at the next stage in the isolation of appreciable quantities of 2:4-dichloropyrimidine from unreacted uracil. Preliminary reflux with fuming nitric acid ensured complete nitration.

Earlier workers[93], trying to chlorinate 5-nitrouracil (XXXV) and its 6-methyl derivative, found that they were extremely resistant to the action of phosphorus oxy- and pentachloride and adopted techniques such as heating in a rotating sealed tube at elevated temperatures for lengthy periods. The device discovered by Baddiley and Topham[94] of adding dimethylaniline to chlorinating mixtures allowed the reaction to proceed smoothly. The 2:4-dichloro-5-nitropyrimidine (XXXVI), after vacuum distillation, was found to keep unchanged for periods of six months or more if well stoppered.

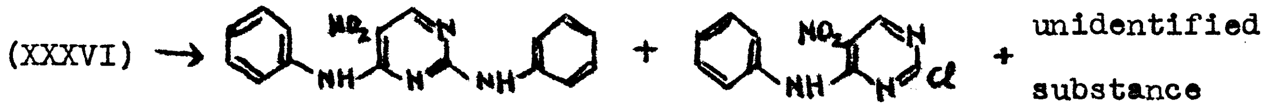
Of the two chlorine atoms in (XXXVI) the 4-chloro atom is slightly more reactive (c.f. 2:4-dichloroquinazoline[56]) presumably due to the inductive effect of the nitro group rendering the 4-position more accessible to attack by nucleophilic reagents. Thus on the addition of two equivalents of methylaniline (one equivalent to take up the hydrogen chloride liberated by the other) to a well-stirred chilled solution of (XXXVI) in alcohol only monosubstitution occurs[93a], precipitation of the 2-chloro-4-methylanilino-5-nitropyrimidine (XXXVII) protecting it from further reaction with the amine.



(XXXVII) (XVIII) (XXXVIII)

It was found advantageous to combine the next two stages without isolating the intermediate product. Hydrolysis of the remaining chloro-group was effected by heating with sodium acetate and 90% acetic acid. The acetic acid was removed and the residue, dissolved in dilute potassium hydroxide solution, was hydrogenated in the presence of a catalyst to 2-hydroxy-4-methylanilino-5-aminopyrimidine (XVIII). Diazotisation of (XVIII) yielded a remarkably stable compound, presumably the diazonium chloride monohydrate (XXXVIII). Attempts to cyclise this product by treatment with sodium hydroxide, sodium carbonate, copper bronze in acid or alkaline solution, or by heating its solution in acetic acid did not give homogeneous or consistent products and neither a diazacarbazole nor the compounds (XX) or (XXI) were isolated. In one case a small amount of material was isolated which, according to a nitrogen analysis, had not lost nitrogen. This stability casts doubt on whether (XXXVIII) really is a diazonium salt, and on attempting to couple with β-naphthol, although no definite azo dye precipitate was formed, a red colour was obtained.

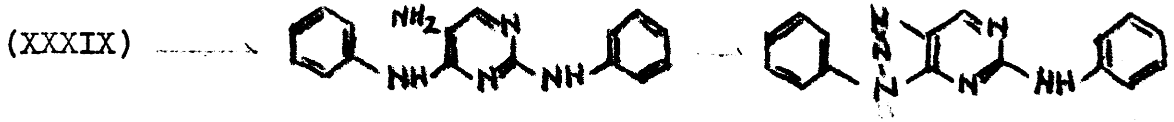
As no progress was being made with this method of synthesis, attention was turned to the triazole decomposition method. Aniline was condensed with 2:4-dichloro-5-nitropyrimidine (XXXVI) in a similar manner to methylaniline, but this time three products were isolated two of which were identified as 2:4-dianilino-5-nitropyrimidine (XXXIX) and 2-chloro-4-anilino-5-nitropyrimidine (XL), whilst the third substance (XLI) although having a sharp melting point



(XXXIX) (XL) (XLI)

could not, from several analyses, be given an empirical formula. It could be obtained in a metastable, and two different stable crystalline forms on crystallisation from light petroleum. It contained no chlorine. A Rast molecular weight determination on (XLI) gave a value of 211.

Hydrogenation of (XXXIX) proceeded very slowly even in the presence of a large excess of catalyst and the amine

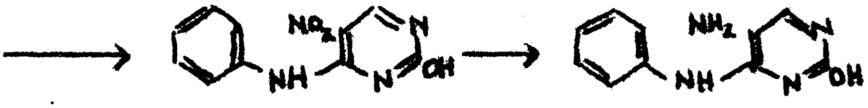


(XLII) (XLIII)

(XLII), in solution, proved to be extremely susceptible to air oxidation giving dark green and blue solutions in petroleum and alcohol respectively. The amine (XLII) was diazotised and from the dark coloured precipitate long bright yellow needles of 5-anilino-3-phenyl-v-triazolo (d) pyrimidine[95] (XLIII) were isolated. On pyrolysis in paraffin oil at 300° a compound was obtained which crystallised in colourless needles from alcohol and had a sharp melting point but which, inexplicably, left a residue on analytical combustion.

The chloro-compound (XL) was hydrolysed with sodium acetate/acetic acid mixture, the resulting hydroxy compound (XLIV) being isolated, dissolved in dilute potassium hydroxide

(XL)



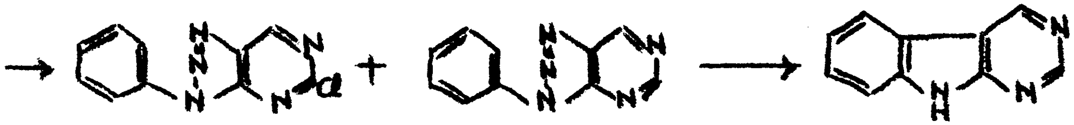
(XLIV) (XLV)

solution, and catalytically hydrogenated to the amine (XLV) which like the N-methyl derivative (XVIII) crystallised in light brown leaflets. On treatment with nitrous acid a product was isolated which evidently, from the analysis, had lost nitrogen but could not be identified.

Catalytic reduction of (XL) gave a solution of bases which, like (XLII), were sensitive to air oxidation though becoming a dark brown colour rather than the green and blue to which (XLII) gave rise. Diazotisation of the hydrogenation product gave a brown precipitate which after fractional vacuum sublimation yielded 5-chloro-3-phenyl-v-triazolo (d) pyrimidine (XLVI) and 3-phenyl-v-triazolo (d) pyrimidine

(XLVII). Several methods[96] are known for reducing nitrochloropyrimidines to aminochloropyrimidines which can then be reduced with a palladium or platinum catalyst to aminopyrimidines. Such a procedure seems preferable to the tedious fractional sublimation involved when the reduction of both groups at once was attempted with palladised strontium carbonate which was apparently unable to completely dehalogenate the chloropyrimidine (XLVI) at atmospheric pressure. Heating (XLVII) in paraffin oil, fused zinc chloride, or syrupy phosphoric acid resulted in total decomposition or partial recovery of unchanged material. Pyrolysis in an atmosphere of nitrogen yielded a very small amount of a substance which could be obtained in the form of tiny high melting orange leaflets. Insufficient material was obtained to allow complete purification but the analysis approximated to that of 1:3-diazacarbazole (XLVIII)

(XL)

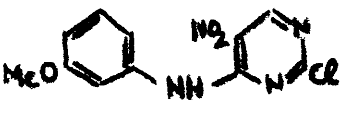


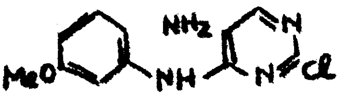
(XLVI) (XLVII) (XLVIII)

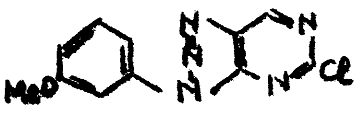
Similar treatment of (XLVI) invariably gave only charred material.

Hydrogenation of the unidentified material (XLI) gave a solution of amine prone to air oxidation, as were previous amines. A small amount was crystallised from $6\bar{N}$ hydrochloric acid but no empirical formula could be deduced from the analysis results. The material (XLI) is probably a nitro compound so on the assumption of the presence of one nitro group a molecular weight determination was carried out by semi-micro hydrogenation which gave a value of 240. The hydrochloride was treated with nitrous acid and again like the previous amines it formed a precipitate which crystallised well from alcohol but again analysis results were inconclusive. Pyrolysis of this material led only to carbonisation. The close parallel of the reactions of (XLI) to those of (XXXIX) and (XL) suggests that there is in the molecule a nitro group ortho to a secondary amino group.

In the expectation that an activating group in the phenyl ring might assist cyclisation of the phenyltriazolopyrimidine, 2-chloro-4-(m-anisidino)-5-nitropyrimidine (XLIX) was prepared, no byproducts analogous to (XXXIX) or (XLI)


(XLIX)


(L)


(LI)

being isolated. Hydrogenation with Raney nickel catalyst[97] gave (L) which on diazotisation cyclised to 5-chloro-3-(m-anisyl)-v-triazolo (d) pyrimidine (LI) which could not be cyclised to a diazacarbazole by pyrolysis.

EXPERIMENTAL.

Uracil (XXXIV, p.79).

This was prepared by adding malic acid to a mixture of urea in oleum as described by Davidson and Baudisch[98] and modified by Chi and Chen[99].

5-Nitrouracil (XXXV, p.79).

Uracil was gently boiled under reflux with fuming nitric acid for 1 hour then treated as described by Johnson and Matsuo[3]. The 5-nitrouracil was obtained in good yield and may be crystallised from much boiling water.

2:4-Dichloro-5-nitropyrimidine (XXXVI, p.79).

A mixture of freshly distilled phosphoryl chloride (152 g.), dimethylaniline (32.7 g.) and 5-nitrouracil (31.4 g.) was gently boiled under reflux in an oil bath for 5 hours, the excess phosphoryl chloride distilled off under reduced pressure, the residue poured on to crushed ice (ca. 1000 g.) and the mixture extracted several times with ether (1 l. in all). The extract was washed with dilute sodium bicarbonate solution, then water, dried over sodium sulphate, the ether distilled off, and the residue distilled at 103° under 3 mm. pressure giving a pale yellow distillate which solidified on standing, m.p. 28-30°. Yield, 20.5 g., 53%.

2-Chloro-4-methylanilino-5-nitropyrimidine (XXXVII, p.80).

To a well stirred ice-cooled solution of 2:4-dichloro-5-nitropyrimidine (19.4 g.) in alcohol (70 cc.) was added dropwise a solution of methylaniline (21.4 g.) in alcohol (60 cc.) for over 3 hours, and the mixture then stirred for 1 hour in a freezing mixture. The orange yellow precipitate was filtered, washed with a little alcohol, dried over potash in a vacuum desiccator and crystallised from ligroin (b.p. 100-120°) in small yellow prisms, m.p. 128-129°. Yield, 19 g., 72%.

(Found: C, 50.1; H, 3.6; N, 20.9 $C_{11}H_9O_2N_4Cl$ requires C, 49.9; H, 3.4; N, 21.2%).

2-Hydroxy-4-methylanilino-5-aminopyrimidine (XVIII, p.80).

2-Chloro-4-methylanilino-5-nitropyrimidine (10 g.) was dissolved in 90% acetic acid (50 cc.) and the solution heated with anhydrous sodium acetate (8 g.) on a steam bath for 3 hours, the pressure then being reduced and the mixture distilled to dryness. The residue was washed free of sodium salts with water, and added with 2% palladised strontium carbonate (10 g.) to a solution of potassium hydroxide (10 g.) in water (350 cc.). The mixture was shaken with hydrogen for two hours during which 2.5 l. were absorbed. The catalyst was filtered, the filtrate made just acid with acetic acid, then sodium bicarbonate (2 g.) stirred into the mixture which was left in a refrigerator overnight. The light brown precipitate was filtered, treated with charcoal in boiling water (2 l.), filtered, and allowed to crystallise in pale brown leaflets. Concentration of the mother liquors afforded more material, m.p., 270-280° (dec.). Yield, 6.8 g., 60%.

(Found: C, 61.15; H, 5.7; N, 26.1. $C_{11}H_{12}ON_4$ requires
C, 61.1; H, 5.6; N, 25.9%).

2-Hydroxy-4-methylanilinopyrimidine-5-diazonium chloride monohydrate (XXXVIII, p.80).

To a solution of the amine (XVIII) (2.2 g.) in dilute hydrochloric acid (10 cc.) was gradually added a solution of sodium nitrite (0.7 g.) in water (5 cc.), both solutions being ice-cold. Before all the nitrite had been added a bright yellow crystalline precipitate began to separate. The mixture was left for 1 hour in an ice bath, then filtered. A small amount of the solid was quickly crystallised from hot water, the slightly orange solid which separated had probably undergone some decomposition and analysed rather poorly as a monohydrate.

(Found: C, 47.7; H, 4.2; N, 23.2. $C_{11}H_{12}O_2N_5Cl$ requires
C, 46.9; H, 4.3; N, 24.9%).

Attempted preparation of 2-hydroxy-9-methyl-1:3-diazacarbazole.

(a). An ice cold solution of the amine (XVIII) (0.1 g.) in 2$\bar{N}$ sulphuric acid was diazotised, made just alkaline with 2$\bar{N}$ sodium hydroxide solution and heated on a steam bath for several minutes. On cooling an orange solid separated which turned black above 300°.

(b). When the diazotised solution, having been made just alkaline, was acidified with acetic acid a gummy precipitate separated, which was dissolved in alkali, reprecipitated, and crystallised from light petroleum as a light yellow solid, m.p. 125-127°. (Found: N, 28.0%).

(c). Attempts to couple the diazonium compound (XXXVIII) with dimethylamine to obtain a triazene were unsuccessful.

(d). The solid diazonium salt (1 g.) was heated in acetic acid at 100° for 5 minutes, then the solution evaporated to dryness under reduced pressure. The residue was dissolved in water and after standing several days fibrous brown crystals were deposited. These, on vacuum sublimation, yielded pale yellow material. M.p. 314-318°.

(e). A solution of the diazotised amine (0.5 g.) in 2$\bar{N}$ hydrochloric acid was stirred with copper bronze effervescence occurring. The mixture was heated, filtered, hydrogen sulphide bubbled in, and the copper sulphide filtered. On cooling a white solid was deposited and crystallised from water, m.p. 300-310°.

None of the above solids could be obtained in a pure crystalline condition.

Condensation of aniline with 2:4-dichloro-5-nitropyrimidine.

A solution of aniline (9.3 g.) in alcohol (18 cc.) was added dropwise over 3 hours to an ice-cooled, well stirred solution of 2:4-dichloro-5-nitropyrimidine (9.7 g.) in alcohol (30 cc.) and the mixture stirred for 1 hour in a freezing mixture. The orange precipitate was filtered, washed with alcohol (5 cc.), and dried over potash.

(a). 2:4-Dianilino-5-nitropyrimidine (XXXIX, p.82).

The precipitate was extracted with hot chloroform (150 cc.) and the residue crystallised from acetic acid in fine yellow needles, m.p. 202-203°. Yield, 1.2 g.

(Found: C, 62.7; H, 4.3; N, 22.9. $C_{16}H_{13}O_2N_5$ requires
C, 62.5; H, 4.3; N, 22.8%).

(b). 2-Chloro-4-anilino-5-nitropyrimidine (XL, p.82).

The above chloroform solution was evaporated to dryness under reduced pressure from a water bath and the residue dissolved in boiling ligroin (200 cc.). When the solution was cold the walls of the flask were coated with a crust of orange crystals while the bulk of the solution contained a mass of pale yellow plates. By stirring and decanting the yellow plates could be separated from the intact crust. The filtered decantate was used to redissolve the crust and the decantation process repeated giving an almost complete separation. Repeated crystallisation of the crusted material from petroleum gave orange needles, m.p. 168-170°. Yield, 6 g.

(Found: C, 48.1; H, 3.0; N, 22.3; Cl, 14.1. $C_{10}H_7O_2N_4Cl$ requires C, 47.9; H, 2.8; N, 22.4; Cl, 14.2%).

(c). Unidentified substance (XLI, p.82).

The yellow places were purified by several recrystallisations from light petroleum. On slow cooling of these solutions orange needles of a metastable nature separated out which slowly, or rapidly if warmed or agitated, became yellow. Rapid cooling resulted in the deposition of yellow plates. Needle and plate forms had the same melting point, undepressed by mixing, of 117-119°. Yield, 1.7 g.

In a Rast molecular weight determination 14.1 mg. in camphor (133.7 mg.) depressed the freezing point by 20°. Mol.wt. 211.

(Found: C, 55.7; 55.8; H, 4.7, 4.9; N, 22.1, 22.2%).

5-Anilino-3-phenyl-v-triazolo (d) pyrimidine (XLIII, p.82).

A mixture of 2% palladised strontium carbonate (15 g.) and 2:4-dianilino-5-nitropyrimidine (XXXIX) (1.2 g.) in acetone (100 cc.) was shaken with hydrogen, 260 cc.

being absorbed in 3 hours. The catalyst was filtered, well washed with acetone, and the filtrate with washings evaporated to dryness from a water bath and the residue dissolved in $\bar{N}$ hydrochloric acid (200 cc.). To this solution cooled in an ice bath was added slowly with stirring a solution of sodium nitrite (0.3 g.) in water (10 cc.). The dark coloured precipitate was filtered, then, on making the filtrate alkaline with concentrated ammonia solution, a further amount of almost black solid was precipitated.

The first precipitate was dissolved in boiling alcohol (150 cc.), filtered, boiled with charcoal for 1 hour, refiltered, and on concentration short bright yellow needles separated, softening at 185°, m.p. 190°.

The second precipitate was sublimed at 200° under 1 mm. pressure then crystallised as before. Total yield, 0.7 g., 62%.

(Found: C, 66.5; H, 4.1; N, 29.5. $C_{16}H_{12}N_6$ requires C, 66.7; H, 4.2; N, 29.2%).

Solutions of the intermediate 2:4-dianilino-5-aminopyrimidine (XLII) in ligroin or alcohol rapidly turned deep green and blue respectively on exposure to air. The solid separated from ligroin as dirty grey crystals with a silvery sheen, m.p. 180-200°.

Pyrolysis of (XLIII).

To liquid paraffin (5 cc.) heated to 300° in a metal bath was added portionwise the anilinophenyltriazolopyrimidine (XLIII) (1 g.) over 1 minute. The mixture, which became very dark and showed a slight effervescence, was stirred for 1 minute more then allowed to cool.

The residue after filtration was washed with a little ether, extracted with boiling alcohol (100 cc.), the extract filtered, boiled with charcoal, refiltered, concentrated and left to crystallise. Short colourless needles were obtained, m.p. 247-250°. Yield, 0.1 g.

On analysis 3.135 mg. left an incombustible brown residue 0.530 mg.

(Found: C, 51.0; H, 5.1; N, 16.4%).

2-Hydroxy-4-anilino-5-nitropyrimidine (XLIV, p.83).

A solution of the 2-chloro derivative (XL) (6 g.) in 90% acetic acid (40 cc.) was heated on a steam bath with anhydrous sodium acetate (5 g.) for 10 hours. The cooled mixture was poured into water (250 cc.) and the yellow solid filtered and washed. A small amount was crystallised several times from much boiling water from which it separated in tiny glistening pale yellow plates, m.p. 275-276°, softening at 220°. Yield, 5.2 g., 93%.

(Found: C, 52.4; H, 3.5; N, 24.5. $C_{10}H_8O_3N_4$ requires C, 51.7; H, 3.5; N, 24.1%).

2-Hydroxy-4-anilino-5-aminopyrimidine (XLV, p.83).

A mixture of 2-hydroxy-4-anilino-5-nitropyrimidine (5 g.) and 2% palladised strontium carbonate (5 g.) in 5% potassium hydroxide solution (50 cc.) was shaken with hydrogen, 1350 cc. being absorbed. The catalyst was filtered, washed with a little hydroxide solution, and the filtrate plus washings made just acid with acetic acid then sodium bicarbonate (1 g.) added and the mixture left overnight in a refrigerator. The brown precipitate was filtered, washed, and crystallised from much water in light brown leaflets. Concentration of the mother liquors yielded more material. M.p. 273° (dec.). Yield, 2.8 g., 64%. (Found: C, 59.5; H, 4.9; N, 27.3. $C_{10}H_{10}ON_4$ requires C, 59.4; H, 5.0; N, 27.7%).

Diazotisation of 2-hydroxy-4-anilino-5-aminopyrimidine (XLV).

To a solution of the above amine (1 g.) in $3\bar{N}$ hydrochloric acid (10 cc.) was gradually added with stirring a solution of sodium nitrite (0.35 g.) in water (5 cc.), both solutions being ice-cold. The brown precipitate was collected, dissolved in dilute ammonia solution, filtered, and reprecipitated with dilute acetic acid. Crystallisation from alcohol gave a pale brown powder, m.p. 245° (dec.).

A small amount was sublimed in vacuo and crystallised

from alcohol, m.p. 245-250° (dec.). The analysis indicated loss of nitrogen.
(Found: C, 59.9; H, 3.5; N, 18.6%).

Hydrogenation of 2-chloro-4-anilino-5-nitropyrimidine (XL).

A mixture of 2-chloro-4-anilino-5-nitropyrimidine (4 g.) and 2% palladised strontium carbonate (4 g.) in alcohol (100 cc.) was shaken with hydrogen for 7 hours, 1400 cc. being absorbed mainly in the first 2 hours. The catalyst was filtered and washed with alcohol, the filtrate and washings being distilled to dryness from a water bath under reduced pressure. A solution of the residue in 2$\bar{N}$ hydrochloric acid (300 cc.) was cooled to 0° and a solution of sodium nitrite (1.1 g.) in water (10 cc.) slowly added with stirring. The precipitate was filtered, and the filtrate made alkaline with concentrated ammonia solution giving an additional small amount of material.

(a). 3-Phenyl-v-triazolo(d) pyrimidine (XLVII, p.84).

The combined precipitates were heated in a boiling water bath under 2 mm. pressure when (XLVII) slowly sublimed and was further purified by crystallisation from water or aqueous alcohol from which it separated in long lustrous needles, m.p. 111-112°. Yield, 1 g.
(Found: C, 61.0; H, 3.6; N, 35.4. $C_{10}H_7N_5$ requires
C, 60.9; H, 3.6; N, 35.5%).

(b). 5-Chloro-3-phenyl-v-triazolo (d) pyrimidine (XLVI,p.84).

When sublimation at 100° became negligible the process was continued from an oil bath at 120-130° giving (XLVI) which also crystallised in lustrous needles from alcohol, m.p. 145-147°. Yield, 0.7 g.
(Found: C, 51.7; H, 2.6; N, 29.9, 30.5. $C_{10}H_6N_5Cl$ requires C, 51.9; H, 2.6; N, 30.2%).

Attempted cyclisation of (XLVII) and (XLVI).

(a). A solution of (XLVII) (0.1 g.) in syrupy phosphoric acid (0.5 cc.) was heated at 170-180° under 2 mm. for 1 hour. On cooling the deep red solution was diluted with water (10 cc.) and a small amount of dark flocculent precipitate removed. Neutralisation of the solution with sodium hydroxide solution yielded a small amount of precipitate which could not be purified.

(b). Addition of (XLVII) to fused anhydrous zinc chloride gave a dark melt which, on addition of excess sodium hydroxide, yielded nothing on ether extraction.

(c). Small amounts of (XLVII) (50 mg.) in evacuated sealed tubes were immersed in an oil bath at 200° and at 300°. Effervescence occurred but only (XLVII) was recovered.

(d). A flask (250 cc.) was fitted with an air condenser, flooded with nitrogen, and heated in a bunsen flame so that a few crystals of (XLVII) dropped into the flask immediately decomposed with a puff of brown smoke. The rest of the material (1 g.) was added in portions, avoiding loss of smoke, and keeping the flask just hot enough to cause decomposition at each addition. When the flask had cooled alcohol (150 cc.) was added, refluxed for 1 hour on a steam bath and filtered. The brown filtrate after two successive treatments of 1 hour each with small amounts of charcoal became pale yellow and on concentration to small bulk deposited orange-yellow leaflets over several days, which were recrystallised from alcohol, m.p. ca. 365-370°. Yield, 10 mg., 1%.

(Found: C, 68.0; H, 4.0; N, 24.5. $C_{10}H_7N_3$ requires
C, 71.0; H, 4.2; N, 24.8%).

All the above reactions were carried out with (XLVI) which however yielded no positive result and under (d) proved even more prone to give carbonaceous residues than had (XLVII).

Hydrogenation and diazotisation of unidentified substance (XLI).

A solution of the above compound (3 g.) in alcohol (50 cc.) was shaken with 2% palladised strontium carbonate (3 g.) and hydrogen for 4 hours, absorbing 850 cc. The catalyst was filtered and washed with alcohol, filtrate and

washings evaporated, and the residue extracted with $2\bar{N}$ hydrochloric acid (300 cc.). A sample of the hydrochloride was crystallised from dilute, and finally from $6\bar{N}$, hydrochloric acid, m.p. 165° (frothing).
(Found: C, 44.15; H, 5.7; N, 17.95%).

The rest of the material in very dilute hydrochloric acid (100 cc.) was cooled to 0° and a solution of sodium nitrite (0.4 g.) in water (10 cc.) dropped in with stirring and the mixture left for an hour. The precipitate was filtered and from the filtrate, which turned almost black on neutralisation with ammonia solution, there was isolated a further small quantity of material which was sublimed in vacuo and crystallised with the previous precipitate, after charcoal treatment, in colourless short needles, m.p. 106-107°. Yield, 1.6 g.
(Found: C, 59.3; H, 4.7; N, 28.1, 31.2%).

Pyrolysis experiments on this material, m.p. 106-107°, gave only charred product.

A molecular weight determination on (XLI) was carried out by hydrogenation in a semi-micro hydrogenation apparatus in which 0.5465 g. absorbed 153 cc. of hydrogen in 3 hours. Mol.wt. 240.

2-Chloro-4-(m-anisidino)-5-nitropyrimidine (XLIX, p.85).

m-Nitrophenol was methylated with methyl iodide and the product steam distilled.

A solution of m-nitroanisole (12.75 g.) in methanol (300 cc.) was shaken with 2% palladised strontium carbonate (12.75 g.) and hydrogen, 5.6 l. being absorbed in about 1 hour, the reaction evolving considerable heat. The catalyst was filtered, thoroughly washed with methanol, and the filtrate plus washings, initially colourless but gradually becoming brown, concentrated then made up to 50 cc. and used as a solution containing m-anisidine (0.205 g./cc.).

To a well stirred ice-cooled solution of 2:4-dichloro-5-nitropyrimidine (3.2 g.) in methanol (25 cc.) was added dropwise over 2 hours the above m-anisidine solution (15 cc.). The orange yellow precipitate was filtered, washed with a little methanol, dried at room temperature in air and crystallised from ligroin in short orange needles, m.p. 147-148°. Yield, 3.5 g., 76%.

(Found: C, 47.3; H, 3.5; N, 20.2; Cl, 13.1. $C_{11}H_9O_3N_4Cl$ requires C, 47.1; H, 3.2; N, 20.0; Cl, 12.6%).

2-Chloro-4-(m-anisidino)-5-aminopyrimidine (L, p.85).

Raney nickel (1 g.) in alcohol (5 cc.) was saturated with hydrogen, 2-chloro-4-(m-anisidino)-5-nitropyrimidine

(1.23 g.) was rinsed into the hydrogen flask with Raney-nickel-treated alcohol (10 cc.), reduction taking 20-30 minutes. The solution was filtered, the nickel thoroughly washed with boiling alcohol, then with ether. The filtrate and washings were evaporated to dryness and the residue extracted with boiling benzene. Thick plate-like pale brown crystals separated from the concentrated extract, m.p. 145°. Recrystallisation from 30% alcohol gave colourless plates, m.p. 146-148°. Yield, 0.84 g., 76%.
(Found: C, 52.7; H, 4.3; N, 22.4. $C_{11}H_{11}ON_4Cl$ requires C, 52.7; H, 4.4; N, 22.4%).

5-Chloro-3-(m-anisyl)-v-triazolo d) pyrimidine (LI, p.85).

The above amine (L) (1.25 g.) was dissolved in glacial acetic acid (7.5 cc.) and diluted with water (5 cc.). The clear solution was then treated with an excess of sodium nitrite in water (2 cc.) giving immediately a blue grey precipitate. After cooling it was filtered and crystallised from aqueous acetic acid in pale brown crystals. Recrystallisation from benzene/light petroleum (80-100°) and finally from acetonitrile gave colourless rectangular plates, m.p. 144-145°. Yield, 1.12 g., 86%.
(Found: C, 50.3; H, 3.25; N, 26.8; Cl, 13.45. $C_{11}H_8ON_5Cl$ requires C, 50.5; H, 3.1; N, 26.8; Cl, 13.55%).

Pyrolysis on hot glass or in paraffin oil gave mainly charred material with a little unchanged triazolopyrimidine.

SUMMARY.

2-Chloro-4-methylanilino (and anilino)-5-nitropyrimidines have been prepared, converted to the 2-hydroxy-5-amino derivatives and Pschorr type cyclisation attempted.

Triazolopyrimidines resulting from diazotisation of amines obtained by reduction of the 2:4-dianilino-, 2-anilino-, 2-anilino-4-chloro, and 2-(m-anisidino)-4-chloro derivatives of 5-nitropyrimidine have been subjected to the standard methods of carbazole and carboline synthesis.

Only in the case of 3-phenyl-v-triazolo (d) pyrimidine, by pyrolysis, has there been an indication of 1:3-diazacarbazole formation.

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