THE SYNTHESIS OF SOME ACRIDINE DERIVATIVES OF POSSIBLE PHARMACOLOGICAL VALUE.

by

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Thesis Submitted for the Degree of Ph.D.,
University of Edinburgh.

May, 1943.

"Es lässt sich daher darüber streiten, ob man auf der Suche nach neuen Heilmitteln sich mehr von Einfällen oder von dem gesammelten Erfahrungsschatz leiten lassen soll. Eines aber lässt sich nicht bestreiten: dass in jedem Fall ein sehr hohes Mass von Geduld sich hinzugesellen muss."

H. Iensch,
Angew. Chemie., 1937, 50, 891.

THE SYNTHESIS OF SOME ACRIDINE COMPOUNDS OF POSSIBLE PHARMACOLOGICAL VALUE.

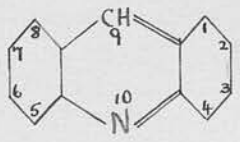
INDEX OF PREPARATIONS.

New compounds are denoted by *

Reduction by hydrogen gas and Raney Nickel by R.N.

The numbering of the acridine nucleus in this account is that recommended in "A Scheme of Chemical Nomenclature" issued by Imperial Chemical Industries Limited in May 1940.

The acridine ring is numbered as below:-



I N T R O D U C T I O N.

The German chemist Ehrlich may be regarded as the father of chemotherapy for, as early as 1904, he said, with true vision, "What we seek is 'specific chemotherapy.' That is, we are in search of a drug capable of destroying certain parasites without, at the same time, causing too much damage to the host" and his words still hold good to-day. His aim and that of all subsequent workers in this field has been expressed in other words by saying that "we seek a hidden key which can alone open a certain door."

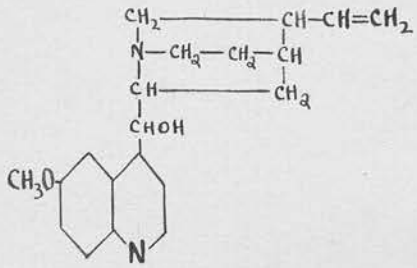
Although a considerable amount of work was accomplished in the field of chemotherapeutic agents during the intervening years modern research was given a great impetus following the publication in 1935 of the work of Domagk dealing with the clinical use of prontosil against diseases caused by haemolytic

streptococci. The investigation of this branch of chemistry is, however, still in its infancy.

At the present time, in spite of the recent most intensive research, there are no general rules to guide the research work in chemotherapy and it is recognised that much experimental work has yet to be accomplished before any attempt can be made to formulate a satisfactory theory which would give a general correlation between chemical structure and chemotherapeutic action. "Meantime, it is possible to argue as to whether, in the search for new drugs, intuition is still of more value for guidance than the collected fruits of experience. One thing, however, is not arguable and that is that in either case one must still apply a great deal of patience to the search."

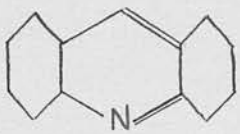
Despite the fact, therefore, that it was by accident that Ehrlich, while working on dyes suitable for microscopic staining, discovered the bactericidal activity of certain acridine derivatives yet it is almost certain that, eventually, chemical intuition would have suggested a search amongst acridine derivatives for compounds possessing bactericidal and other valuable pharmacological properties.

Quinine (I) has long been known to have a pronounced



(I)

(II)

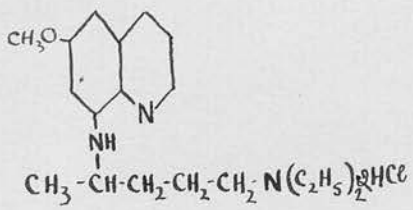


(III)

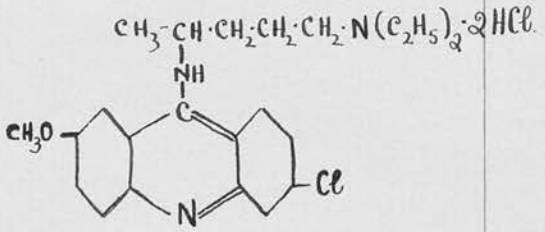
anti-malarial activity and contains a quinoline ring (II), the possession of which is common to many compounds of proved chemotherapeutic value. Acridine (III) may be regarded as a "benz-quinoline" type of compound and has itself been shown to have some protozoicidal activity even at high dilutions. The search amongst its derivatives warranted by the similarity to quinoline in structure has been fully justified by the results obtained during recent years.

It is interesting to note how discoveries of pharmacologically valuable substances in the quinoline series have been followed by discoveries in the acridine group and how sometimes the order of discovery has been reversed. Thus plasmoquin (IV), which acts on the gametocytes of the malarial parasite, was discovered in 1926 by Horlein, while atebrin (V), which destroys the schizonts, followed in 1933 (Mauss

and Mietzsch, Klin. Wchschr., XII, 1276).

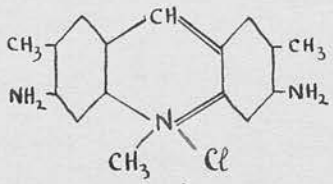


(IV)

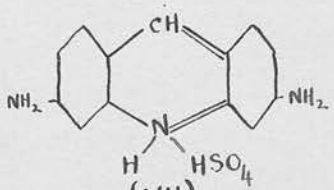


(V)

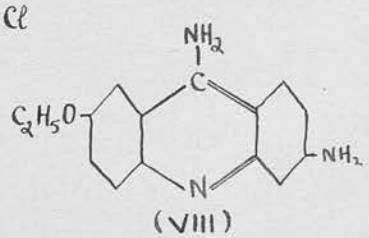
On the other hand the long established use as bactericides of aminoacridines such as acridine yellow (VI), proflavine (VII) and rivanol (VIII) suggested a search amongst derivatives of 4-amino-quinoline.



(VI)



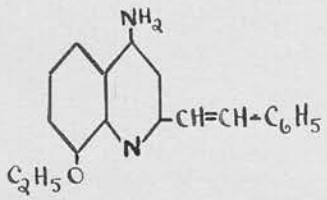
(VII)



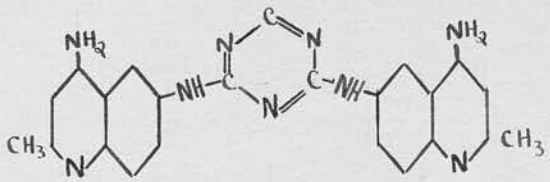
(VIII)

Here the discovery of remarkable bactericidal

properties in the compound 2-styryl-4-amino-8-ethoxy-quinoline (IX) was followed by a systematic extension of the investigation and brought to light many substances with highly developed antiseptic properties and moreover some compounds with valuable trypanocidal activity, such as Surfen C (X).



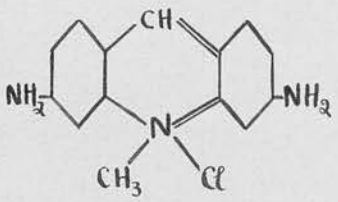
(IX)



(X)

As has been observed above, the pharmacological value of amino-acridines has been known for a long time. Ehrlich and Benda (Ber., 1912, 45, 1787) prepared 3:6-diamino-10-methylacridinium salts of which the chloride of the 2:7-dimethyl compound, acridine yellow (VI), was found to have bactericidal properties. By removal of the methyl groups in positions 2 and 7 proflavine base was obtained and the sulphate of this (VII) is strongly antiseptic.

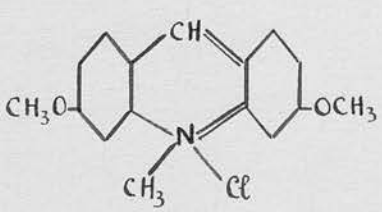
Introduction of a metho-chloride group instead of the sulphuric acid group gave acriflavine (XI)



(XI)

which was employed successfully as an antiseptic in the war of 1914-18.

Acriflavine possesses toxic properties which are believed to be due to the amino groups in positions 3 and 6, since 3:6-dimethoxy-10-methylacridinium chloride (XII) is equal to

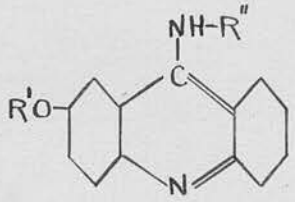


(XII)

acriflavine in bactericidal effect and is only one half as toxic. It has been claimed that an amino group in the 9 position of sinflavine (XII) lowers the

toxicity even further (c.f. "Chemistry of the Synthetic Drugs", May & Dyson, 4th Edition, page 248).

Morgenroth, in 1921, worked on compounds of the general type (XIII)

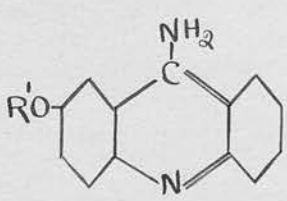


(XIII)

where R' = Alkyl group

and R" = $-CH_2-CH_2-OH$

From his results he concluded that the group R" caused a diminution of activity and proved further that 9-amino-2-alkoxy-acridines (XIV)



(XIV)

had enhanced activity. Maximum efficiency was obtained with an amino group in position 6 and 6:9-diamino-2-ethoxy-acridine has attained a wide clinical use under the name of rivanol (VIII).

It is apparent, therefore, that the introduction of amino groups in the acridine nucleus gives rise to compounds of bactericidal and trypanocidal activity. The importance of this type of compound has been emphasised by Albert, Rubbo and Goldacre (Nature, 1941, 147, 332-333) in the following words:- "The amino-acridines are unique among antiseptics in combining a high bacteriostatic activity in the presence of tissue fluids with a relative inocuousness to leucocytes. Hence, any information that relates their physical and chemical properties with their bacterial action is of general interest." Albert and Ritchie (J.S.C.I., 1941, 60, 120) further state that "the monoaminoacridines have received scant attention because of their comparative inaccessibility." The influence of the position of the amino group on the antiseptic action is well shown in work published by Albert, Rubbo and Goldacre (loc. cit.) from which Table I is abstracted. They include proflavine (3:6-diamino-acridine sulphate) to show the significance of their results.

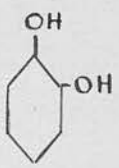
Table I.

Substance	Bacteriostatic Index
	(Strong antiseptics)
9-aminoacridine	43
3:6-diaminoacridine (proflavine)	41
3-aminoacridine	41
1-aminoacridine	17
2-aminoacridine	17
acridine	12
4-aminoacridine	8
	(Weak antiseptics)

Note:- These compounds have been renumbered from the original table in order to conform to the scheme of nomenclature adopted in this report.

It is apparent from this table that the introduction of an amino group in positions 9 or 3 gives a high, in positions 1 or 2 gives an intermediate, and in position 4 gives a low bacteriostatic index.

It is well known that the introduction of alkoxy groups or a methylenedioxy group into pharmacologically active compounds is often attended with considerable reduction in toxicity and sometimes with increased activity. Thus catechol (XV), guiacol (XVI) and veratrole (XVII) show a progressive reduction in toxicity.



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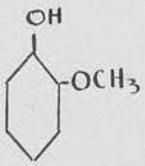
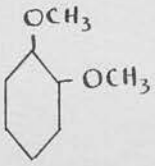


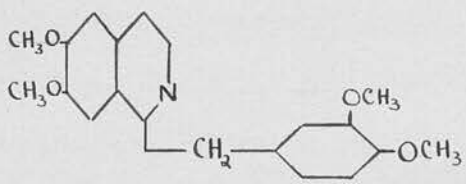
(XVI)



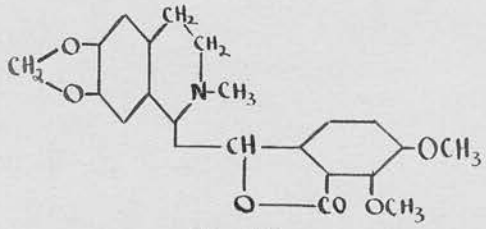
(XVII)

Codeine, the methyl ether of morphine, is less toxic than the latter.

Prescott (Chem. and Druggist, 1941, 213) suggests that in the sympatheticomimetic amines the presence of a methylenedioxy group in the molecule results in an increase in the central stimulant action. Moreover, many naturally occurring substances used as drugs contain alkoxy groups or methylenedioxy groups. Thus papaverine (XVIII) contains four methoxy groups and hydrastine (XIX) contains two methoxy groups and one methylenedioxy group.



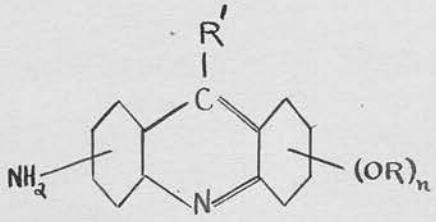
(XVIII)



(XIX)

Amongst acridine derivatives it has already been observed that the replacement by methoxy groups of the two amino groups in positions 3 and 6 in acriflavine gives rise to sinflavine (XII) which is equal to the diamino compound in bactericidal activity but is only half as toxic.

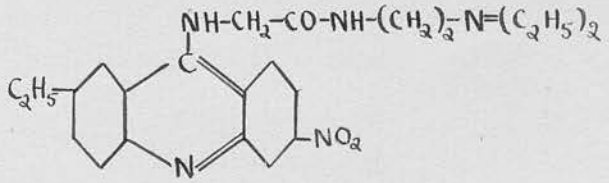
The attempted syntheses, therefore, of acridine derivatives of the type (XX) in which one nucleus carries one



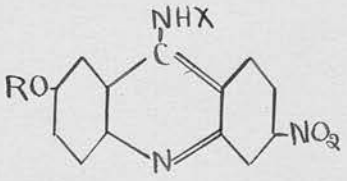
(XX)

or more alkoxy groups $(OR)_n$, or a methylenedioxy group while the other nucleus carries an amino group, preferably in position 2 or 3, and position 9 (R') is substituted by hydrogen, by an amino or alkylamino group or a basic aromatic heterocyclic ring appeared justifiable, and this thesis deals with the chemical work involved in the investigation of possible routes to such compounds.

Schnitzer and Silberstein (Zeit. fur Hyg., 1929, 109, 519) state that 3-nitro-7-ethyl-9-[glycylamino-(diethyl substituted) ethylamino] acridine (XXI) is a very effective trypanocide and also show that 3-nitro-4-alkoxy-9-basically substituted acridines of general formula (XXII)



(XXI)



(XXII)

are very strong bactericides. Compounds of somewhat similar structure were prepared during the course of this investigation.

In the course of these synthetical studies it became apparent that methoxy groups and methylenedioxy

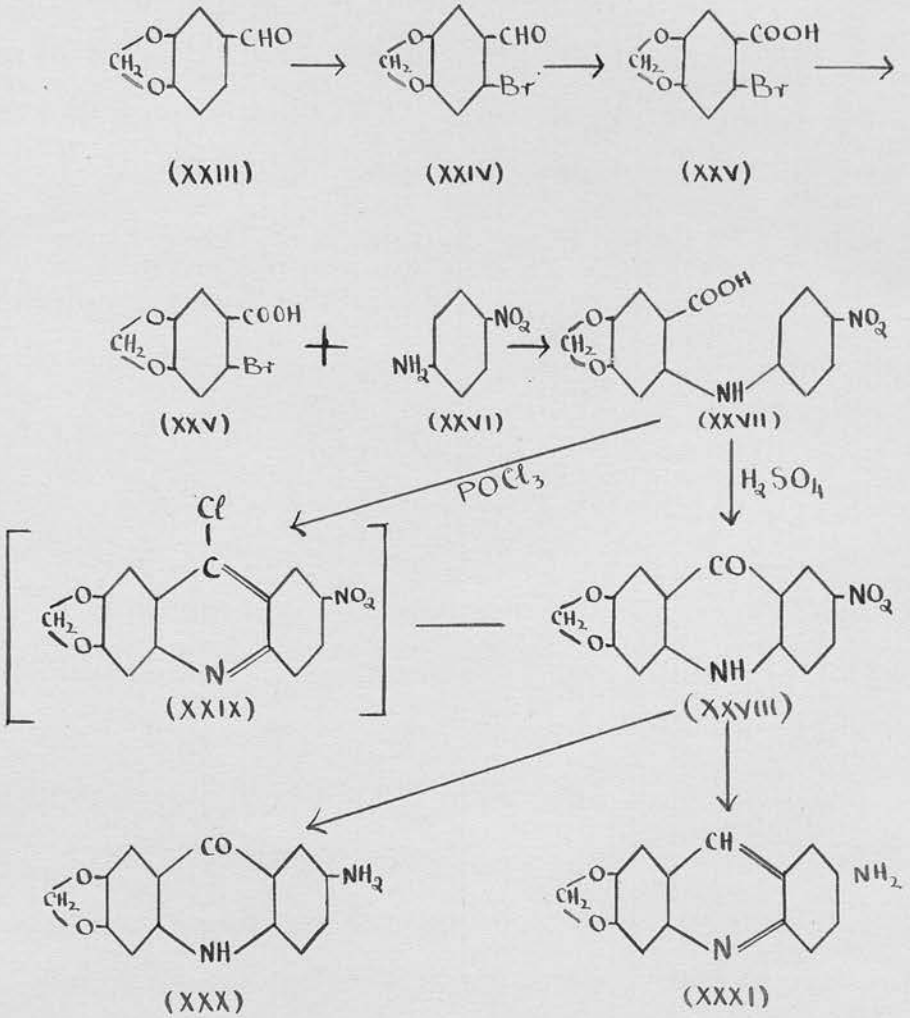
groups substituted in the 4:5 positions to a 2-carboxyl group in a diphenylamine-2-carboxylic acid in many cases led to inefficient ring closure with sulphuric acid or phosphorus oxychloride. On the other hand a chlorine substituted in the 5-position appears to lead to successful ring closure.

A possible theoretical explanation is advanced for this effect and a suggestion made that further information on the influence of substituents on such ring closures is highly desirable.

Acridines containing methylenedioxy group in 6:7 position

Synthesis I.

Outline:-



The most suitable starting material in the synthesis of this type of acridine was piperonal (XXIII). The method was to prepare the 6-bromo derivative of piperonal (XXIV) and by oxidising this to obtain 6-bromopiperonylic acid (XXV). The potassium salt of this acid could then be condensed with an aminobenzene derivative, e.g. p-nitraniline (XXVI) to yield a 2-carboxy-4:5-methylenedioxy-4'-nitrodiphenylamine derivative (XXVII). From this, by treatment with concentrated sulphuric acid or phosphorus oxychloride, the corresponding acridone (XXVIII) or 9-chloracridine (XXIX) might be obtained. The 9-chloracridine on hydrolysis with 10% hydrochloric acid would yield the required acridone. From the acridone, by reduction, it might be possible to obtain the desired 2-aminoacridone (XXX) or the 2-aminoacridine (XXXI).

Oelker (Ber., 1891, 24, 2593) gave a method for the preparation of 6-bromopiperonal which appeared to be an improvement on the method described by Fittig and Mielk (Ann., 1869, 152, 48). Oelker's method was the direct bromination of piperonal in carbon disulphide solution. He did not state the yields obtained but when an attempt was made to prepare 6-bromopiperonal by this method the reaction was very unsatisfactory, the yields being low and so variable as to preclude the use of the method on a large scale.

It is of interest to note that Naik & Wheeler (J.C.S., 1938, 1781) cite Oelker's method when referring to their preparation of 6-bromopiperonal but state that they carried out the bromination in acetic acid rather than in carbon disulphide.

A search of the literature revealed a preparation of 6-bromopiperonal by Robinson (J.C.S., 1917, 946) wherein the bromination is carried out in acetic acid solution, the yield claimed being in the region of 63% theory (4:5-dibromocatechol is a side product of the reaction). This method was the one adopted for the preparation of 6-bromopiperonal. Oertling and Pictet (Ber., 1910, 43, 1339) proved that the bromine entered in the 6 position.

The next step in the synthesis was the oxidation of the 6-bromopiperonal to 6-bromopiperonylic acid (XXV). Some difficulty was experienced in carrying out this oxidation using the usual methods owing, apparently, to the relative insolubility of the bromopiperonal in water. Finally, the method was adopted of oxidation by potassium permanganate in aqueous alkaline solution with the aldehyde in acetone solution (Lassar Cohn, "Arbeitsmethoden", page 711; Ber., 1910, 43, 2140). This method gave fair yields of 6-bromopiperonylic acid. The potassium salt of the acid was prepared by neutralising the acid with the calculated weight of potassium carbonate in aqueous solution and obtaining the salt of the acid by

evaporation to dryness.

The potassium bromopiperonylate was condensed with p-nitraniline in amyl alcohol solution with a trace of copper bronze present. The compound so obtained was purified by crystallisation from chlorobenzene and analysed. The analysis agreed with that required for the expected 4'-nitro-4:5-methylenedioxydiphenylamine-2-carboxylic acid (XXVII) and since no alternative reaction appeared possible the result was accepted as indicating the required compound.

An attempt was made to prepare the acridone (XXVIII) from the above methylenedioxy-nitrodiphenylamine-carboxylic acid using sulphuric acid as the agent for ring closure but this was not successful. The acridone was prepared using the method outlined by Albert and Linnell (J.C.S., 1936, 1616) wherein the 9-chloracridine is prepared and hydrolysed to the acridone by treatment with 10% hydrochloric acid. The crude 2-nitro-6:7-methylenedioxy-acridone (XXVIII) so obtained was found to be insoluble in most common organic solvents and could not be prepared in a state sufficiently pure for analysis. It was decided to attempt the reduction of this crude methylenedioxy-nitro-acridone in the hope that the corresponding aminoacridone (XXX) or the aminoacridine (XXXI) would be more easily purified and could be analysed.

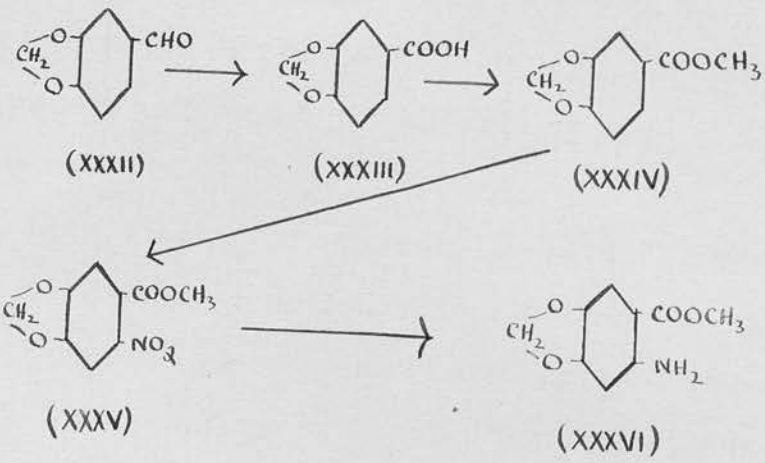
The reduction was attempted using anhydrous

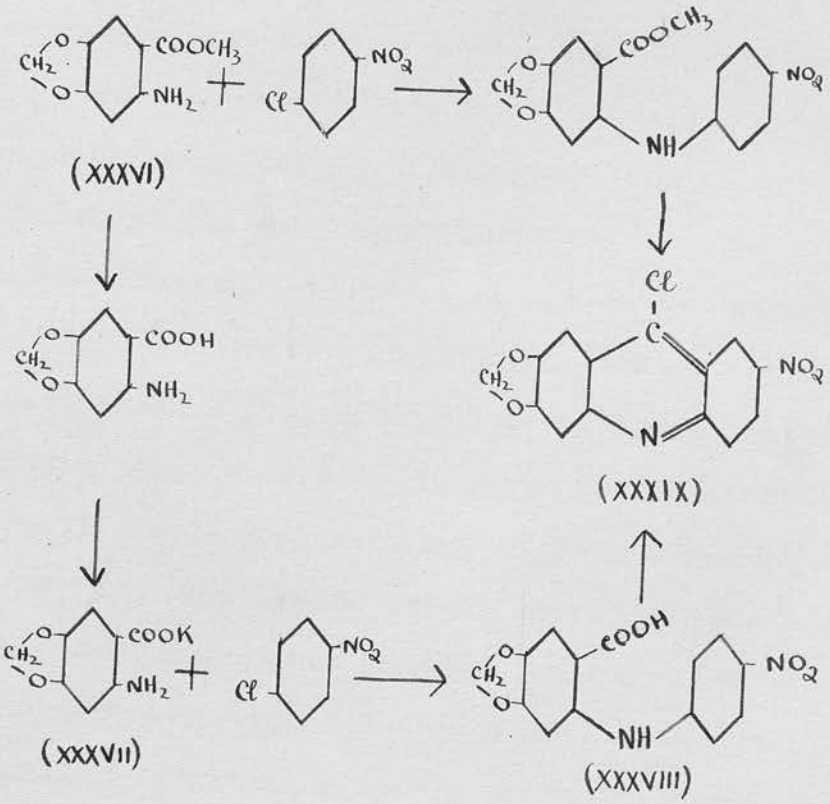
stannous chloride reagent (Albert and Linnell, loc. cit.) but no satisfactory result was achieved. Reduction by iron and hydrochloric acid (West's method) was tried without success. Finally, an attempt was made to reduce the nitro-acridone (XXVIII) using sodium amalgam in an atmosphere of carbon dioxide, again without success.

Synthesis II.

In view of the difficulties encountered in Synthesis I it was decided to attempt the preparation of 2-nitro-6:7-methylenedioxy-9-chloracridine (XXXIX). If this chloracridine could be obtained it would be possible to introduce a basic group in position 9 (e.g. piperidino), the presence of which might render the 2-nitro group more readily susceptible to reduction. When the synthesis of this chloracridine was undertaken a modified scheme was followed in an attempt to increase the final yield of the diphenylamine carboxylic acid. The starting material was piperonal and the scheme, in outline, was as follows:-

Outline:-


CHO
COOH
$COOCH_3$
CH_2
O
(XXXII)
(XXXIII)
(XXXIV)
NO_2
NH_2
(XXXV)
(XXXVI)


$COOCH_3$
NH_2
Cl
NO_2
NH
(XXXVI)
COOH
C
N
(XXXIX)
COOK
(XXXVII)
(XXXVIII)

The first step in this synthesis, oxidation of piperonal (XXXII) to piperonylic acid (XXXIII), was tried, first by the method outlined by Van Linge (Rec., Trav., Chim., 1897, 16, 44-56), which method was found to be unsatisfactory and secondly by the method described in Organic Synthesis, 1930, 10, 82-83. This second method was found to be very good and was the one used.

The methyl ester of piperonylic acid (XXXIV) was prepared by refluxing piperonylic acid with methyl alcohol in the presence of sulphuric acid. Then, following the procedure of Oertley and Pictet (Ber. 1910, 43, 1336-1339) the piperonylic acid methyl ester was nitrated to yield the nitro-piperonylic acid methyl ester (XXXV).

Attempts were made to reduce the nitro-piperonylic acid methyl ester using Albert and Linnell's anhydrous stannous chloride reagent (loc. cit.) and also by West's method using iron and hydrochloric acid. The method which was adopted finally was reduction by hydrogen gas in the presence of Raney nickel catalyst at room temperature and a pressure equivalent approximately to atmosphere plus three feet of water (c.f. Albert and Ritchie, J. Proc. Roy. Soc. N.S. Wales, 1940, 74, 74-81). This method was satisfactory, simple and clean.

An attempt was then made to condense the methyl ester of amino-piperonylic acid (XXXVI) with p-chloro-nitrobenzene but this, however, proved unsuccessful.

It is known that diphenylamine-2-carboxylic acid does not form esters and it appeared, therefore, that the methyl group may have been causing steric hindrance. Accordingly the methyl group was hydrolysed off and the potassium salt of the amino-piperonylic acid was prepared (XXXVII). Again the condensation with p-chloro-nitrobenzene was attempted, this time using the potassium salt of the acid (XXXVII). The reaction appeared to be proceeding very slowly and refluxing was continued for eighteen hours. When the crude liquor was steam distilled over 50% of the p-chloro-nitrobenzene was recovered and the required diphenyl-amine acid could not be obtained from the final liquor. The potassium salt of anthranilic acid condenses readily with chloro-nitrobenzenes and it would appear, therefore, as if the methylenedioxy group were exerting some restraining influence on the condensation.

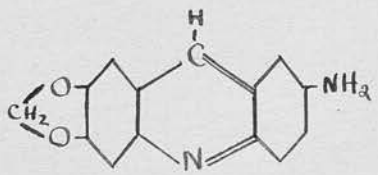
With the lack of success in this modified scheme it was necessary to revert to the initial method of synthesising the compound 4'-nitro-4:5-methylenedioxy diphenylamine-2-carboxylic acid (XXXVIII).

This was done and when a quantity had been obtained an attempt was made to prepare the 2-nitro-6:7-methylenedioxy-9-chloracridine (XXXIX) by the method given by Albert and Linnell (loc. cit.) but the resulting compound possessed the characteristics of the acridone. The chloracridine, if formed, probably

undergoes immediate hydrolysis in the phosphorus oxychloride reaction mixture to give the acridone. This difficulty appears to occur in many ring closures with phosphorus oxychloride and special precautions must be taken to avoid such hydrolysis.

Synthesis III & IV.

With the failure of the foregoing methods for the synthesis of the required 2-amino-6:7-methylenedioxyacridine (XL) two fresh methods of attack were tried.

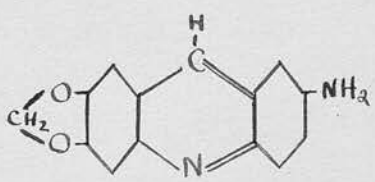


(XL)

undergoes immediate hydrolysis in the phosphorus oxychloride reaction mixture to give the acridone. This difficulty appears to occur in many ring closures with phosphorus oxychloride and special precautions must be taken to avoid such hydrolysis.

Synthesis III & IV.

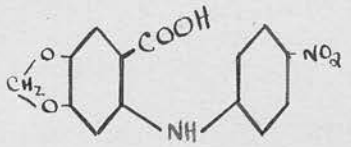
With the failure of the foregoing methods for the synthesis of the required 2-amino-6:7-methylenedioxyacridine (XL) two fresh methods of attack were tried.



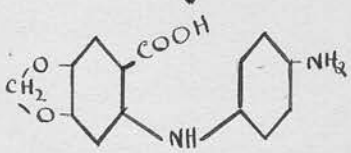
(XL)

Outline:-

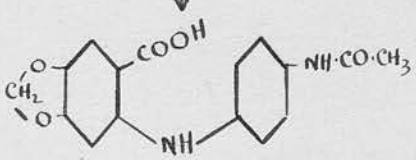
Synthesis III.



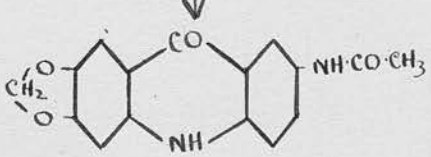
(XLI)



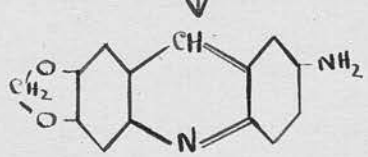
(XLII)



(XLIII)

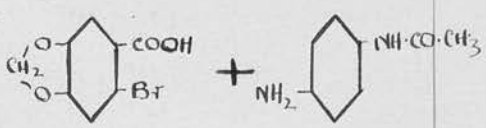


(XLIV)

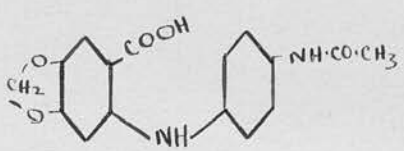


(XLV)

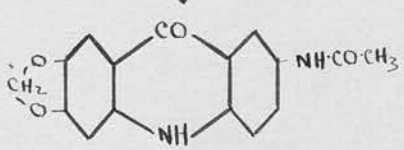
Synthesis IV.



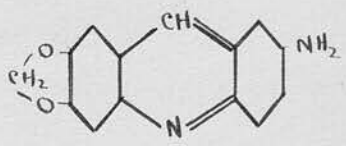
(XLVI)



(XLVII)

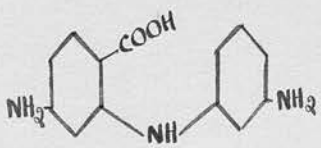


(XLVIII)



(XLIX)

Several methods (c.f. page 18) of reducing 4'-nitro-4:5-methylenedioxy-diphenylamine-2-carboxylic acid (XLI) were tried in the hope that the corresponding amino acid (XLII) or its acetyl derivative (XLIII) might be more easily converted to the acridone (XLIV) and hence to the acridine (XLV) but no success was encountered along these lines. This may have been due to the instability of the amino-acid. The methylenedioxy group may be responsible for this but it is possible that acids of this type (XLII) are easily decomposed since Albert and Ritchie (J. Proc. Roy. Soc. N.S. Wales, 1940, 74, 74) state that acids of the type (L) decarboxylate easily and



(L)

they cite work by Seidel and Bittner (Monat., 1902, 23, 430-444), Ullmann (Ber., 1903, 36, 1803) and Blanksma (Rec. Trav. chim., 1904, 23, 210 and 1903, 24, 320) in support of this observation.

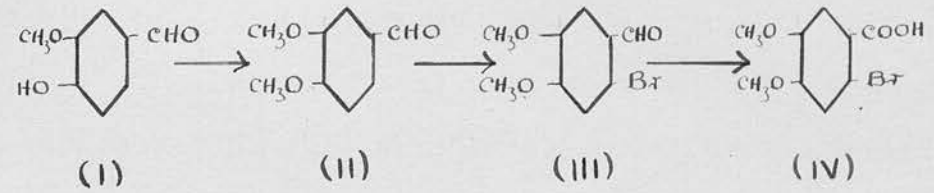
There was some evidence that synthesis IV would prove unsatisfactory because of hydrolysis of the protective acetyl group in (XLVII) with subsequent

decarboxylation of the resulting amino-acid.

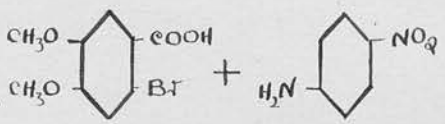
Summarising, it was noted that it was possible to obtain 4'-nitro-4:5-methylenedioxydiphenylamine-2-carboxylic acid although the yields obtained were not satisfactory. But from this it was found impossible to prepare the corresponding 2-aminoacridine or the 2-nitroacridine in any quantity. Attempts also failed to prepare the corresponding 9-substituted chloracridine (XXXIX). It was decided, therefore, to direct attention to the synthesis of similar compounds with dimethoxy substitution in positions 6:7 of the acridine nucleus instead of the methylenedioxy group. If such syntheses proved successful it would indicate to some extent the effect of the methylenedioxy group in the above attempted syntheses.

6:7-Dimethoxy substituted Acridines

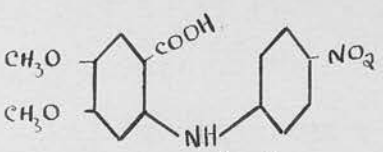
Synthesis V.



(I) (II) (III) (IV)

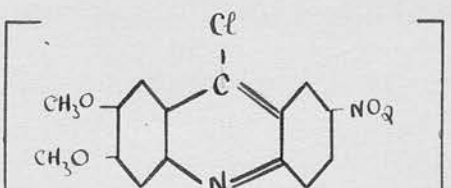


(IV)

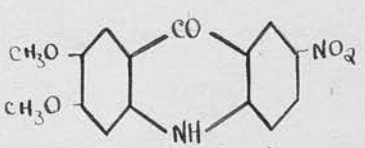


(V)

$POCl_3$

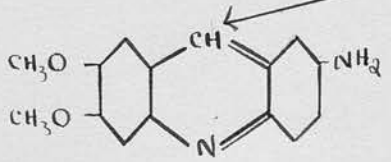


10% HCl

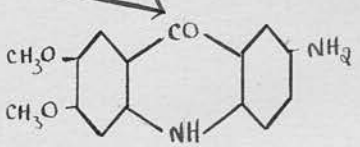


(VI)

Al. Hg; Fe + HCl;
$SnCl_2$ + HAc;
or H_2 + Raney Ni



(VII)



(VIII)

The starting material in the synthesis of 6:7-dimethoxy acridines was vanillin, 4-hydroxy-5-methoxy-benzaldehyde (I). This was methylated (Barger and Silberschmidt, J.C.S., 1928, 2924) to give methyl vanillin (3:4-dimethoxy-benzaldehyde or veratricaldehyde). The reaction went very well and the yields of veratricaldehyde (II) were excellent. 6-bromveratricaldehyde (III) was obtained by direct bromination using the method described for 6-bromopiperonal by Robinson (loc. cit.).

No satisfactory method was found in the literature for the oxidation of 6-bromveratricaldehyde to 6-bromveratric acid (IV) but after carrying out experiments conditions were found whereby this oxidation could be accomplished by alkaline potassium permanganate solution, with an excellent yield of the 6-bromveratric acid. Potassium bromveratrate was obtained from the acid in the usual manner by treatment with potassium carbonate.

The 6-bromo-potassium veratrate was condensed with p-nitraniline in the usual way by refluxing equimolecular quantities in amyl alcohol solution, a trace of copper bronze being present. 4:5-dimethoxy-4'-nitrodiphenyl-amine-2-carboxylic acid (V) was obtained in a state sufficiently pure for the ring closure with phosphorus oxychloride to yield the corresponding acridone (VI).

The 2-nitro-6:7-dimethoxy-acridone was obtained in a similar manner to the 2-nitro-6:7-methylenedioxy-acridone (see Albert and Linnell loc. cit.) after sulphuric acid had been found unsatisfactory for the ring closure. This acridone could not be obtained in a state pure enough to give a satisfactory analysis so it was decided to attempt to reduce the nitroacridone to the amino-acridine (VII) or the amino-acridone (VIII) which would probably be more soluble in organic solvents than the nitro-acridone and so more easily purified.

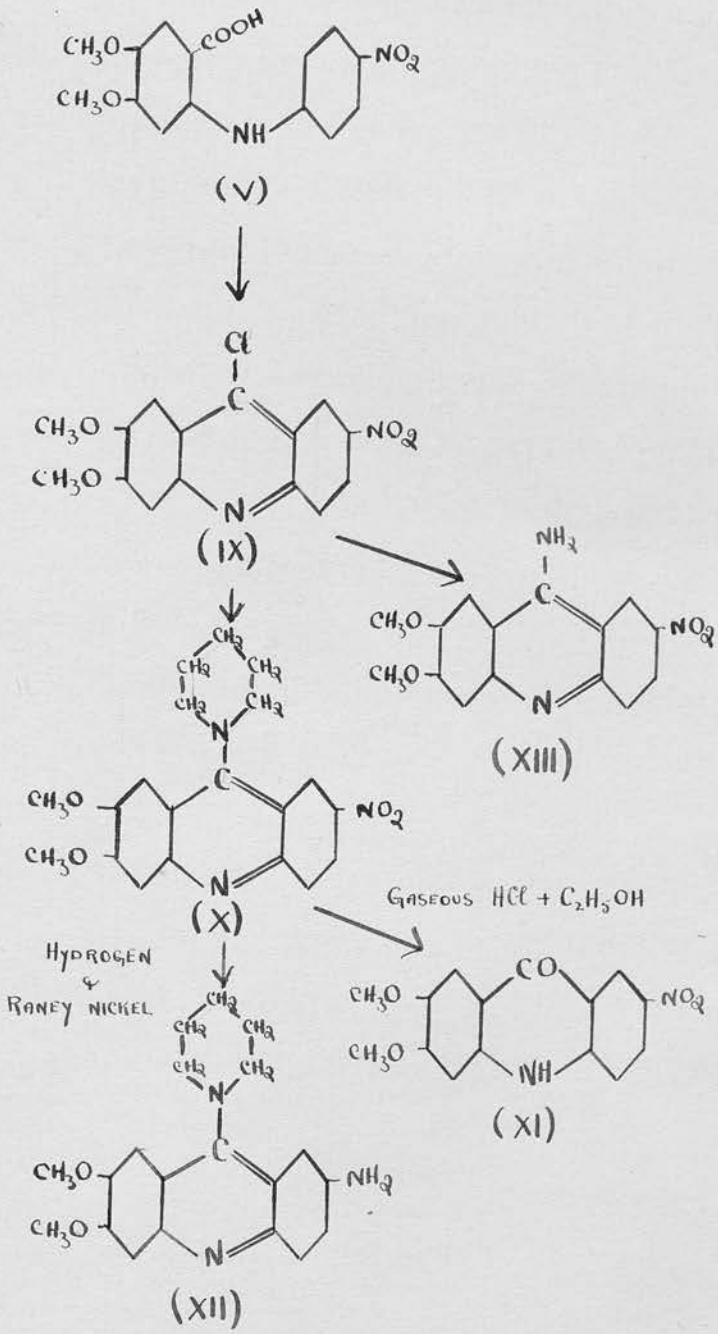
The usual methods of reduction were tried but did not prove satisfactory. Hydrogen and Raney nickel catalyst was tried but the results were inconclusive. In the final solution there was evidence of the characteristic fluorescence of acridine compounds but the amino acridine was not isolated.

Albert and Ritchie (J.S.C.I., 1941, 60, 120) give a method for the preparation of aminoacridines from the corresponding nitroacridones by reduction using aluminium amalgam. This method was tried for the preparation of 2-amino-6:7-dimethoxy acridine from the corresponding 2-nitro-acridone but it was not found successful. In view of the excellent results obtained by Albert and Ritchie (loc. cit.) it was thought that the methoxy groups might be exerting some influence which hindered reduction of the nitro group in the

2-position. This was borne out in some measure by the failure of sodium amalgam reduction and Raney nickel reduction with gaseous hydrogen.

Synthesis VI.

Outline:-



It was thought that a basic group such as "piperidino -" in position 9 might assist the reduction of the nitro group in nitroacridones. To introduce this basic group it was necessary to prepare the 2-nitro-6:7-dimethoxy-9-chloracridine. The required chloracridine (IX) was obtained by refluxing the 4:5-dimethoxy-4'-nitrodiphenylamine-2-carboxylic acid (V) with phosphorus oxychloride (Albert and Linnell, loc. cit.) special precautions being taken to avoid hydrolysis of the 9-chloroacridine. The crude 2-nitro-6:7-dimethoxy-9-chloracridine (IX) was extracted with chloroform in a Soxhlet extractor, the chloracridine crystallised from the chloroform in yellow needles. These crystals were filtered off and recrystallised from chlorobenzene. This pure chloracridine had a melting point of 275°-276° C.

The yields were small but sufficient chloracridine was obtained for the next step in the synthesis.

The low yield may be explained by the fact that treatment with phosphorus oxychloride appeared to yield a variety of products and also that the 9-chloracridine hydrolyses readily to the acridone (contrast pages 45-53).

The 2-nitro-6:7-dimethoxy-9-chloracridine (IX) was condensed with piperidine simply by refluxing the chloracridine with excess of piperidine and filtering off the crystals which separated on cooling the liquor. These crystals were washed with water and dried. Analysis of the crystals thus obtained agreed with that required for 2-nitro-6:7-dimethoxy-9-piperidino acridine (X) and from it were prepared a crystalline tartrate and diethyl malonate. An attempt to isolate a hydrochloride by treating the nitro-piperidino-acridine in suspension in alcohol with gaseous hydrochloric acid resulted in elimination of the piperidino group and formation of the nitro-acridone (XI).

An attempt was next made to reduce the 2-nitro-6:7-dimethoxy-9-piperidino acridine (X) using hydrogen and Raney nickel catalyst. The reduction appeared to proceed smoothly but some difficulty was experienced in attempting to isolate the 2-amino-6:7-dimethoxy-9-piperidino acridine (XII) from the resulting alcoholic solution. The compound appeared to undergo decomposition when the alcoholic solution was concentrated. A quantity of the supposed compound (XII) was obtained and recrystallised three times from cyclohexane. It was then analysed but the values obtained for % Carbon and % Hydrogen were very erratic. The theoretical

values for $C_{20}H_{23}O_2N_3$ are

% Carbon = 71.22

% Hydrogen = 6.82

The mean values obtained over five analyses were

% Carbon = 69.92

% Hydrogen = 7.15

This indicated that the substance isolated consisted largely of the required amino-acridine (XII).

An attempt was made to isolate the hydrochloride of 2-amino-6:7-dimethoxy-9-piperidino-acridine without immediate separation of the base. This time the corresponding 2-nitro acridine (X) was reduced by hydrogen and Raney nickel catalyst in a minimum volume of alcohol. After the reduction appeared to be complete the filtered alcoholic solution was made slightly acid by addition of alcohol saturated with hydrochloric acid gas. The solution was set aside to crystallise. The crystals so obtained were filtered off, washed with alcohol and dried. These crystals were analysed:-

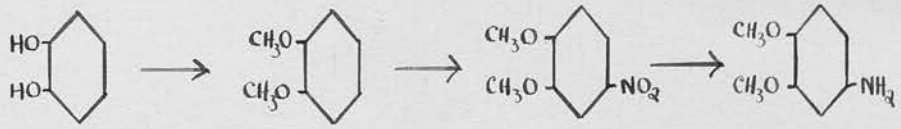
Found	Theory, for trihydrochloride
% Carbon = 53.15	% Carbon = 53.75
% Hydrogen = 6.18	% Hydrogen = 5.82
% Nitrogen = 9.31	% Nitrogen = 9.40

An attempt was made to prepare the 2-nitro-6:7-

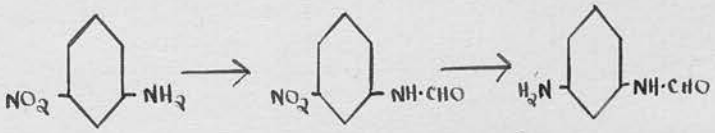
dimethoxy:9-aminoacridine (XIII) from the corresponding 9-chloracridine (IX) by heating with ammonia and methyl alcohol in a sealed tube (c.f. Albert, Dyer and Linnell, Quart. Jour. Pharm., 1937, 10, 649-658) but this did not meet with any success.

Synthesis VII.

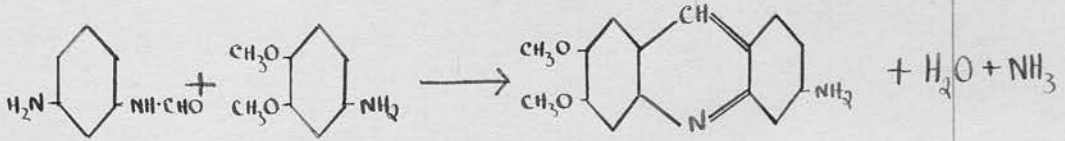
Outline:-



(XIV) (XV) (XVI) (XVII)

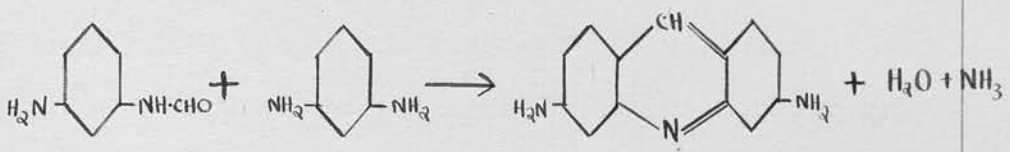


(XVIII) (XIX) (XX)



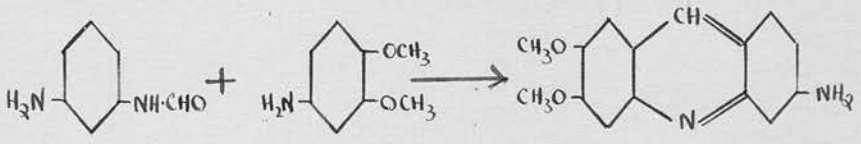
(XX) (XVII) (XXI)

Albert (J.C.S. 1941, 121) described a modification of D.R.P. 347, 819 (1921) wherein is outlined a method of synthesis of acridine compounds. The modification described by Albert consisted, essentially, in condensing m-aminoformanilide (XX) with m-phenylenediamine (XXII). The condensation was carried out in glycerol in the presence of zinc chloride and resulted in the production of proflavine base (XXIII).



(XX) (XXII) (XXIII)

It appeared possible that this scheme could be modified to bring about a condensation between m-aminoformanilide and a monoamine such as 4-amino-veratrole (XVII) whereby 3-amino-6:7-dimethoxy acridine (XXI) might be formed:-



(XX) (XVII) (XXI)

If this method proved successful it was to be applied to the corresponding synthesis of 3-amino-6:7-methylenedioxy acridine.

The starting materials in synthesis VII were catechol (o-dihydroxy benzene) (XIV) and m-nitraniline (XVIII).

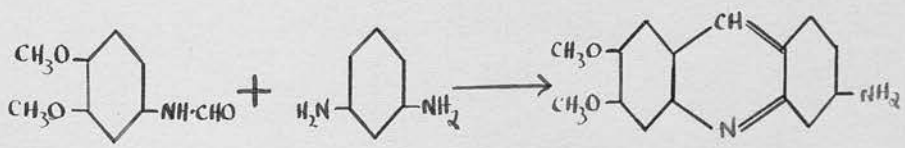
Catechol was methylated by the method given by Perkin and Weizmann (J.C.S. 1906, 1649) but this method proved unsatisfactory and the yields claimed could not be achieved. An abstract of a paper by Tanaka, Ishimasa and Koyama (J. Pharm. Soc. Japan, 1925, 525, 986-991) in Chem. Abstracts, 1926, 20, 2670 indicated that the methylation had to be performed under strict conditions and a reference was made to the method used by Ullmann (Ann. 1903, 327, 115). This method was tried and found to be satisfactory.

The veratrole (XV) thus prepared was nitrated (XVI) and reduced to give 4-amino-veratrole (XVII) as outlined by Clark (J.A.C.S. 1931, 53, 3434). The reduction of the 4-nitro-veratrole (XVI) was tried, using hydrogen and Raney nickel catalyst but this method offered no marked advantage over Clark's method using tin and hydrochloric acid.

m-Nitroformanilide (XIX) was prepared from m-nitraniline (XVIII) after the general method described by Hirst and Cohen (J.C.S. 1895, 829). This method was slightly modified to suit conditions. The m-nitroformanilide (XIX) was reduced to m-aminoformanilide (XX) by treatment with hydrogen in the presence of Raney nickel catalyst (Albert, J.C.S., 1941, 123).

The condensation of the 4-amino-veratrole with the m-aminoformanilide was then attempted under the conditions outlined by Albert (loc. cit.). Despite repeated attempts the 3-amino-6:7-dimethoxy-acridine could not be isolated. There was evidence in the mix of the characteristic acridine fluorescence but this may have been due to some slight condensation of two molecules of m-aminoformanilide to give a molecule of proflavine. If so, it was not in sufficient quantity to have been isolated readily.

An attempt was made to prepare the formyl derivative of 4-amino-veratrole (XXII) with the intention of condensing it with m-phenylenediamine (XXIII),

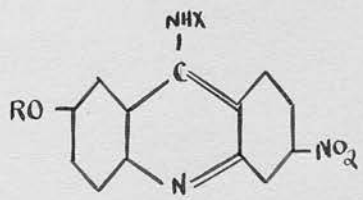


(XXII) (XXIII)

but the attempted preparation of (XXII) resulted in a viscous liquid which could not be crystallised. Later, a chance reference indicated that Fetscher and Bogert (J. Org. Chem., 1939, 4, 71-87) had found it impossible to prepare the formyl derivative of 4-amino-veratrole. This method of approach, therefore, was dropped. (Albert (private communication) has confirmed that this type of condensation fails with mono-amines).

Synthesis VIII.

Attention was directed to the work of Schnitzer and Silberstein (Z. fur Hyg., 1929, 109, 519). These workers stated that compounds of the general type (XXIV) are very strong bactericides.

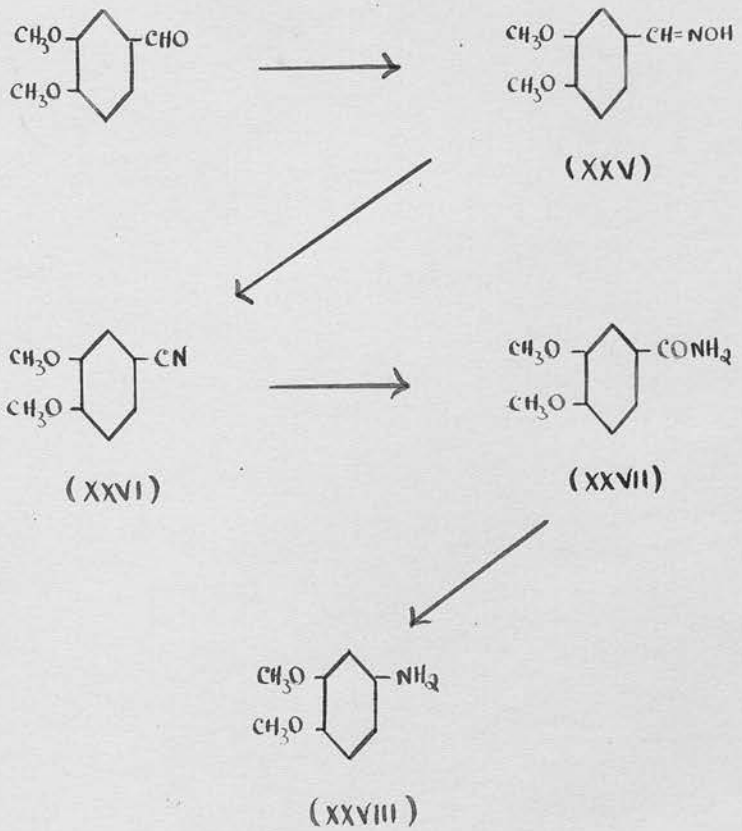


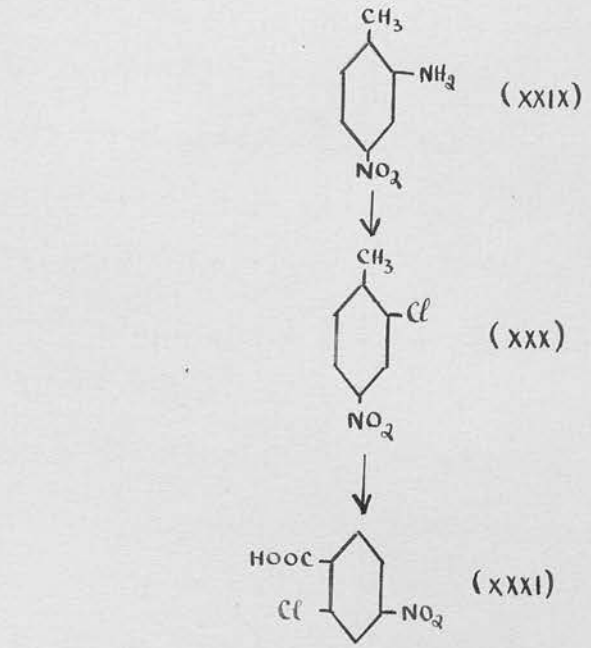
(XXIV)

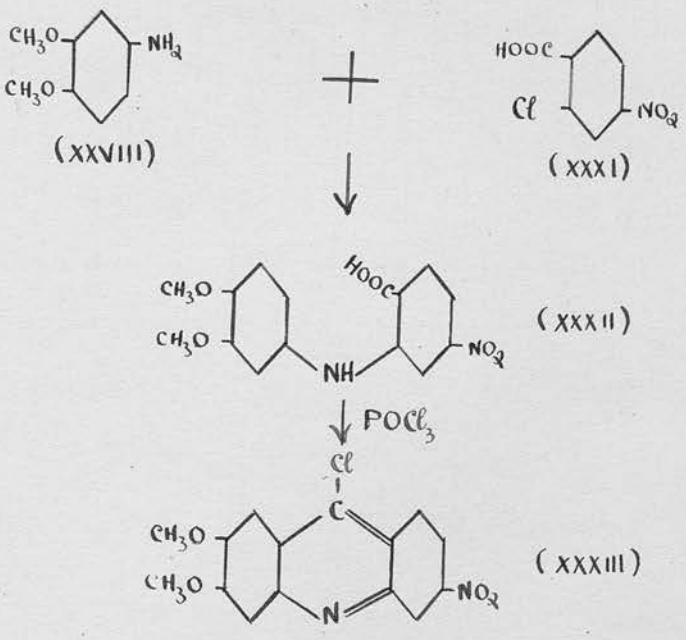
It was suggested that it might be worth while to synthesise 3-nitro-6:7-dimethoxy-9-chloracridine which would be the parent compound for similar dimethoxy types.

The synthesis of 3-nitro-6:7-dimethoxy-9-chloracridine was undertaken but by a different method from those previously used in this work. From veratric aldehyde, obtained by methylating vanillin, 4-aminoveratrole was prepared as described in Organic Synthesis (1935, 15, 85; 1936, 16, 4).

Outline:-




CH3
NH2
NO2
(XXIX)
CH3
Cl
NO2
(XXX)
HOOC
Cl
NO2
(XXXI)


CH3O
NH2
CH3O
(XXVIII)
HOOC
Cl
NO2
(XXXI)
CH3O
CH3O
HOOC
NH
NO2
(XXXII)
POCl3
Cl
C
CH3O
CH3O
N
NO2
(XXXIII)

The oxime (XXV) of the aldehyde was converted to the nitrile (XXVI) and this was converted to the acid amide (XXVII) which by Hofmann's reaction gave the required amine (XXVIII).

2-chloro-4-nitrobenzoic acid (XXXI) was prepared as described by Albert and Linnell (J.S.C.I., 1936, 54T). p-Nitro-o-toluidine (XXIX) was converted by Sandmeyer's reaction to the corresponding nitro-chloro-toluene (XXX) which was then oxidised under carefully regulated conditions to the required acid (XXXI). The potassium salt of this acid was prepared in the usual manner and condensed with 4-aminoveratrole in amyl alcohol solution containing a trace of copper bronze. The 5-nitro-4':5'-dimethoxydiphenylamine-2-carboxylic acid (XXXIII) was precipitated from the alkaline, steam-distilled filtrate by the addition of dilute hydrochloric acid. Further purification was effected by reprecipitating the acid from alkaline solution. The acid was washed with water, dried and analysed.

Analysis:-

Found	Theory for $C_{15}H_{14}O_6N_2$
% C = 55.89	% C = 56.60
% H = 4.23	% H = 4.40

Attempts were made to purify the compound further but they did not meet with success. Despite this it was decided to proceed with the preparation of the

3-nitro-6:7-dimethoxy-9-chloracridine (XXXIII) from the above crude acid. The method adopted was that described by Albert and Linnell (J.C.S., 1936, 1616). Purification of the final product was carried out by extraction with chloroform in a Soxhlet apparatus. Crystals were obtained from the chloroform extract. These crystals were washed with chloroform, dried in air and analysed:-

M.p. of first crop 266°-268° C Found C = 56.40
" H = 3.04
M.p. of second crop 261°-263° C " C = 56.77
" H = 3.43

$C_{15}H_{11}O_4N_2Cl$ requires C = 56.51; H = 3.45

Mixed m.p. of two crops - 262°-263° C

The 9-piperidino derivative of XXXIII was prepared and analysed.

Analysis:-

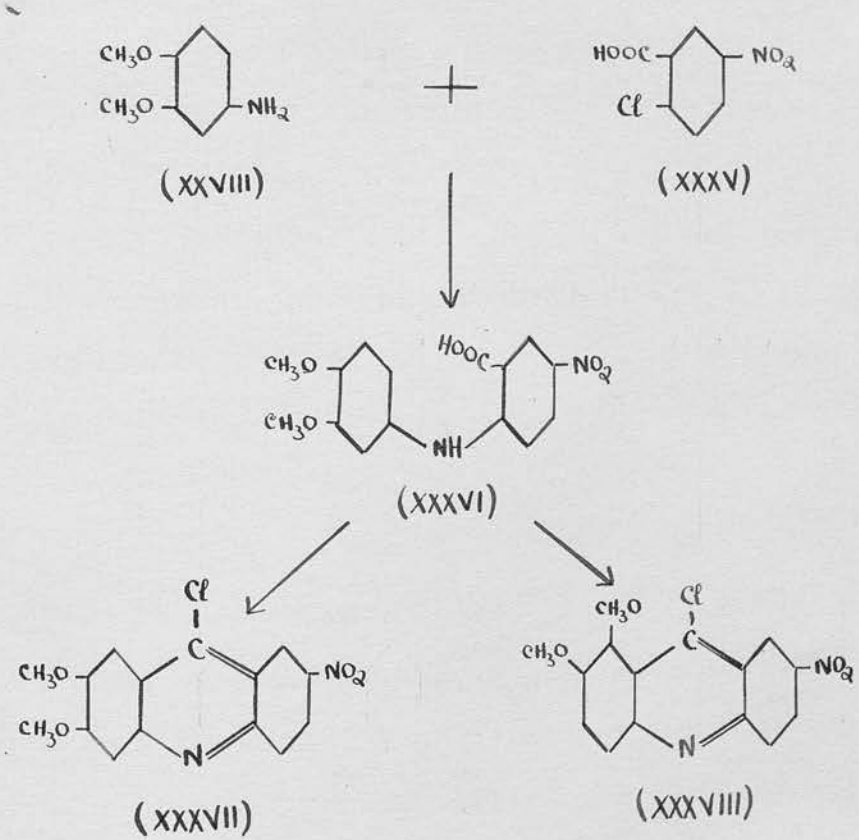
Found	Required for $C_{20}H_{21}O_4N_3$
% C = 65.19	% C = 65.40
% H = 6.04	% H = 5.70

It was evident that the synthesis had proved successful and that the 3-nitro-6:7-dimethoxy-9-chloracridine could be obtained fairly readily.

Synthesis IX.

Some indication of improved yield was obtained in synthesis VIII, where the ring closure with phosphorus oxychloride appeared to proceed more smoothly when the carboxyl group and the dimethoxy groups were attached to different phenyl nuclei in the diphenylamine carboxylic acid. It was, therefore, thought profitable to adopt a similar scheme in the synthesis of the 2-nitro-6:7-dimethoxy-9-chloracridine.

Outline:-



4-Aminoveratrole (XXXIV) was condensed with 2-chloro-5-nitrobenzoic acid (XXXV) to give 4-nitro-4':5'-dimethoxydiphenylamine-2-carboxylic acid (XXXVI). This acid, on treatment with phosphorus oxychloride, may ring close in two ways to give either 2-nitro-6:7-dimethoxy-9-chloracridine (XXXVII) or 2-nitro-7:8-dimethoxy-9-chloracridine (XXXVIII). The former ring closure appeared the more likely to occur and in this case the final product should be identical with the 2-nitro-6:7-dimethoxy-9-chloracridine obtained by the original method of synthesis (c.f. Synthesis VI).

The above synthesis was carried out exactly as in previous cases and the supposed 2-nitro-6:7-dimethoxy-9-chloracridine extracted with chloroform. The crystals so obtained were crystallised from chlorobenzene. The compound crystallised in yellow needles, m.p. 275°-277° C (Found C = 56.33; H = 3.06; $C_{15}H_{11}O_4N_2Cl$ requires C = 56.51; H = 3.45) identical with the crystals of 2-nitro-6:7-dimethoxy-9-chloracridine, m.p. 275°-276° C (c.f. Synthesis VI, page 41). The mixed melting point was 275°-276° C.

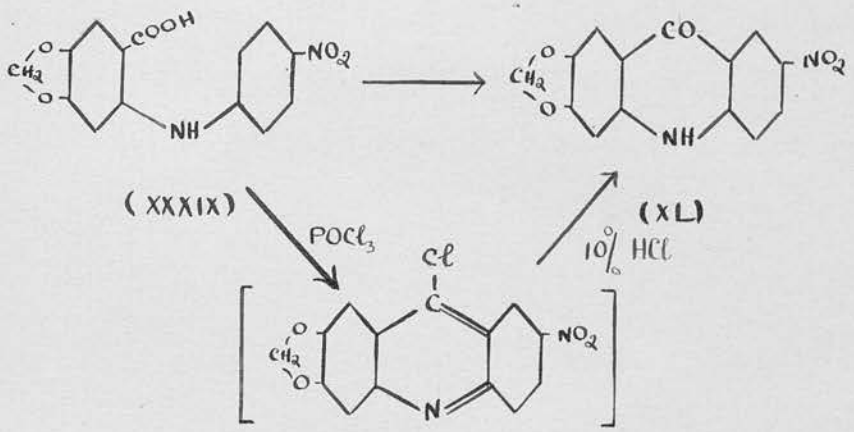
From the experimental data it was observed that this method of synthesis again gave more satisfactory yields than the method used earlier in this investigation, when the dimethoxy groups and the carboxyl group were attached to the same phenyl nucleus.

Other Acridine Derivatives

Introduction

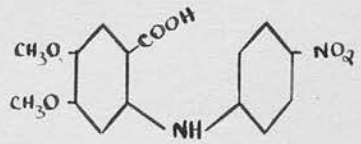
During the course of the preceding syntheses it had become apparent that in many cases unexpectedly poor yields had been obtained in acridine or acridone ring closures where the 2-carboxyl group concerned in the reaction was substituted in the same phenyl nucleus of the diphenylamine as a 4:5-methylenedioxy group or two methoxy groups in position 4 and 5.

Thus, 4'-nitro-4:5-methylenedioxydiphenylamine-2-carboxylic acid (XXXIX) on treatment with sulphuric acid did not yield the required acridone (XL) nor did the modified procedure of Albert and Linnell (loc.cit.) whereby treatment with phosphorus oxychloride should yield the chloracridine (XLI) which, in turn, should be hydrolysable with 10% hydrochloric acid to the acridone (XL), give a satisfactory product (See Synthesis I and II, p.17 and p.21).

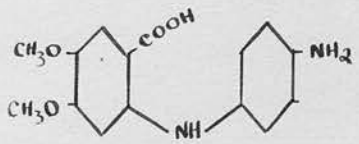


(XLI)

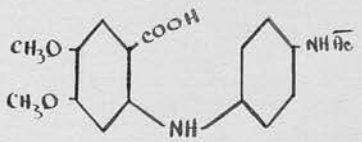
Similar difficulties were encountered in ring closures of this type with the dimethoxy compound (XLII) and it was thought that (XLIII) and (XLIV) could not be isolated because of decarboxylation.



(XLII)

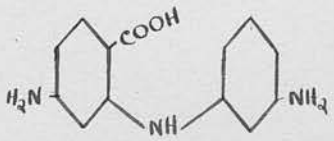


(XLIII)



(XLIV)

While it is known that many diphenylamine-2-carboxylic acids may be decarboxylated by heating to the melting point and that special instability had been recorded, in the case of acids of the type (XLV), by Albert and Ritchie and others (c.f. p.24), such an



(XLV)

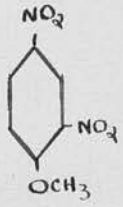
explanation of the difficulties encountered with the methylenedioxy and dimethoxy compounds did not appear to be completely satisfactory. As has been observed in Synthesis VIII and IX, if the alkoxy groups are substituted in a different phenyl nucleus to that in which the carboxyl group is substituted better yields of the chloracridine, for example, are obtainable on treatment with phosphorus oxychloride.

It seemed possible, therefore, that the alkoxy groups and the methylenedioxy group substituted in the same phenyl nucleus may exert a special influence on the stability of a carboxyl group in the position 2

in the same phenyl nucleus when treated with sulphuric acid or phosphorus oxychloride.

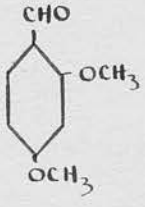
Such an influence is not unknown in organic chemistry. For example, p-methoxybenzoic acid (XLVI) on nitration gives 2:4-dinitroanisole (XLVII), (Lange, Rec. trav. chim., 1926, 45, 45).

(XLVI)

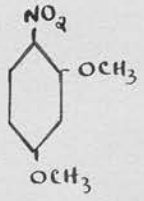


(XLVII)

2:4-Dimethoxybenzaldehyde (XLVIII) on nitration gives 2:4-dimethoxynitrobenzene (XLIX), (ibid., 49)

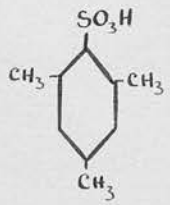


(XLVIII)

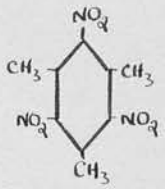


(XLIX)

and mesitylene sulphonic acid (L) on nitration gives trinitro-mesitylene (LI), (ibid., 56-57).

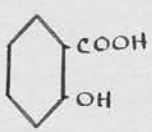


(L)

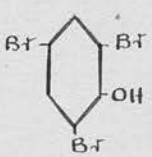


(LI)

Salicylic acid (LII) on bromination gives tribromo-phenol (LIII) (Robertson, J.C.S. 1902, 1482).



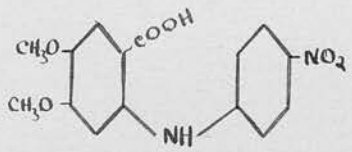
(LII)



(LIII)

De Lange (loc. cit.), who studied and reviewed this type of reaction, noted the fact that if an anionoid group - OH, NH_2, NHR, OR or CH_3 is attached to a nucleus then groups in the ortho and para positions will be replaced on cationoid attack if the group already present in the ortho and para position precedes

the replacing group in the series COOH, CHO, SO_3H, Br, Cl, NO_2. An alkoxy group in the para position to a carboxyl group such as we have in 4'-nitro-4:5-dimethoxydiphenylamine-2-carboxylic acid (LIV) should, therefore, render

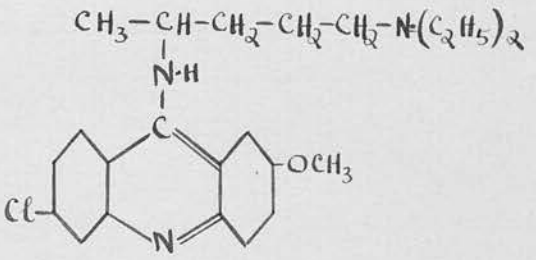


(LIV)

the carboxyl group liable to replacement on treatment with concentrated sulphuric acid and probably with phosphorus oxychloride. This, therefore, would appear to be a reasonable explanation of the failure of acridonation with sulphuric acid and of the difficulty in obtaining good yields on ring closure with phosphorus oxychloride. The same argument may be applied to explain the similar difficulties encountered with the 4:5-methylenedioxy substituted diphenylamine-2-carboxylic acids.

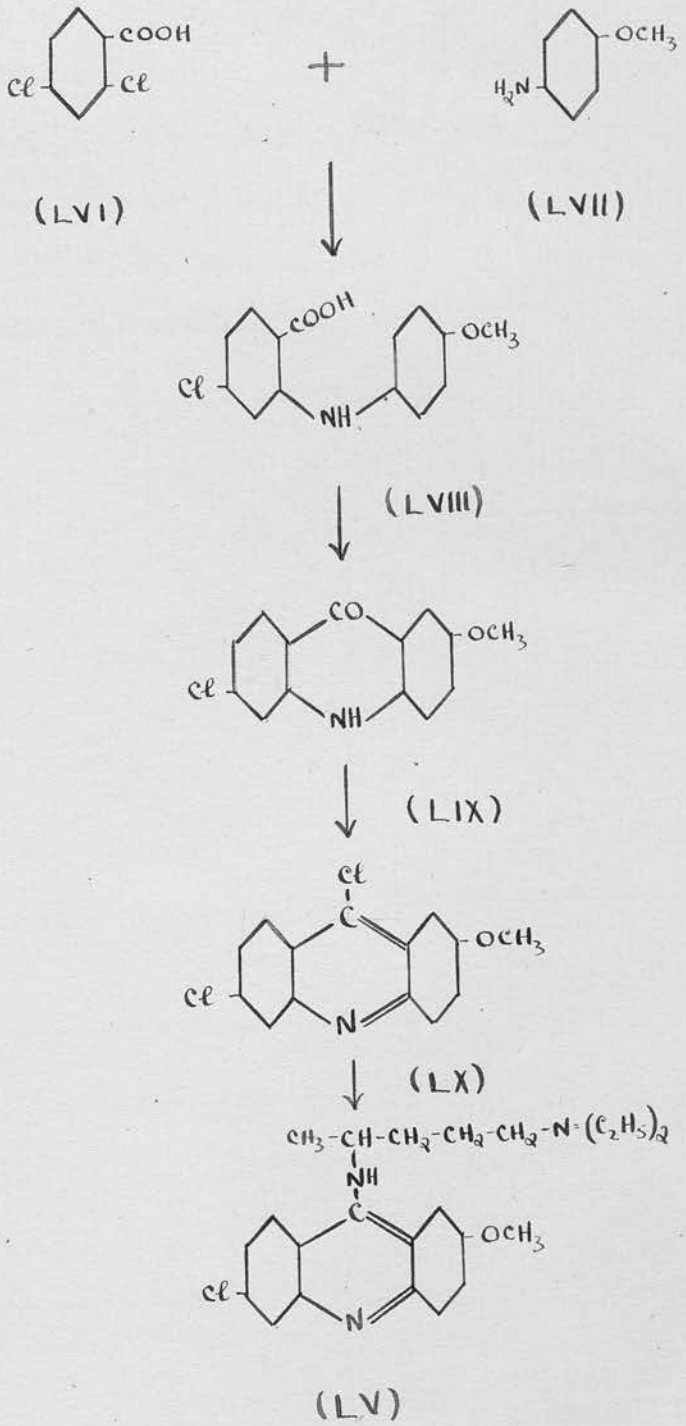
Amongst acridine compounds of recognised anti-

malarial activity the most important is atebrin (LV).



(LV)

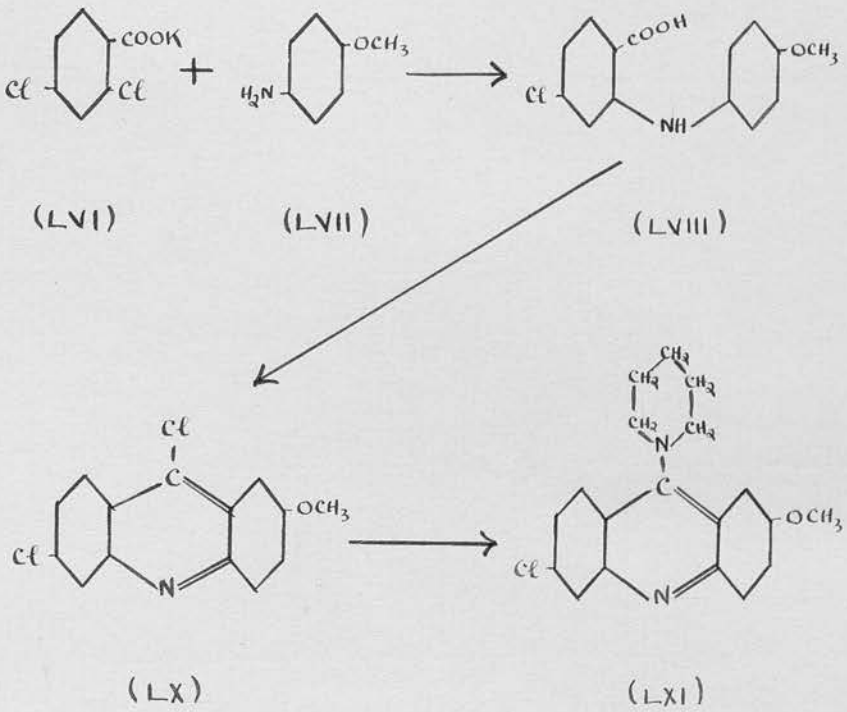
The synthesis of this compound, as described in E.P. 353, 537, is accomplished by condensing 2:4-dichlorobenzoic acid (LVI) with p-anisidine (LVII). The resulting diphenylamine carboxylic acid (LVIII) is converted by treatment with phosphorus oxychloride and alumimium chloride followed by hydrolysis with hydrochloric acid to the acridone (LIX). This latter is then re-treated with phosphorus pentachloride in suspension in chlorobenzene to yield the chloracridine (LX) which, heated in phenolic solution with 2-amino-5-diethylamino-pentane, yields atebrin (LV).


COOH
Cl
Cl
+
OCH3
H2N
(LVI)
(LVII)
COOH
OCH3
Cl
NH
(LVIII)
CO
OCH3
Cl
NH
(LIX)
Cl
C
OCH3
Cl
N
(LX)
CH3-CH-CH2-CH2-CH2-N:(C2H5)2
NH
C
OCH3
Cl
N
(LV)

The yields claimed in the patent are very good and it seemed desirable to examine this synthesis and especially to modify the ring closure of the diphenylamine carboxylic acid (LVIII) to the chloracridine (LX) in such a way as to bring it into line with earlier ring closures in which phosphorus oxychloride was used. In this way it was hoped to discover whether or not the chlorine in the para position to the carboxyl group had any stabilising effect on the carboxyl group. This is discussed in Synthesis X.

Synthesis X.

Outline:-



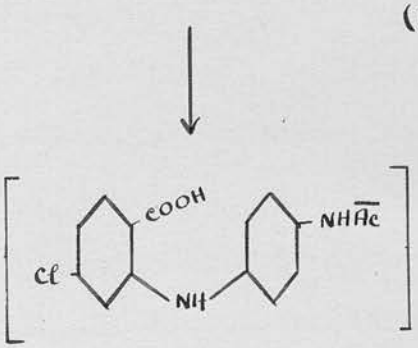
The synthesis of 4'-methoxy-5-chlorodiphenylamine-2-carboxylic acid (LVIII) was carried out as in E.P. 353, 537. Ring closure to the chloracridine (LX) with phosphorus oxychloride gave very good yields and from this compound the corresponding 9-piperidino derivative (LXI) was easily obtained.

Synthesis XI.

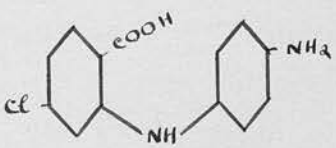
2-Amino-6:9-Dichloracridine

Outline:-

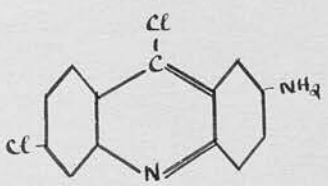
(LXII) (LXIII)



LXIV



(LXV)



(As hydrochloride)

(LXVI)

Because of the success attained in the previous synthesis it was considered desirable to investigate the condensation of 2:4-dichlorobenzoic acid (as its potassium salt) (LXII) with p-aminoacetanilide (LXIII). The intermediate acetylated 4'-amino-5-chlorodiphenylamine-2-carboxylic acid (LXIV) was hydrolysed to the free amino acid (LXV) which was isolated as its hydrochloride in a fair degree of purity. Ring closure with phosphorus oxychloride gave the 2-amino-6:9-dichloroacridine (LXVI), again as hydrochloride, in a fair degree of purity.

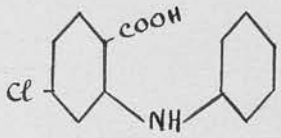
Bradbury and Linnell (J.C.S., 1942, 379) report the isolation of 4'-amino-5-chlorodiphenylamine-2-carboxylic acid by Dr. Adrien Albert. His preparation involves the condensation of 2:4-dichlorobenzoic acid with p-phenylenediamine and it is stated that this diphenylamine carboxylic acid undergoes ring closure with sulphuric acid to give 8-chloro-3-aminoacridine. (Albert (private communication) has indicated that the corresponding acridone is separated first).

Discussion on Synthesis X and XI.

It is apparent from Synthesis X and XI that a chlorine atom in the para position to the 2-carboxylic acid group in a diphenylamine carboxylic acid appears to give rise to fairly smooth ring closures with sulphuric acid and phosphorus oxychloride. On the other hand, numerous examples have been noted in the preceding syntheses in which methoxy groups and a methylene-dioxy group in positions 4 and 5 in the same nucleus as the 2-carboxyl group appear to render ring closures inefficient with these reagents.

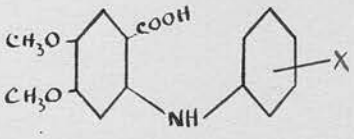
Chlorine substituted in a benzene ring is, however, usually regarded as an anionoid group just as the methoxy group is considered to be anionoid. Both give rise to ortho and para substitution on cationoid attack, e.g. nitration. It is to be noted, however, that de Lange (loc. cit.) does not include chlorine in his list of anionoid groups (see page 49) and it is well known that chlorobenzene is more difficult to nitrate than phenol, etc. To put this in other words, chlorine does not activate positions ortho and para to itself for cationoid attack to the same extent as do other anionoid substituents. It is,

therefore, reasonable to assume that chlorine will not activate a carboxylic group para to itself for replacement when treated with a cationoid reagent such as sulphuric acid or phosphorus oxychloride. This is advanced, therefore, as an explanation of success in ring closures of the type (LXVII)

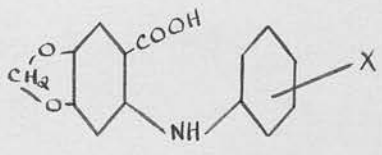


(LXVII)

and of inefficient ring closures with the corresponding dimethoxy and methylenedioxy compounds (LXVIII) and (LXIX) respectively.



(LXVIII)

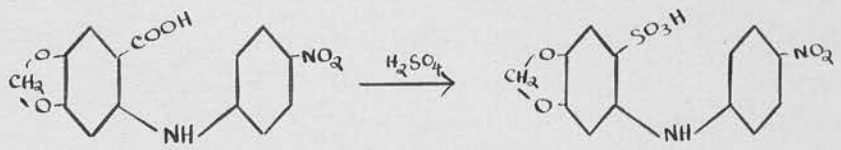


(LXIX)

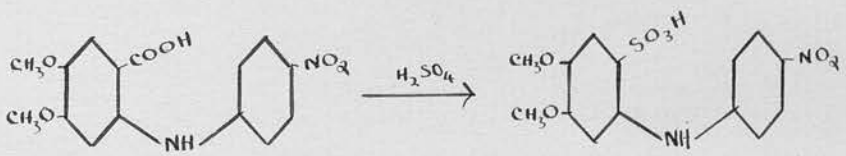
It would appear desirable that a systematic study of the influence of substituents on this type of ring closure should be undertaken.

For example, to test the validity of the explanation advanced above for the difficulties encountered in ring closures with sulphuric acid and phosphorus oxychloride of diphenylamine-carboxylic acids when the nucleus carrying the carboxyl group also carries the methylenedioxy or two methoxy groups in positions 4 and 5 the following suggestions may be mentioned as deserving further investigation:-

(1) A search might be made amongst the reaction products of the action of sulphuric acid on the diphenylamine-carboxylic acids (LXX) and (LXXI) for sulphonic acids resulting from the replacement of the carboxylic group by the sulphonyl group.

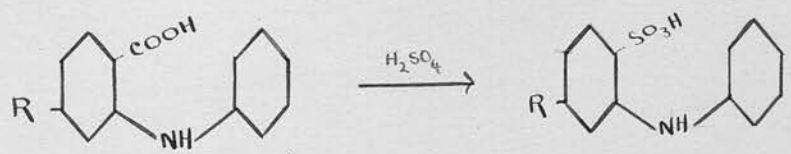


(LXX)



(LXXI)

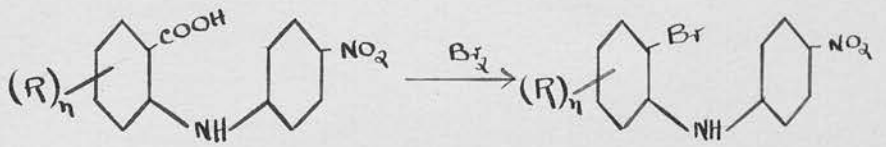
(2) The influence of other anionoid groups such as NH_2, NHR and CH_3 para to the carboxyl group might be examined and the possibility of replacement of the carboxyl group by sulphonyl group tested in the same way.



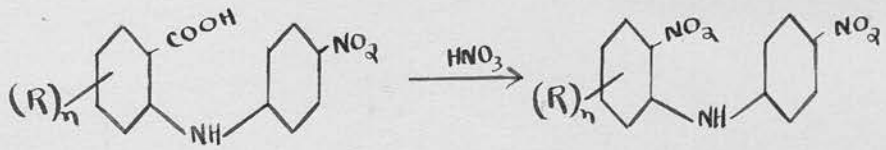
(LXXII)

[R = NH_2 ; NHR' ; CH_3]

(3) Since an activated carboxyl group is more readily replaced by bromine or a nitro group, such cationoid attack might be studied in compounds of type (LXXIII) and (LXXIV) in the hope of isolating compounds of type (LXXV) and (LXXVI) from the reaction.



(LXXIII) (LXXV)

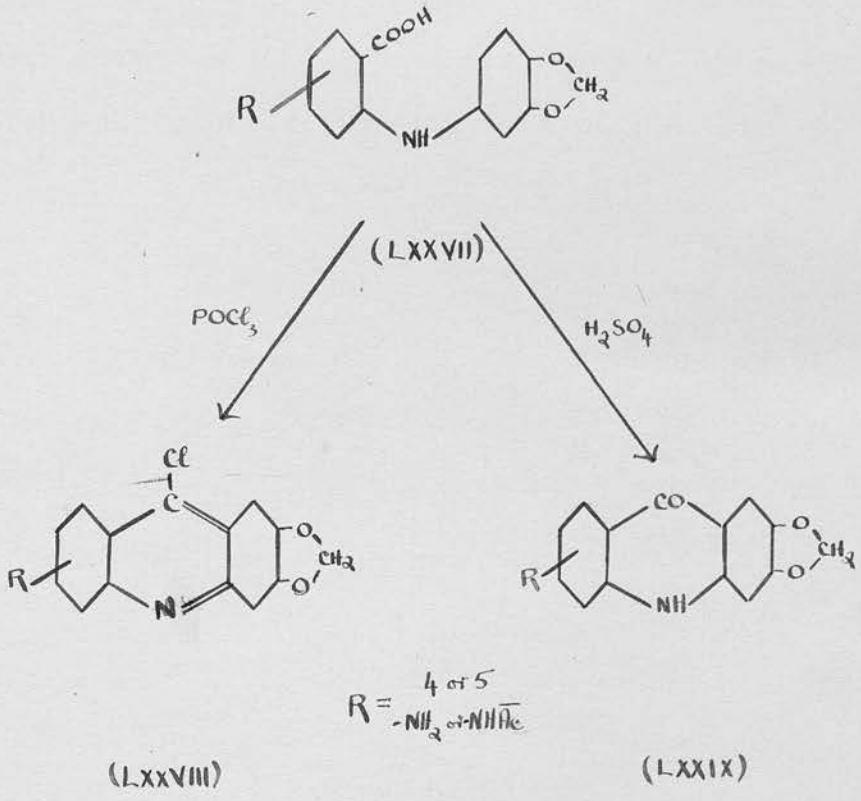


(LXXIV) (LXXVI)

$$(R)_n = \begin{cases} 4{:}5\text{-}O_2CH_2\ ;\ 4{:}5\text{-}(OCH_3)_2 \\ 5\text{-}NH_2\ ;\ 5\text{-}NHR;\ 5\text{-}CH_3 \end{cases}$$

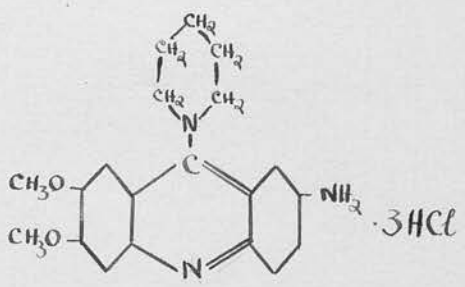
Moreover, the following subjects are worthy of future investigation:-

(1) Ring closures with sulphuric acid and phosphorus oxychloride of methylenedioxy compounds of type (LXXVII) should be examined.



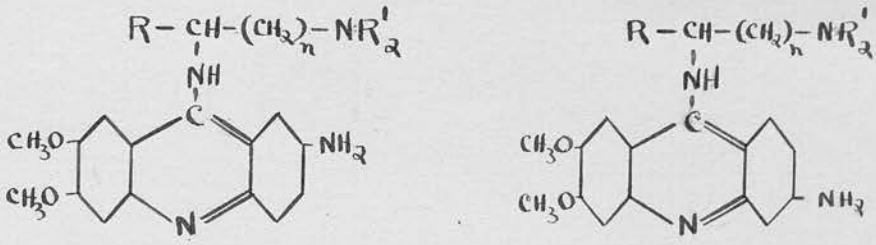
In the event of the 9-chloracridine (LXXVIII) being obtained it should yield a series of amino substituted derivatives (See below).

(2) The isolation of compound (LXXX) in Synthesis VI



(LXXX)

indicates the possibility of preparing a series of amino substituted derivatives of type (LXXXI)



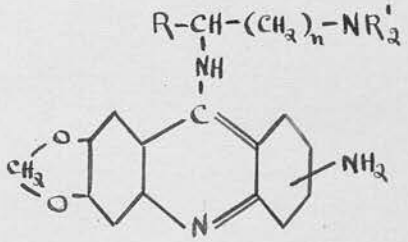
R + R' - Alkyl Group.

(LXXXI) (LXXXII)

and, in this case, it is possible that the intermediate 9-alkylamino-2-nitroacridines may be more easily reduced than the rather unstable 9-piperidino derivative.

The corresponding 3-amino compounds (LXXXII) also might be synthesised.

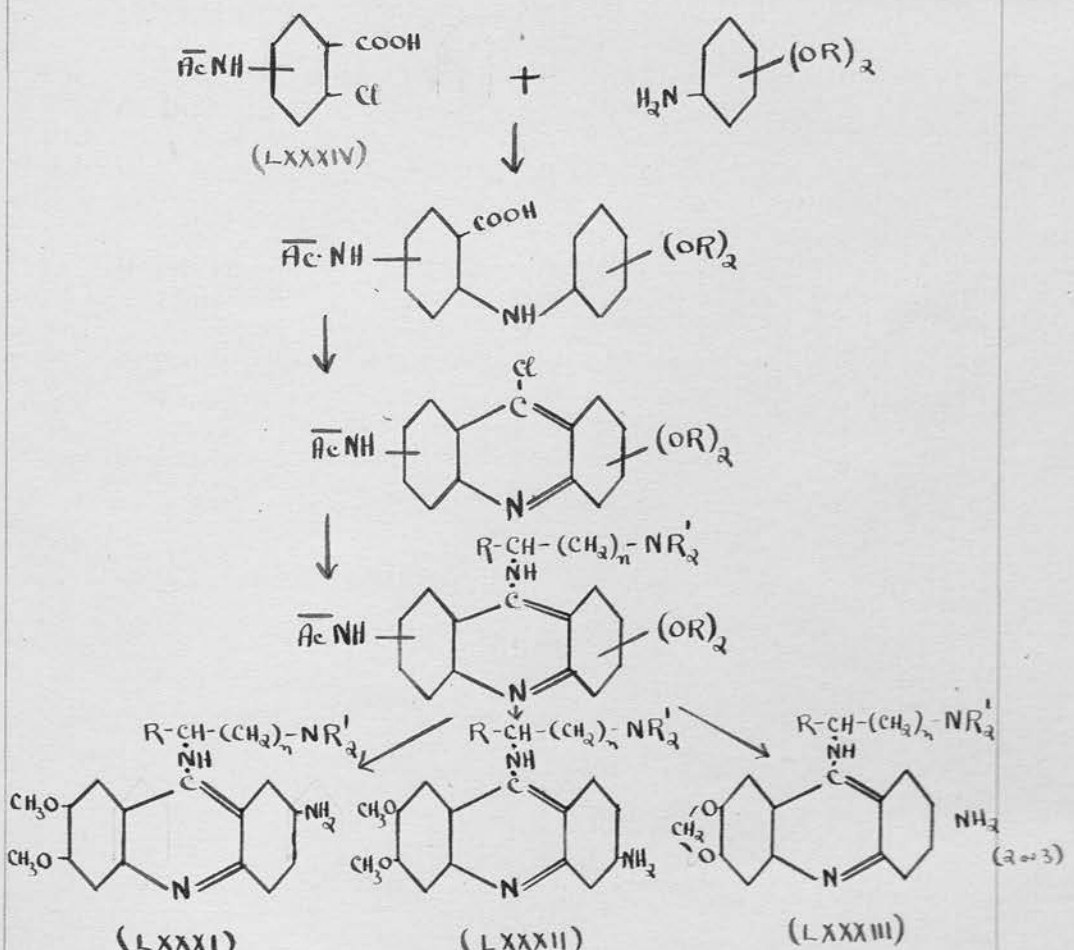
(3) By a similar course of syntheses the 3-amino-6:7-methylenedioxy compounds (LXXXIII) might be obtained.



R & R' = Alkyl Group

(LXXXIII)

(4) The routes to compounds of types (LXXXI), (LXXXII) and (LXXXIII) might be made easier by utilising 5-acetylamino-2-chlorobenzoic acid (LXXXIV), or the 4-acetyl derivative, as outlined below:-



III.

EXPERIMENTAL.

Synthesis I.

6-Bromopiperonal (XXIV)

100 gms. (1.4 moles) of piperonal were dissolved in 200 mls. glacial acetic acid. 40 mls. (0.8 moles) of bromine in 100 mls. glacial acetic acid were added with constant stirring to the solution of piperonal. In order to check any temperature rise the reaction vessel was surrounded with ice-water. When the bromine had been added the solution was set aside to crystallise over-night. The crystals which separated out were filtered off and washed with water. The filtrate was diluted with water and the solid thus obtained was filtered off and treated with a hot solution of sodium hydrogen sulphite. The hot extract was filtered and treated with a slight excess of sodium carbonate solution when a further quantity of bromo-piperonal was obtained. It was filtered off, washed with water and recrystallised from methyl alcohol.

The crystals obtained from the original solution were sufficiently pure for all ordinary purposes.

Weight of bromo-piperonal from the original solution	27 gms.
Melting point	129°-130° C.
Weight of bromo-piperonal crystallised from lethyl alcohol	70 gms.
Melting point	129°-130° C.
Total yield of 6-bromopiperonal	97 gms.
% Yield on theory	62

6-Bromopiperonylic acid (XXV).

40 gms. (0.18 moles) of 6-bromopiperonal were dissolved in 290 mls. acetone and the solution warmed on a water-bath. To this solution contained in a flask under a reflux condenser, a warm solution of 140 gms. potassium permanganate in one litre of water was added cautiously. When addition of the permanganate solution was completed the mixture was warmed on the water-bath and the acetone distilled off. The solution was then filtered to remove the precipitate of manganese dioxide. The manganese dioxide precipitate was extracted with boiling water and the filtrate and extract were combined. The combined solutions were concentrated and the bromo-piperonylic acid was precipitated by addition of dilute acid to the solution. The precipitate was filtered off, washed with water and dried.

If necessary, the 6-bromopiperonylic acid may be purified further by dissolving in aqueous alkaline

solution and reprecipitating by the addition of dilute acid.

Yield of 6-bromopiperonylic acid	16 gms.
Melting point	204°-206° C.
% Yield on theory	39

The potassium salt of 6-bromopiperonylic acid was obtained by adding the acid to a hot aqueous solution of the equivalent weight of potassium carbonate, filtering the solution and evaporating the filtrate to dryness.

4'-Nitro-4:5-methylenedioxy-diphenylamine-2-carboxylic acid (XXVII).

5.6 gms. (1/50 mole) of the potassium salt of 6-bromopiperonylic acid were refluxed with 2.8 gms. (1/50 mole) of p-nitraniline in 10 mls. amyl alcohol with 0.1 gm. Copper Bronze present. After refluxing for four to six hours the mixture in the flask was made slightly alkaline with sodium hydroxide solution, then steam-distilled to remove excess amyl alcohol and any unchanged p-nitraniline. The hot solution was filtered through a cotton-wool filter pad and the filtrate made slightly acid by the addition of hydrochloric acid. The crystals which separated on cooling were filtered off, well washed with water and dried.

This compound was crystallised twice from chlorobenzene and analysed.

Analysis:

First crystallisation: m.p. 199°-201° C.

Second crystallisation: m.p. 204°-206° C.

Found % C, 55.81; % H, 3.32

Required for $C_{14}H_{10}O_6N_2$: % C, 55.63; % H, 3.31

Crude yield: 3.6 gms.

% Yield on theory: 59

2-Nitro-6:7-methylenedioxy-acridone.

3.6 gms. (0.012 moles) of 4'-nitro-4:5-methylene-dioxy-diphenylamine-2-carboxylic acid were refluxed with 20 mls. phosphorus oxychloride for twenty minutes. The liquor was poured into water and the precipitate so obtained was filtered off and boiled for fifteen minutes with a 5% solution of hydrochloric acid. Next the solid was treated with a solution of sodium carbonate, filtered off, well washed with water and dried. No method of crystallising this compound was found and it could not be obtained in a state sufficiently pure for analysis.

Yield of crude compound: 2.8 gms.

Melting point: does not melt below 300° C.

Attempts to reduce this compound were made -

(1) By means of anhydrous stannous chloride reagent

(2) Using iron and hydrochloric acid.

(3) With sodium amalgam in an atmosphere of carbon dioxide.

The attempts at reduction by means of these methods were unsuccessful.

Synthesis II.

Piperonylic acid (XXXIII).

60 gms. (0.4 mole) of piperonal and 1,500 mls. of water were placed in a 5 litre flask fitted with an efficient mechanical stirrer. The flask was placed on a steam-bath and the mixture warmed to 70°-80°C. A solution of 90 gms. potassium permanganate in 1,800 mls. water was allowed to flow into the continuously stirred mixture of piperonal and water over a period of forty to forty-five minutes. After the addition of the permanganate solution heating and stirring were continued for one hour. A 10% solution of potassium hydroxide was added until the solution was alkaline. The hot solution was filtered and the manganese dioxide precipitate washed

with three 200 ml. portions of hot water. The combined filtrate and washings were cooled, filtered to remove any unchanged piperonal and the filtrate made acid by the addition of hydrochloric acid. The piperonylic acid so obtained was filtered off and crystallised from ten times its weight of 95% ethyl alcohol.

Yield:	50 gms.
Melting point:	227°-228° C.
% Yield on theory:	78

Methyl ester of piperonylic acid (XXXIV).

14 gms. (0.08 mole) of piperonylic acid, 130 mls. methyl alcohol and 10 mls. concentrated sulphuric acid were refluxed until all the piperonylic acid had gone into solution. The crude methyl ester was obtained by pouring the solution into excess of water. The ester was filtered off and crystallised from the minimum quantity of methyl alcohol.

Yield:	15.4 gms.
Melting point:	51°-52° C.
% Yield on theory:	99

Methyl ester of 2-nitro-piperonylic acid (XXXV).

29 gms. (0.16 mole) of piperonylic acid methyl ester were dissolved in 75 gms. glacial acetic acid and the flask placed in an ice-salt cooling mixture.

To the solution 150 mls. of fuming nitric acid were added over a period of two hours, with continuous stirring. Stirring was continued for a further half-hour and the solution then poured on to ice when crystals of nitro-piperonylic acid methyl ester were obtained. These were filtered off and crystallised from ethyl alcohol.

Yield:	26 gms.
Melting point:	101°-102°C.
% Yield on theory:	75

Reduction of methyl ester of 2-nitropiperonylic acid by gaseous hydrogen and Raney nickel catalyst.

Methyl ester of 2-amino-piperonylic acid (XXXVI).

Preparation of the catalyst:

The catalyst was prepared as described by Albert and Ritchie (J. Proc. Roy. Soc. N.S. Wales, 1940, 74, 74).

Reduction:

26 gms. (0.11 mole) of 2-nitro-piperonylic acid methyl ester were placed in a bolt-head flask with 300 mls. ethyl alcohol and 20 gms. Raney nickel catalyst. The flask was closed by a rubber stopper (previously treated by shaking for ten hours with

Raney nickel catalyst in alcohol) through which passed a glass tube fitted with a stop-cock. The flask was evacuated and then connected to a Boyle gas holder containing hydrogen. The stop-cock was opened and the hydrogen allowed to enter the flask. The flask was then shaken mechanically until the theoretical volume of hydrogen required for reduction had been absorbed and for a further half-hour. The contents of the flask were warmed and filtered free from mickel (the nickel residue will burn if allowed to dry on the filter paper). The hot alcoholic filtrate was concentrated and allowed to cool when the amino-piperonylic acid methyl ester crystallised out.

It is fairly pure but may be recrystallised from alcohol, hot water or petrol-ether.

Yield of 2-amino-piperonylic acid methyl ester: 21 gms.

Melting point: 108°C. (recrystallised)

% Yield on theory: 93

Analysis:

Found: % C, 55.16; % H, 4.40; % N, 7.18

Required for $C_9H_9O_4N$: % C, 55.38; % H. 4.61; % N, 7.40

Attempted condensation of the methyl ester of 2-amino-piperonylic acid with p-chloronitrobenzene.

5 gms. (0.03 mole) of 2-amino-piperonylic acid methyl ester were refluxed in 15 mls. amyl alcohol solution with 4 gms. p-chloronitrobenzene, a trace of Copper Bronze being added to the mixture. The mixture was refluxed at 110°-115°C. for three hours and the solution was allowed to cool.

On cooling, two compounds separated out. The first crop of crystals was yellowish in colour, melted at 106°-107°C. and weighed 3.3 gms. The mixed melting point of this compound with the methyl ester of 2-amino-piperonylic acid (m.p. 108°C.) was 107°C. so this was probably the original amino acid methyl ester.

On concentrating the filtrate a second crop of crystals was obtained, melting point 57°-60°C. and weight 1 gm. No conclusion was made as to the identity of this product save that it did not appear to be the required condensation product.

It appeared possible that the methyl ester group, through steric hindrance, was preventing the condensation taking place.

2-Amino-piperonylic acid.

10 gms. of the methyl ester of 2-amino-piperonylic acid, 5.5 gms. potassium hydroxide in 30 mls. water and 30 mls. absolute alcohol were refluxed together for three hours. The final solution was diluted with water and made faintly acid with hydrochloric acid. The precipitate so obtained was filtered off, washed with water and dried.

Yield: 8 gms.

Melting point: 191°-193° C. (with decomposition)

The potassium salt of 2-amino-piperonylic acid was prepared in the usual manner by treating a given weight of the acid with the equivalent weight of potassium carbonate dissolved in water.

Condensation of 2-amino-potassium piperonylate with p-chloronitrobenzene.

9 gms. (0.04 mole) of 2-amino potassium piperonylate, 6.5 gms. (0.04 mole) of p-chloronitrobenzene, 30 mls. of amyl alcohol and a trace (0.2 gm.) of Copper bronze were refluxed together for eighteen hours. The hot solution was made alkaline and steam-distilled to remove any unchanged base, amyl alcohol

and any unchanged p-chloronitrobenzene. The solution was filtered and cooled. Nothing separated from the filtrate on cooling and it was then reduced in volume. A solid separated out which appeared to decompose in the region of 300° C. It did not appear to be the required diphenylamine compound.

In the experiment 3.3 gms. of p-chloronitrobenzene were recovered unchanged.

Preparation of 2-nitro-6:7-methylenedioxy-9-chloracridine.

3 gms. (0.01 mole) of 4'-nitro-4:5-methylenedioxy-diphenylamine-2-carboxylic acid were refluxed with 18 mls. phosphorus oxychloride for one and a half hours. The mixture was cooled in ice, washed free from phosphorus oxychloride with petrol-ether and treated with ice and a 10% solution of ammonia. The solid thus obtained was filtered off, dried and extracted in a Soxhlet apparatus with chloroform. The crystals which separated from the chloroform extract were dark brown in colour, decomposed c. 309°-311° C. and appeared to contain no chlorine (flame test). It was concluded that hydrolysis had taken place and that the final product was the acridone instead of the required 9-chloracridine.

Synthesis III.

Attempts were made to reduce 4'-nitro-4:5-methylenedioxy-diphenylamine-2-carboxylic acid, using the methods indicated on page 69 but these attempts were unsuccessful.

Synthesis IV.

As there was some evidence that this suggested synthesis would prove unsatisfactory (c.f. page 24) it was not proceeded with.

6:7-Dimethoxy substituted Acridines

Synthesis V.

Preparation of methyl vanillin (3:4-dimethoxy-benzaldehyde) (II).

(Barger and Silberschmidt, J.C.S. 1928, 2924)

152 gms. (1 mole) of vanillin were melted in a wide-mouthed bottle provided with a reflux condenser, a mercury-sealed stirrer and two tap funnels.

With rapid stirring 82 gms. (1.5 moles) of potassium hydroxide in 120 mls. water were run in at the rate of two drops a second and twenty seconds after this had started the addition of 160 mls. dimethyl sulphate was commenced at the same rate. (The dimethyl sulphate had been allowed to stand over potassium carbonate and was neutral to Congo Red).

When all the reagents had been added stirring was continued for a further ten minutes and then the reaction mixture was poured into a porcelain basin and allowed to cool. The upper layer solidified to a hard white mass of practically pure methyl vanillin. The mass was broken up, washed with water and dried in

a desiccator.

Yield:	164 gms.
Melting point:	42°-43° C. (as quoted in lit.)
% Yield on theory:	98

Preparation of 6-bromoveratricaldehyde (III).

The bromination of methyl vanillin was carried out exactly as described for 6-bromopiperonal (Robinson, loc. cit.).

Weight of methyl vanillin taken:	63 gms.
Yield of 6-bromoveratricaldehyde:	53 gms.
Melting point:	149°-150° C.
% Yield on theory:	57

Preparation of 6-bromoveratric acid (IV).

43 gms. sodium hydroxide were dissolved in 1½ litres of water in a large round bottomed flask which was provided with a mechanical stirrer. The solution was raised to a temperature of 90° C. by placing the flask on a water-bath. This temperature was maintained during the experiment.

46 gms. (0.18 mole) of 6-bromoveratricaldehyde and 63 gms. potassium permanganate were added in small quantities at a time to the hot, continuously stirred

alkaline solution, the rate of addition being governed by the following rules:-

(1) Potassium permanganate was added only when the colour of the solution indicated that the previous addition had been reduced.

(2) 6-Bromoveratricaldehyde was added only when no trace of the previous addition was visible as solid suspended in the solution.

The rate of addition of the 6-bromoveratricaldehyde and the potassium permanganate appeared to govern the yield of 6-bromoveratric acid.

When the aldehyde and the permanganate had been added stirring was continued until all trace of the solid 6-bromoveratricaldehyde had vanished. The hot solution was filtered, the precipitate of manganese oxide washed with hot water and the washings combined with the filtrate. The filtrate was treated with sulphurous acid to reduce any potassium permanganate remaining in the solution. The resultant clear solution was made acid by addition of dilute sulphuric acid and the 6-bromoveratric acid precipitated out. It was filtered off, washed with water and dried.

Yield of 6-bromoveratric acid: 44 gms.

Melting point of acid: 185°-187° C.
(Lit. 186° C.)

% Yield on theory: 89

The potassium salt of 6-bromoveratric acid was prepared in the usual manner by treatment with potassium carbonate solution.

4:5-Dimethoxy-4'-nitrodiphenylamine-2-carboxylic acid (V).

24 gms. (0.08 mole) of potassium bromoveratrate were refluxed with 11.2 gms. (0.08 mole) of p-nitraniline in 40 mls. amyl alcohol solution with a trace (0.1 gm.) of Copper bronze present. The crude 4:5-dimethoxy-4'-nitrodiphenylamine-2-carboxylic acid was obtained from the reaction mixture after refluxing for six hours by the same method as was used to obtain the 4:5-methylenedioxy-4'-nitrodiphenylamine-2-carboxylic acid (page 67).

The crude acid was not sufficiently soluble in the usual organic solvents to permit of satisfactory recrystallisation. It was purified further by reprecipitating from alkaline solution.

Yield of acid: 18.3 gms.

Melting point: decomposes 250°-252°C.

% Yield on theory: 64

Analysis:

Found: % C, 56.41; % H, 4.39

Required for $C_{15}H_{14}O_6N_2$: % C, 56.60; % H, 4.40

2-Nitro-6:7-dimethoxy acridone (VI).

An attempt was made to prepare this compound using the method which was adopted for the preparation of 2-nitro-6:7-methylenedioxy acridone (page 68). The crude compound which was obtained could not be crystallised from any of the usual organic solvents and no satisfactory analysis of the product could be obtained.

If this product was 2-nitro-6:7-dimethoxy-acridone it was thought that the corresponding 2-amino compound might be purified more readily. The usual methods of reduction were tried but the attempts at reduction were not successful. Reduction by gaseous hydrogen and Raney nickel catalyst was tried but though there was evidence of the characteristic acridine fluorescence in the final solution the required base could not be isolated. The method of reduction described by Albert and Ritchie (J.S.C.I. 1941, 60, 120) was tried but was not successful. This method utilises aluminium amalgam as reducing agent.

Synthesis VI.

2-Nitro-6:7-dimethoxy-9-chloracridine (IX).

3 gms. of 4:5-dimethoxy-4'-nitrodiphenylamine-2-carboxylic acid and 18 mls. of phosphorus oxychloride were heated together under a reflux condenser for one hour at c. 150° C. The solution was cooled and treated with petrol-ether to remove the excess phosphorus oxychloride. When the pasty mass in the flask had been freed from phosphorus oxychloride as much as possible it was treated with a mixture of crushed ice and 10% ammonia solution. The whole was shaken and stirred until the pasty mass had separated as a yellowish solid which was filtered off, well washed with ice-cold water containing a trace of ammonia, and then dried in a vacuum desiccator. The dry product was extracted with chloroform in a Soxhlet apparatus.

The yellowish needles obtained from the chloroform extract were filtered off, washed with chloroform and dried.

Yield: 0.5 gms.

Melting point: 259°-261° C.

Analysis:

Found: % C, 56.53; % H, 3.46

Required for $C_{15}H_{11}O_4N_2Cl$: % C, 56.51; % H, 3.45

Further purification of the 2-nitro-6:7-dimethoxy-

9-chloracridine may be achieved by recrystallisation from monochlorobenzene.

Melting point on recrystallisation: 275°-276° C.

2-Nitro-6:7-dimethoxy-9-piperidino acridine (X).

4 gms. of 2-nitro-6:7-dimethoxy-9-chloracridine were refluxed with 24 mls. of piperidine until all had gone into solution. Refluxing was continued until solid commenced to separate from the solution. At this point the heat was removed and the flask allowed to cool. Red, needle-shaped crystals were obtained which were filtered off, well washed with water and dried.

Yield: 4.2 gms.

Melting point: 242°-244° C.

Analysis:

Found: % C, 65.51; % H, 5.84

Required for $C_{20}H_{21}O_4N_3$: % C, 65.39; % H, 5.72

Salts of 2-nitro-6:7-dimethoxy-9-piperidino acridine.

A solution of 2-nitro-6:7-dimethoxy-9-piperidino-acridine in acid was added to an acetone solution of tartaric acid. The resulting red crystals of the tartrate were filtered off, washed, dried and analysed.

Melting point: 188°-192° C.

Analysis:

Found: % C, 60.00; % H, 5.30

Required for $C_{44}H_{48}O_{14}N_3$: % C, 59.75; % H, 5.40

In a similar manner the di-ethylmalonate was obtained and analysed.

Melting Point: Compound shows signs of decomposition between 167-170°C but decomposes sharply at 279°C.

Analysis:

Found: % C, 61.58; % H, 6.36

Required for $C_{27}H_{33}O_8N_3$: % C, 61.48; % H, 6.26

2-Amino-6:7-dimethoxy-9-piperidino acridine (XII).

3 gms. of 2-nitro-6:7-dimethoxy-9-piperidino-acridine were placed in a bolt-head flask along with 20 mls. absolute alcohol and approximately 5 gms. Raney nickel catalyst. The flask was attached to a vacuum pump and the air removed. Next, the flask was placed in a mechanical shaker and connected by pressure tubing to a Boyle gas-holder containing hydrogen. Hydrogen was admitted to the flask and the flask and contents shaken mechanically. The progress of the reduction was followed by observing the absorption of hydrogen from the gas-holder. When the theoretical volume of hydrogen had been absorbed shaking was continued for a further period until it was evident that absorption of hydrogen had ceased.

The alcoholic solution was warmed and the nickel

catalyst was filtered off. To the filtrate was added a quantity of alcohol saturated with hydrochloric acid gas and it was placed in the ice-chest. Crystals separated out and these were filtered off, washed with alcohol, dried in air and finally in a desiccator.

The crystals were needle shaped and a dark brownish colour. They were soluble in water and on addition of alkali to the aqueous solution a precipitate was obtained, probably the base itself, which appeared to decompose readily.

Melting point: No definite melting point was observed up to 300°C. The compound appeared to decompose slowly while being heated

Analysis:

Found: % C, 53.15; % H, 6.18: % N, 9.31

Required for trihydrochloride $C_{20}H_{23}O_2N_3.3HCl$

% C, 53.75; % H, 5.82; % N, 9.40

This compound was submitted for pharmacological testing.

Synthesis VII.

Preparation of veratrole (XV).

22 gms. (0.2 mole) of catechol were dissolved in 50 mls. of 20% sodium hydroxide solution and to the rapidly darkening solution a volume of 20 mls. dimethyl sulphate was added and the mixture was vigorously shaken. Considerable heat was evolved and after the solution had cooled it was extracted with ether. The ethereal extract was dried over calcium chloride. The extract was then placed in a distilling flask and the ether removed by distillation. The residual veratrole was then distilled over and collected at 205° C.

Yield of veratrole:	15.4 gms.
% Yield on theory:	55
Yield reported by Ullmann (loc. cit.):	23 gms.
% Yield on theory:	83
Boiling point reported:	205° C.

Preparation of nitroveratrole (XVI).

27 gms. (0.2 mole) of veratrole dissolved in 27 mls. glacial acetic acid were added drop-wise to a continuously stirred, ice-cold solution of 34 mls. concentrated nitric acid in 68 mls. water. After the addition of the veratrole solution stirring was con-

tinued for two hours. The temperature of the mixture was kept at 0° C. for the first hour and then allowed to rise to room-temperature. At the end of the two hours the nitroveratrole had crystallised out. The crystals were filtered off, washed with water and recrystallised from hot methyl alcohol after addition of sufficient water to the hot solution to cause slight turbidity.

Yield:	31.8 gms.
Melting point:	95°-96° C. (Lit. 95°-96° C.)
% Yield on theory:	89

Preparation of 4-aminoveratrole (XVII).

30 gms. of tin, 24 gms. (0.13 mole) of 1-nitro-3:4-dimethoxy benzene (nitroveratrole) and 200 mls. of concentrated hydrochloric acid were allowed to react, with occasional stirring. After the first vigorous reaction had subsided 30 gms. more of tin were added. As the reduction proceeded the amine separated as the stannic chloride double salt. Upon completion of the reduction the mixture was cooled and the precipitate filtered off. This precipitate was dissolved in 300 mls. of water and sodium hydroxide added to the solution in sufficient quantity to dissolve the tin precipitate first formed and to render the solution strongly alkaline. Much of the amine separated as

pearlescent plates but these were not removed. The amine was extracted with ether, the ethereal extract dried over sodium sulphate and evaporated to dryness.

Yield of crude aminoveratrole: 8.7 gms.
Melting point: 74° -76° C.
% Yield on theory: 44

On recrystallisation from ether (n-butyl ether also may be used) snow-white crystals were obtained.

Melting point: 80° -81° C.

Preparation of m-nitroformanilide (XIX).

12 gms. (0.09 mole) of m-nitraniline and 20 mls. glacial acetic acid were warmed together until the nitraniline had dissolved. To the warm solution was added 4 gms. (0.09 mole) of formamide and the mixture was heated under a reflux condenser for two hours. When cold the mixture was filtered and poured into cold water. The precipitate which was obtained was filtered off and recrystallised from boiling water.

Yield of m-nitroformanilide: 8 gms.
Melting point: 132° -134° C.
% Yield on theory: 57

Preparation of m-aminoformanilide (XX).

5.4 gms. (0.03 mole) of m-nitroformanilide were shaken with 5 gms. of Raney nickel catalyst in 100 mls. absolute alcohol under an atmosphere of hydrogen for three hours. After this time absorption of hydrogen had ceased and the Raney nickel was filtered from the solution. The alcoholic filtrate was reduced in volume and the aminoformanilide allowed to crystallise. It crystallises as white needles.

Yield: 2.5 gms.
Melting point: 107°C.
% Yield on theory: 60

Albert's Synthesis (J.C.S. 1941, page 124.)

2.7 gms. (0.02 mole) of m-aminoformanilide and 4 gms. (0.02 mole) of the hydrochloride of 4-amino-veratrole were added to a cold solution of 5 gms. zinc chloride in 15 gms. glycerol. The mixture was warmed to 155°C. during twenty-five minutes and held at that temperature for forty minutes, with occasional stirring. The melt was treated with 2.5N sodium hydroxide and the tarry residue extracted with a minimum quantity of boiling 1N hydrochloric acid. The filtrate was treated with excess of ammonia to remove zinc and the precipitate extracted with the

minimum quantity of dilute acetic acid. This solution was treated with 20% sulphuric acid ($\frac{1}{4}$ of its volume) and then set aside in the ice-chest but no crystals were obtained.

Synthesis VIII.

Preparation of veratronitrile (XXVI).

In a one litre round-bottomed flask 83 gms. (0.5 mole) of veratric aldehyde were dissolved in 250 mls. warm, 95% alcohol. To this solution was added a warm solution of 42 gms. (0.6 mole) of hydroxylamine hydrochloride. The two solutions were mixed thoroughly and a solution of 30 gms. (0.75 mole) of sodium hydroxide in 40 mls. of water was introduced.

The mixture was allowed to stand for two and a half hours at room temperature, then 250 gms. of crushed ice were added and the solution was saturated with carbon dioxide. The aldoxime separated as an oil which solidified on standing in the ice-chest over-night. The crystals were filtered off, washed thoroughly with water and dried in air.

Yield of veratraldoxime: 77 gms.

% Yield on theory: 85

The 77 gms. (0.4 mole) of veratraldoxime were placed with 100 gms. of acetic anhydride in a 300 ml. round-bottomed flask provided with a ground-glass air condenser. The mixture was heated cautiously until a vigorous reaction set in when the flame was removed. When the reaction had subsided the solution was refluxed for twenty minutes and then poured carefully, with stirring, into 300 mls. of cold water. The stirring was continued and on cooling the veratronitrile separated in small, almost colourless crystals which were removed by filtration and dried in air.

Yield of veratronitrile: 59 gms.

Melting point: 66°-67° C.

% Yield on theory: 85

4-Aminoveratrole (XXVIII).

In a five litre flask fitted with a mechanical stirrer were placed 1800 gms. (1.6 moles) of fresh 3% hydrogen peroxide solution and 59 gms. (0.36 mole) of veratronitrile. The mixture was warmed slowly to 45°C. with stirring and then the source of heat was removed. The reaction proceeded with evolution of oxygen and the temperature rose to c. 55° C. Soon the

veratric amide began to separate out and after about one hour the reaction was complete and the temperature commenced to fall. The mixture was cooled to 3°-5° C. and allowed to remain in the cooling bath for two hours. The white crystalline product was filtered off and dried in air.

Yield of veratric amide: 60 gms.

Melting point: 158°-160° C.
(Lit. 162.5°-163.5° C.)

% Yield on theory: 92

An alkaline solution of sodium hypochlorite was prepared by passing chlorine (0.412 gms. for each gm. of amide) into a mixture of 300 gms. cracked ice and a cold solution of 80 gms. of sodium hydroxide in 500 mls. of water contained in a two litre round-bottomed flask. The whole of the veratric amide (60 gms.) was added in one portion and the mixture was warmed slowly in a water-bath with constant stirring. The material soon darkened in colour and at an internal temperature of 50°-55° C. oily droplets began to separate. The temperature was raised to 70° C. and maintained at this point for one hour. A solution of 120 gms. of sodium hydroxide in 120 mls. water was added slowly and the temperature raised to 80° C. for an additional hour. On cooling the mixture the oily layer of amine solidified to a red crystalline mass. The crude amine was filtered off and washed with two

60 ml. portions of ice-cold water. The crystals were dried in air and extracted with ether. The ether extract was dried over sodium sulphate and evaporated to dryness. The 4-aminoveratrole so obtained was crystallised from ether.

Yield of 4-aminoveratrole:	40 gms.
Melting point:	89°-91° C.
% Yield on theory:	82

2-Chloro-4-nitrobenzoic acid (XXXI).

40 gms. (0.26 mole) of commercial 4-nitro-o-toluidine dissolved in 200 mls. hot water and 400 mls. concentrated hydrochloric acid were cooled while stirring vigorously. 200 gms. of ice followed by 60 mls. of concentrated hydrochloric acid were added to precipitate the solid in small crystals. To this mixture maintained at -3° C. and well stirred, 19 gms. of sodium nitrite in 60 mls. of water were added over a period of twenty minutes. The mixture was stirred for a further half-hour and then poured below the surface of a copper solution (60 gms. of cuprous chloride in 150 mls. of concentrated hydrochloric acid and 100 mls. of water) maintained at 40° C. After the addition, the whole was refluxed for one hour, cooled, filtered and the cake steam-distilled. The 2-chloro-4-nitrotoluene obtained from the distillate was crystallised from methyl alcohol.

Yield of 2-chloro-4-nitrotoluene: 27 gms.

Melting point: 62°-64° C.

% Yield on theory: 60

77 mls. of 80% sulphuric acid were mixed with 27 gms. of 2-chloro-4-nitrotoluene and to the mixture 50 gms. of pulverised potassium dichromate were added gradually, the whole being kept well stirred and the temperature maintained at 65° C. When the colour of the dichromate had disappeared the mixture was stirred for a further half-hour and then diluted with its own volume of water. The precipitate was filtered off and the unchanged 2-chloro-4-nitrotoluene removed by treatment with a warm solution of sodium hydroxide. To the warm solution of the sodium salt of the 2-chloro-4-nitrobenzoic acid hydrochloric acid was added and the acid precipitated. The precipitate was filtered off and crystallised from water.

Yield of 2-chloro-4-nitrobenzoic acid: 9 gms.

Melting point: 139°-140° C.

% Yield on theory: 29

% Yield on 4-nitro-o-toluidine: 15

5-Nitro-4':5'-dimethoxydiphenylamine-2-carboxylic acid (XXXII).

8 gms. (0.03 mole) of the potassium salt of 2-chloro-4-nitrobenzoic acid, 5.1 gms. (0.03 mole) of 4-aminoveratrole, 20 mls. of amyl alcohol and a trace of Copper bronze were refluxed at 125° C. for four hours. The solution was made alkaline and the amyl alcohol removed by steam-distillation. The liquor in the flask was filtered hot and the filtrate allowed to cool. The acid was precipitated by the addition of a slight excess of hydrochloric acid. It was filtered off, well washed with water and dried.

The compound could not be crystallised in a satisfactory manner from the usual solvents. Further purification was effected by dissolving in alkaline solution and reprecipitating the acid by the addition of hydrochloric acid.

Yield of the acid: 5.6 gms.

Melting point: appears to melt and decompose at 232° C.

% Yield on theory: 58

Analysis:

Found: % C, 55.89; % H, 4.23

Required for $C_{15}H_{14}O_6N_2$: % C, 56.60; % H, 4.40

Although at this stage the compound was not absolutely pure it was decided to attempt the prepara-

tion of the 3-nitro-6:7-dimethoxy-9-chloracridine from this impure diphenylamine-2-carboxylic acid.

3-Nitro-6:7-dimethoxy-9-chloracridine (XXXIII).

4.2 gms. of 5-nitro-4':5'-dimethoxydiphenylamine-2-carboxylic acid were refluxed with 25 mls. of phosphorus oxychloride for three hours at 150° C. The method used in this preparation was that outlined by Albert and Linnell (J.C.S. 1936, 1616).

The precipitate from the ammoniacal solution was filtered off, washed with dilute ammonia solution and dried. This crude compound was extracted with chloroform in a Soxhlet apparatus. The crystals obtained from the chloroform extract were recrystallised from chlorobenzene. The compound was obtained as fine, yellow, needle-shaped crystals which were filtered off and dried in air.

Melting point: 266°-268° C.

Analysis:

Found: % C, 56.77; % H, 3.43

Required for $C_{15}H_{11}O_4N_2Cl$: % C, 56.51; % H, 3.45

3-Nitro-6:7-dimethoxy-9-piperidino-acridine (XXXIV).

A small quantity of 3-nitro-6:7-dimethoxy-9-chloracridine was refluxed with excess of piperidine. The chloracridine slowly went into solution and after a short time reddish crystals commenced to separate out. Refluxing was continued for about fifteen minutes and then the source of heat was removed. When cold, the liquor was filtered and the crystals washed with water and dried.

Melting point: 224°-226° C.

Analysis:

Found: % C, 65.19; % H, 6.04

Required for $C_{20}H_{21}O_4N_3$: % C, 65.40; % H, 5.70

Synthesis IX.

4-Nitro-4':5'-dimethoxydiphenylamine-2-carboxylic acid (XXVI).

4.6 gms. (0.03 mole) of 4-aminoveratrole and 3.6 gms. (0.015 mole) of the potassium salt of 2-chloro-5-nitrobenzoic acid were refluxed for six hours in 15 mls. of amyl alcohol, a trace of Copper bronze being present. After refluxing, the solution was made alkaline with sodium hydroxide and the amyl alcohol removed by steam-distillation. The hot liquor was filtered and the filtrate acidified with hydrochloric acid. The precipitate was filtered off, washed with water and dried.

Yield: 3 gms.

Melting point: Melts and decomposes 191°-193° C.

% Yield on theory: 63

Analysis:

Found: % C, 54.67; % H, 4.20

% C, 54.16; % H, 4.97

Required for $C_{15}H_{14}O_6N_2$: % C, 56.6; % H, 4.4

2-Nitro-6:7-dimethoxy-9-chloracridine (XXXVII).

3 Gms. (0.01 mole) of 4-nitro-4':5'-dimethoxy-diphenylamine-2-carboxylic acid were refluxed with 18 mls. of phosphorus oxychloride for two hours. The phosphorus oxychloride was removed by washing with petrol-ether. The resulting sticky mass was cooled in ice and treated with an excess of ice-cold 10% aqueous ammonia solution. A yellowish solid was obtained which was filtered off, washed with 10% ammonia and dried. The dry solid was extracted with chloroform in a Soxhlet apparatus. The yellow, needle-shaped crystals obtained from the chloroform extract were recrystallised from chlorobenzene.

Yield: 1 gm.

Melting point: 275°-277° C.

Analysis:

Found: % C, 56.77; % H, 3.43

Required for $C_{15}H_{11}O_4N_2Cl$: % C, 56.51; % H, 3.45

Comparison with 2-nitro-6:7-dimethoxy-9-chloracridine prepared by Synthesis VI:-

Melting point on recrystallisation from chlorobenzene: 275°-276° C.

Analysis:

Found: % C, 56.53; % H, 3.46

Required for $C_{15}H_{11}O_4N_2Cl$; % C, 56.51; % H, 3.45

Mixed melting point of crystals from Syntheses VI and IX: 275°-276° C.

Yield from Synthesis VI: 0.5 gms. (15%)

Yield from Synthesis IX: 1.0 gm. (33%)

Other Acridine Derivatives

Synthesis X.

Preparation of 2-methoxy-6:9-dichloracridine (LX).

This compound was prepared by modifying the method outlined by Magidson et al. in E.P. 353, 537 and in Ber. 1936, 69, 404. These workers condensed 2:4-dichlorobenzoic acid with p-anisidine in amyl alcohol, potassium carbonate and copper being present. The 3'-chloro-4-methoxy-diphenylamine-6'-carboxylic acid was converted to the corresponding acridone by heating with phosphorus pentachloride in benzene, followed by treatment with aluminium chloride and subsequent hydrolysis of the product with hydrochloric acid. From the acridone the corresponding 9-chloracridine was obtained by treatment with phosphorus oxychloride or thionyl chloride.

It was found, as in other syntheses previously described, that the use of the potassium salt of o-chlorobenzoic acid in the preparation of the required diphenylamine carboxylic acid gave satisfactory results in the synthesis of the required 3'-chloro-4-methoxy-diphenylamine-6'-carboxylic acid (LVIII).

Cyclisation of 3'-chloro-4-methoxy-diphenylamine-6'-carboxylic acid.

To bring this preparation into line with similar acridine ring closures already studied, phosphorus oxychloride in chlorobenzene solution was used as the reagent and the 9-chloracridine derivative isolated without separation of the intermediate acridone.

3'-Chloro-4-methoxy-diphenylamine-6'-carboxylic acid (28 gms.) was mixed with mono-chlorobenzene (150 mls.) and phosphorus oxychloride (50 gms.) was added. The mixture was refluxed for one and a half hours, cooled in ice and treated with 400 mls. of light petroleum. The solid product which was deposited was washed with a small quantity of fresh light petroleum and then treated with an ice-cold 10% aqueous ammonia solution, the pasty solid being broken up to facilitate penetration of the alkaline solution. The yellow solid obtained was filtered off, washed, dried in vacuo and extracted with benzene in a Soxhlet apparatus. The crystals of 2-methoxy-6:9-dichlor-acridine were filtered from the benzene extract, washed with benzene and dried.

Yield:	19 gms.
Melting point:	161°C. (Lit. 161°C.)
% Yield on theory:	67

2-Methoxy-6-chloro-9-piperidino acridine (LXI).

A small quantity of the 2-methoxy-6:9-dichloracridine was refluxed with piperidine for c. half an hour and then the solution was allowed to cool. Reddish, needle-shaped crystals were obtained which were analysed.

Melting point: 147°-149° C.

Analysis:

Found: % C, 69.92; % H, 5.65

Required for $C_{19}H_{19}ON_2$: % C, 69.83; % H, 5.81

Synthesis XI.

Preparation of 3'-chloro-4-acetylamino-diphenylamine-6'-carboxylic acid (LXIV).

24.8 Gms. (0.1 mole) of the potassium salt of 2:4-dichlorobenzoic acid and 16.2 gms. (0.1 mole) of p-aminoacetanilide were refluxed together in 60 mls. amyl alcohol for four hours, a trace of Copper bronze being present. The hot solution was made alkaline, steam-distilled to remove amyl alcohol, and the hot solution was filtered. The filtrate was made acid with dilute hydrochloric acid and allowed to cool.

The resultant precipitate appeared to be made up of two compounds, one blue in colour and the other a whitish colour.

The crude blue compound melted in the region of 207°C. and appeared to decompose c. 214°C.

The crude white compound melted and decomposed at 225°C. On recrystallisation from benzene the melting point rose to 228°-230°C.

It appeared probable that in the above treatment hydrolysis had occurred and a mixture of the acetyl derivative and the amino-hydrochloride had been obtained.

The crude product was refluxed for two and a half hours in a 1:1 mixture of ethyl alcohol and concentrated hydrochloric acid. The hot liquor was filtered and the crystals which separated on cooling were filtered off, washed with a little alcohol and dried. A small quantity of the product was recrystallised from alcohol and analysed.

Melting point: 256°C. (Decomposes)

Analysis:

Found: % C, 52.41; % H, 4.25

Required for $C_{13}H_{11}O_2N_2Cl$: % C, 52.17; % H, 4.01

It was decided that the hydrochloride of the 4-amino-3'-chloro-diphenylamine-6'-carboxylic acid

obtained above was pure enough for the next stage.

Preparation of 2-amino-6:9-dichloracridine hydrochloride (LXVI).

3 Gms. of the hydrochloride of 4-amino-3'-chlorodiphenylamine-6'-carboxylic acid and 18 mls. of phosphorus oxychloride were refluxed for four hours. On cooling, the cold liquor was washed with petrol-ether to remove phosphorus oxychloride and the resultant pasty mass was treated with excess ice-cold, 10% ammonia solution. The final product could not be crystallised from the usual solvents and was prepared for analysis by dissolving in alcoholic sodium hydroxide solution, filtering and reprecipitating the salt of the base by addition of hydrochloric acid. The precipitate so obtained was filtered off, washed with a small quantity of water and dried.

Melting point: over 330° C.

Analysis:

Found: % C, 53.05; % H, 2.97

Required for $C_{13}H_8N_2Cl.HCl$: % C, 52.80; % H, 3.00

All analyses recorded in this work were performed on the micro-scale.

Temperatures are quoted as direct readings and are uncorrected.

ACKNOWLEDGMENTS.

The author wishes to thank Dr. H.B. Nisbet for the interest he has shown in this work and for his advice and encouragement throughout its entire course.

The analyses recorded in this work were performed in the Heriot-Watt College by Mr A.T. Macdonald, whose assistance is acknowledged very gratefully.

Imperial Chemical Industries Limited are thanked for a generous grant which enabled the author to carry out this work, and also for gifts of certain chemicals.