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ASPECTS OF THE FORMATION AND USE OF STENHOUSE SALTS AND RELATED COMPOUNDS

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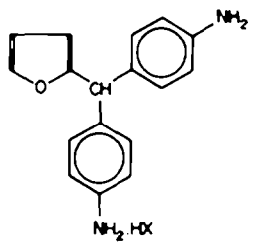
INTRODUCTION

The purple crystalline salts formed from the reaction of two molecules of aromatic primary amine with one molecule of furfuraldehyde in the presence of at least one molecule of hydrochloric acid were first isolated by Stenhouse.[1,2] In subsequent years similar salts were prepared by Schiff,[3-5] Zincke and Mühlhausen[6] and Borsche, Leditschke and Lange[7] from a variety of primary and secondary amines. Schiff[3] reported that tertiary amines such as dimethylaniline gave no formation of coloured salts under such conditions. Fischer[8] and Renshaw and Naylor[9] showed that with dimethylaniline a diphenylfurylmethane leuco base was formed which after subsequent oxidation yielded an analogue of Malachite green. Schiff[3] suggested, despite the lack of formation of coloured salts from tertiary aromatic amines, that the Stenhouse salts possessed a triphenylmethane type structure **1**. Zincke and Mühlhausen[6] on the other hand, preferred an open chain representation **2** which was based on analogy with the formula proposed by Zincke[10] for the products formed in the ring opening of pyridine with chlorodinitrobenzene, and this view was favoured by other workers.[11-13]

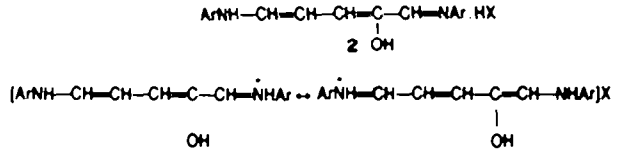
Following upon a revival of interest in these compounds in *ca.* 1940, Riegel and Hathaway[14] put forward evidence in support of the triphenylmethane type structure **1** but the evidence was added to by Williams and Wilson[15] and reinterpreted by them in terms of the hydroxyglutaconic aldehyde dianil formula **2** of Zincke.[6] Koelsch and Carney[16] provided further support for the open chain structure from hydrogenation experiments leading to a 1,5-dicyclohexylaminopentane system while Foley *et al.*[17] first explicitly stated that such a structure must represent a resonating system **3**. All subsequent work has been based upon formula **3**, and PMR studies[18] of similar systems are in agreement with a planar all *trans* structure.

Products derived from the treatment of Stenhouse salts with base and of furfuraldehyde with aromatic amines

Stenhouse[2] had made unsuccessful attempts to isolate the free base corresponding to the purple salt and had obtained a plastic mass which, if treated immediately with concentrated acid re-formed the typical purple salt but which after standing overnight gave no such colour with acid. Other workers also tried unsuccessfully to isolate this free base[3,5,6] until McGowan[19] eventually isolated a creamy coloured solid ($C_{17}H_{16}N_2O$) for which he proposed the possible structures **4a, b** mainly upon chemical and UV spectral evidence. Subsequently the structure was revised[20] to **5**, principally upon the basis of the observation of IR carbonyl absorption around 1710 cm^{-1} which was assigned to a carbonyl group in a saturated 6-membered ring. McGowan also reported[20] that the same substance could be isolated simply by heating together in alcohol solution 2 moles of aromatic amine and 1 mole of furfuraldehyde, a technique which had earlier been used by Rombaut and Smets[21] who had accepted McGowan's initial structure **4** for the products they had isolated by treating furfuraldehyde and various furfuraldehyde anils with a wide variety of substituted aromatic amines. In their review Dunlop and Peters[22] also suggested structure **5** for these products. In 1961 Barvinok *et al.*,[23] by using the neat reagents plus a trace of hydrochloric acid, obtained a compound which they considered identical with that of McGowan. They investigated the mild catalytic hydrogenation of the product and obtained both a dihydro and a tetrahydro derivative. They interpreted the change in infrared carbonyl absorption frequency upon formation of the dihydroketone (from 1710 cm^{-1} to 1750 cm^{-1}) as favouring a 5-membered 3-pyrrolidone ring system for the dihydroketone and so suggested structure **6** for the parent.[24,25] A further investigation by Lewis and Mulquiney[26,27] showed, mainly from PMR evidence (Fig. 1), that the compound isolated, either by base treatment of the Stenhouse salt or from the nominally neutral heating of furfural with aniline in alcohol solution, had the carbocyclic structure **7** rather than a heterocyclic one. In agreement with McGowan[19] it was found that only a monoacetyl and a monobenzylidene derivative was isolable. Initial evidence for the second -NH-Ar group was obtained from PMR and mass spectral deuterium exchange experiments on the parent. This was confirmed by the PMR spectrum of the monoacetyl derivative of **7a** which still showed one exchangeable proton and in the IR spectrum showed typical N-Ac carbonyl absorption, excluding the possible formation of an enolic acetate. The simplification of the signal attributed to H4 in the PMR spectrum of **7a**, together with its downfield shift upon acetylation (from δ4.67 to 6.12), indicated which of the two NH groups formed the stable acetyl derivative. A di-



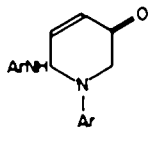
1



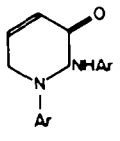
2

3

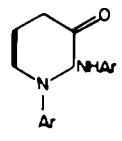
3a: Ar = C_6H_5
3b: Ar = m-NO_2-C_6H_4
3c: Ar = p-NO_2-C_6H_4
3d: Ar = 4-CH_3, 3-NO_2-C_6H_3
3e: Ar = p-CH_3-C_6H_4
3f: Ar = p-Cl-C_6H_4



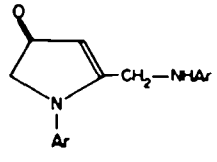
4a



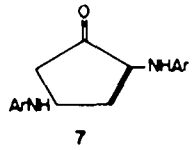
4b



5

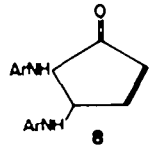


6



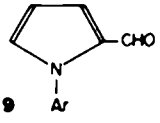
7

7a: Ar = C_6H_5
7b: Ar = m-NO_2-C_6H_4
7c: Ar = p-NO_2-C_6H_4
7d: Ar = p-Cl-C_6H_4
7e: Ar = m-Cl-C_6H_4

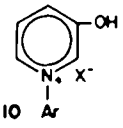


8

8a: Ar = p-NO_2-C_6H_4
8b: Ar = m-NO_2-C_6H_4
8c: Ar = o-NO_2-C_6H_4
8d: Ar = C_6H_5



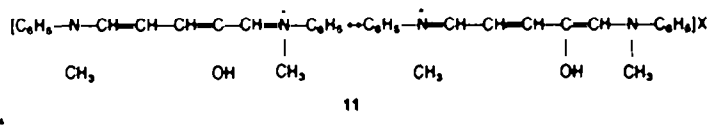
9



10

9a: Ar = p-NO_2-C_6H_4
9b: Ar = m-NO_2-C_6H_4
9c: Ar = 4-CH_3, 3-NO_2 C_6H_3
9d: Ar = C_6H_5

10a: Ar = C_6H_5
10b: Ar = p-CH_3 C_6H_4
10c: Ar = p-NO_2-C_6H_4



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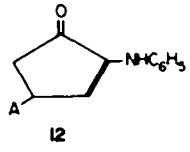
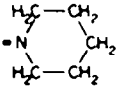


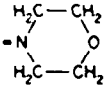
12

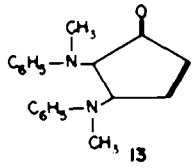
12a: A = $NHCH_3$
12d: A = $CH(CO_2CH_3)_2$
12e: A = SO_3Na
12f: A = OMe

12b: A =

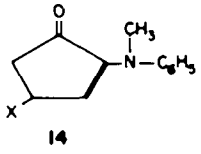


12c: A =





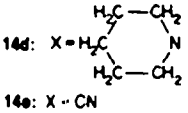
13



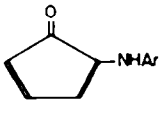
14

14a: X = C_6H_5N
14b: X = C_6H_5NH
14c: X = MeO

14d: X =

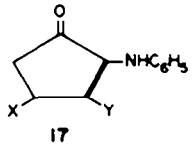


14e: X = CN



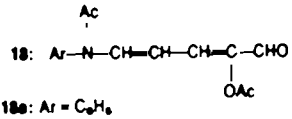
16

16a: Ar = C_6H_5
16b: Ar = p-Cl C_6H_4
16c: Ar = m-Cl-C_6H_4



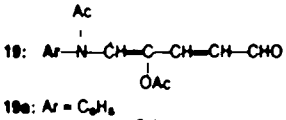
17

17a: X = H, Y = Br
17b: X = Br, Y = H
17c: X = C_6H_5-NH, Y = Br



18

18a: Ar = C_6H_5
18b: Ar = p-CH_3-C_6H_4
18c: Ar = p-Cl-C_6H_4



19

19a: Ar = C_6H_5
19b: Ar = p-CH_3-C_6H_4
19c: Ar = p-Cl-C_6H_4

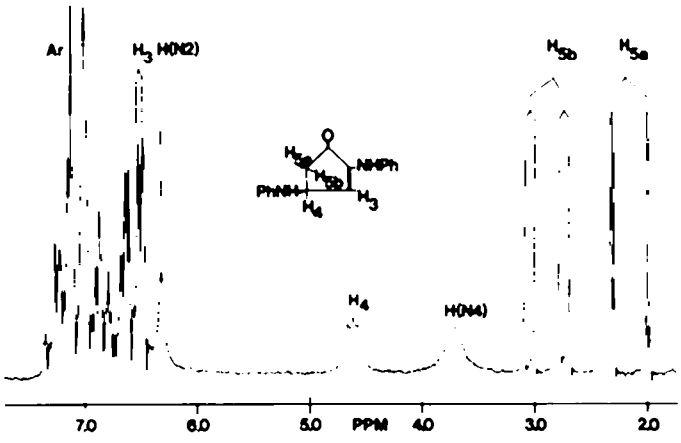


Fig. 1.

N-acetyl derivative could not be obtained and the reason for this is not clear. It is possible that approach to the NH attached to C2 is sterically hindered or that, as part of an enamine system, it is unreactive. Another alternative, based on attempts to synthesise a model compound of type 7, is that the acetyl derivative is very readily hydrolysed (see later section).

Hydrogenation to the dihydroketone stage yielded a pair of isomeric derivatives,[27] addition of hydrogen occurring from both sides of the ring system. The formation of two isomers of the dihydroketone is expected on the basis of the cyclopentenone structure 7. Both isomers showed signals for two exchangeable NH protons in their PMR spectra. Finally the tetrahydro compound formed an N,N',O-triacetyl derivative under vigorous conditions.

McGowan[19,20] had used aniline and *p*-toluidine as aromatic amines and the reaction was extended[27] to include *p*-anisidine and *p*-bromoaniline, with the products in each case showing closely similar PMR spectra in the region of the cyclopentenone ring protons. Rombaut and Smets[21] had included *m*-nitroaniline in their examination, and they reported that from this amine three isomeric products were obtained depending on the conditions used. This work was repeated and eventually two isomers only were obtained,[29] the reported third isomer being attributed to differences in methods of m.p. determination used by the original workers. One of the pair, on the basis of its IR and PMR spectra, was assigned structure **7b**. The other showed similar carbonyl absorption at 1710 cm^{-1} but lacked the strong C=C band at 1645 cm^{-1} typically present in compounds of type 7 and its PMR spectrum lacked the characteristic AB quartets of the methylene group adjacent to carbonyl, no proton absorption upfield from δ4.0 being observed. The products derived from the reaction of *o*- and *p*-nitroaniline with furfuraldehyde had properties in agreement with those reported by Rombaut and Smets[21] but showed IR and PMR spectral properties similar to those of the latter *m*-nitroaniline isomer. In the case of the compound derived from *p*-nitroaniline, deuterium exchange of the active protons on nitrogen led to appreciable simplification of the PMR spectrum, and revealed the signals of two further protons which had been hidden under those of the NH protons. Spin decoupling experiments then enabled structure **8a**[30] to be assigned (Fig. 2). Similar results were obtained with the isomeric products derived from the *o*-

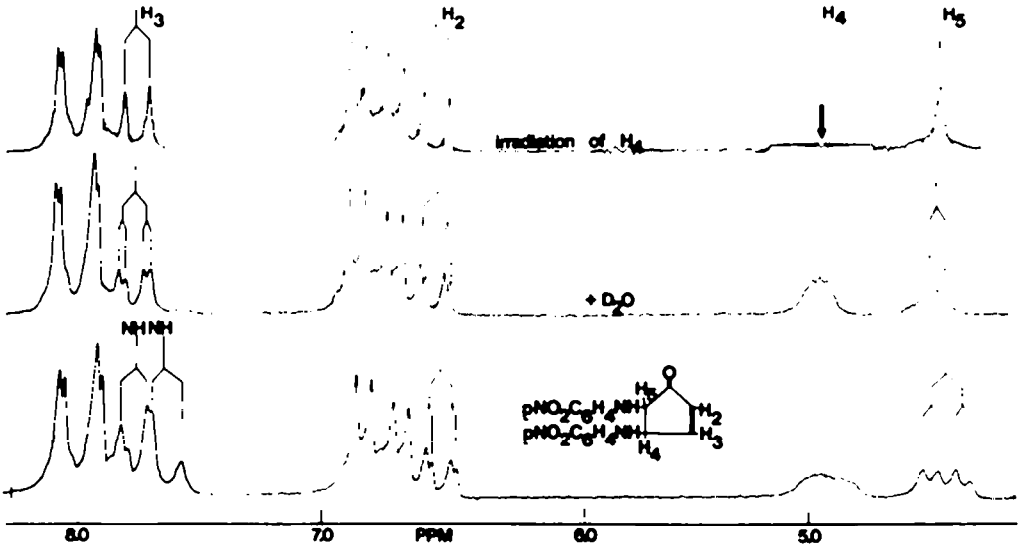
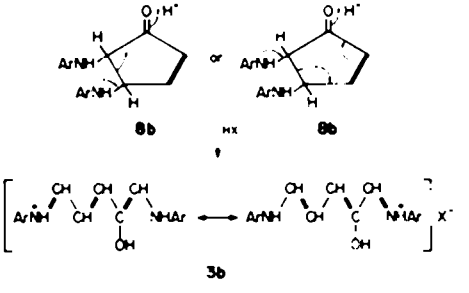


Fig. 2.

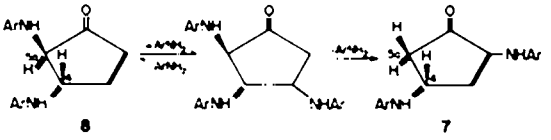
and *m*-nitroanilines although, in the former case, one of the vinyl proton signals was obscured by the absorption of the aromatic protons. On the basis of the values of J4-5 a *trans* arrangement of protons H4 and H5, and thus of the two arylamino groups in **8** is proposed.

A subsequent fairly extensive survey[29] covering about thirty-five amines showed that in most cases reaction of non-hindered primary aromatic amines with furfuraldehyde gave products of type **7**. Where the amine group was flanked by two bulky substituents no reaction occurred (e.g. 2,4,6-tribromoaniline), while the presence of two nitro groups also prevented reaction (2,4- and 3,5-dinitroanilines). In only the one case, that of *m*-nitroaniline, was it found readily possible to isolate two isomeric forms while only two further examples of primary amines forming readily isolable products of type **8** were found. The conditions used[21] for the isolation of the isomer **7b** involved a prolonged reflux period in ethanol, and gave a quite small yield of product, while **8b** was formed in good yield if the reflux time was short. It seemed possible that **8b** was slowly being converted in part to **7b** and to other products. In attempts to achieve more controllable conversion into **7b** in better yield, a variety of solvents and possible catalysts were tried. In attempting to catalyse the reaction with acids it was found that the room temperature addition of strong acids to **8b** in a variety of solvents led to the precipitation of the corresponding Stenhouse salt in essentially quantitative yield. This interesting facile opening of the cyclopentenone ring is suggested to occur by protonation of the ketonic oxygen as follows:



Acetic acid was found to catalyse the transformation of **8b** to **7b** without giving rise to the Stenhouse salt. The presence of a small amount of free *m*-nitroaniline also improved the conversion and when both compounds were heated with **8b** in butan-2-one solution a good yield of **7b** resulted. Similar treatment of **8a** gave the previously unknown **7c** in 80% yield.

The above conversions suggested that the 2,4-diarylaminocyclopent-2-enone system **7** is the more stable form, with the possibility that the 4,5-diarylamino-isomer **8** is an intermediate in its formation from the reaction of furfural with aromatic amines. The suggested stability order is supported by a study[29] of the coupling constants between H3-H4 and H4-H5a in both series. The J values for these protons in structures of type **7** are in good agreement with those observed[31] for various substituted cyclopent-2-enones where the ring is most probably planar.[32] Comparison of the corresponding J values of the 2,4-type **7** with those of the 4,5-type **8** (in both **7** and **8** the δH4 values are very close) shows a decrease in $J_{H3\text{-}H4}$ (from *ca.* 2.9 to 1.9 Hz) and an increase in $J_{H4\text{-}H5a}$ (from *ca.* 1.9 to 3.3 Hz) in going from **7** to **8**. This would suggest that the dihedral angle between the H4 and H5a bonds is greater in the latter and that the cyclopentenone ring is distorted in **8**. Examination of space filling molecular models (Courtauld type) also indicates a steric crowding of the *trans* diarylamino groups and a non-planarity of the cyclopent-2-enone ring. Thus **7** would be expected to be more stable than **8** and if conversion of **8** into **7** occurs by amine addition to form the crowded 2,3,4-triarylaminocyclopentanone, subsequent β-elimination should favour the formation of **7** as observed.



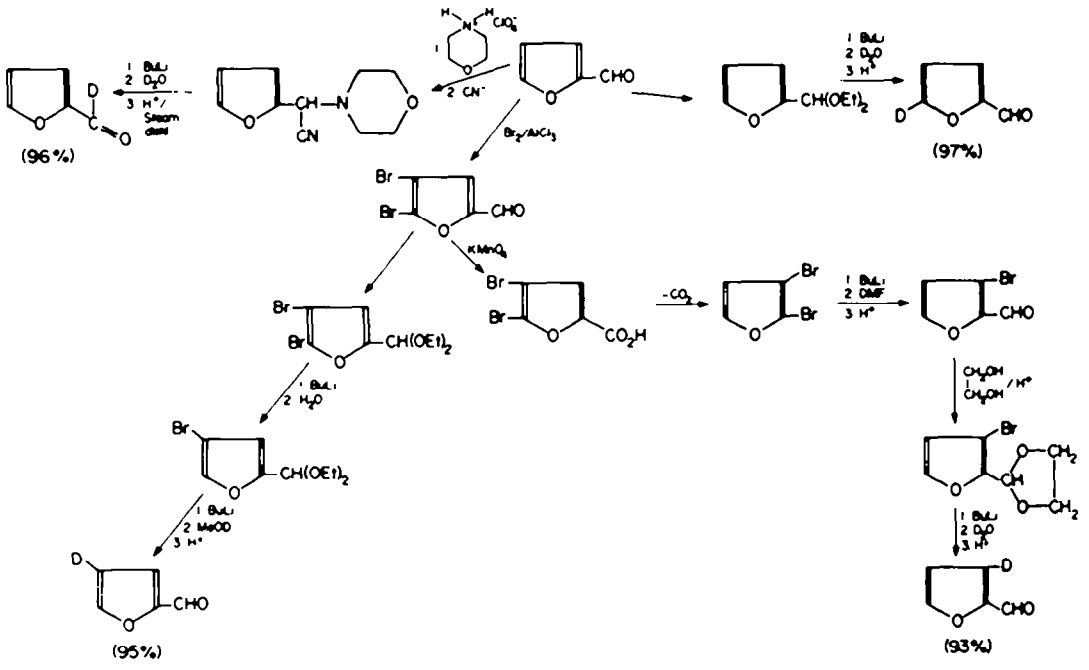
Re-examination of various furfuraldehyde-aromatic amine reaction mixtures subsequently gave evidence (by thin layer chromatography) that two products having the characteristics of the types **7** and **8** were almost invariably present. The difference in R_f between compounds of the two types was considerable but attempts to isolate (by PLC) the intermediate having R_f and colour reaction with acid typical of type **8** were unsuccessful, as the product eventually isolated was, in all cases, the more stable 2,4-diarylamino type **7**. It is evident that with simple aromatic amines the 4,5-diarylaminocyclopent-2-enone system is relatively labile but there is little doubt that compounds of type **8** are intermediates in the formation of the stable products **7**.

Mechanism of formation of diarylaminocyclopent-2-enones 7 and 8

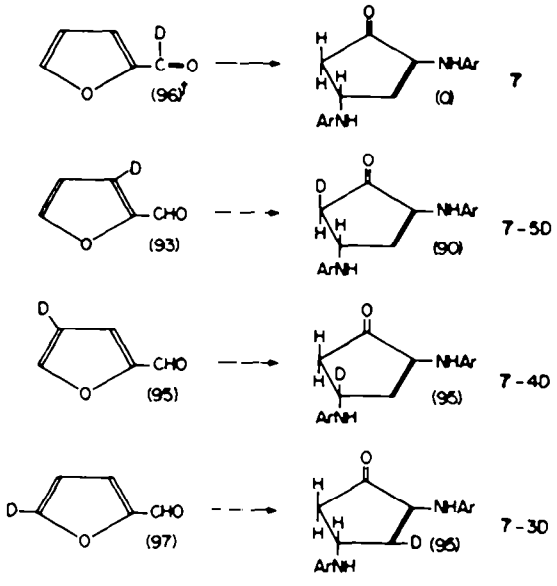
In the initial work when only 2,4-diarylaminocyclopent-2-enones **7** had been isolated it was obvious from the attachment of the nitrogen atoms relative to the carbon carrying oxygen that some form of rearrangement had taken place. As a simple probe to follow this it was considered that the mono-deuterated furfuraldehydes would be useful. At that time only the 5-deuterated isomer had been reported[33] and so methods were devised for the synthesis of the four possible monodeuterated furfuraldehydes† (see Scheme 1). In most cases the reactions were straightforward and gave excellent incorporation of deuterium. It had been expected that the reaction procedure of Walborsky and Niznik[34] involving the reaction of furyl-lithium with 1,1,3,3-tetramethylbutylisonitrile would give a simple route to furfuraldehyde-α-D. In the event only recovered isonitrile was obtained although the respective reagents gave furoic acid or pentanal under the usual reaction conditions. A successful synthesis of furfuraldehyde-α-D was finally achieved by a modification of the method used by Bennett *et al.*[37] for benzaldehyde-α-D. When these deuterated substrates were treated with aromatic amines the position of the label in the resulting cyclopentenone **7** was as indicated.

It thus seemed possible that the C2 vinyl carbon of **7** could be the original aldehyde carbon and that the carbonyl carbon was C2 of the furan ring. Fortunately by this stage the isolation of the compounds of 4,5-diarylamino type **8** from the nitroanilines had been observed and so the

†Subsequently a number of publications have appeared in which some or all of the monodeuterated furfuraldehydes have been prepared.[34,35]



Scheme 1.

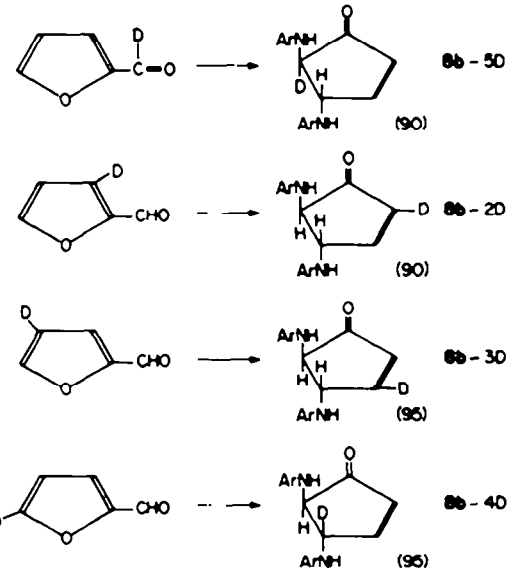


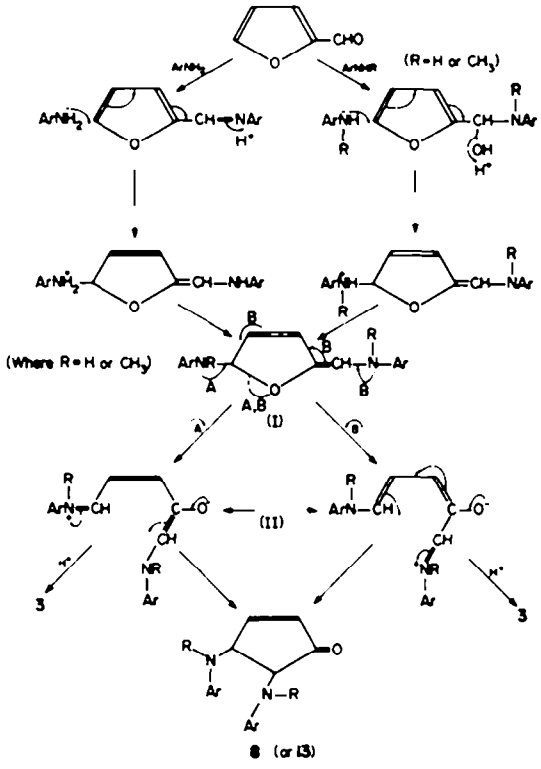
†The figures in parentheses represent percentage deuterium incorporation.

deuterated aldehydes were employed again with the *m*-nitroaniline. The results are as shown below.

In the latter series the position of the deuterium atom locates the carbon atoms nicely and the two arylamino groups now appear attached to carbon atoms which are sensibly related to the known reactions of furan derivatives. One arylamino group obviously initially arises by anil formation while the second is introduced by nucleophilic attack of amine at position 5 of the furfuraldehyde anil. In general this type of attack is not seen in the simple case of furfural which is stable to acidic conditions,[38] but is common in the ring opening of other furan derivatives such as furfuryl alcohol,[39-41] related furan methanols[42] and similar precursors such as furfuryl acrylic acid[43] and related furfurylidene ketones[44,45] under the influence of acids. While the reactions of furfuraldehyde with aromatic amines have been run under nominally neutral conditions[20,21] there would appear to have been no attempts made to ensure the absence of traces of acid. (These are usually present in samples of furfuraldehyde that have not been rigorously purified.[46]) In our preferred procedure for preparation of **7a** the reagents are left at room temperature in ether solution and stoppered only with dried cotton wool. The reaction proceeds slowly over several days but the yields are good and tar formation is minimised.

A trace only of acidic catalyst is required as nucleophilic attack at C5 of the furfuraldehyde anil and subsequent proton loss provides a continuing source of acid catalyst. When the deuterated products of type **8b**

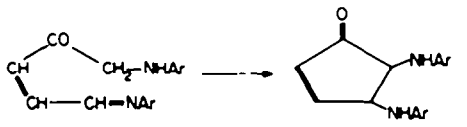




Scheme 2.

were subjected to conditions which led to conversion into those of type **7b** the label (except in the case of **8b**-5D where, as predicted above, it was completely lost) was completely retained and appeared in the expected position. The suggested mechanism for the reaction is outlined in Scheme 2. Formation of the intermediate (I) in Scheme 2 is followed by ring opening to form an open chain intermediate (II) which is ideally set up for internal cyclisation to form the 4,5-diarylamino derivative **8**. In the presence of an excess of strong acid the open chain intermediate is probably trapped by reaction with proton to form the Stenhouse salt although this could be formed in a sequential reaction, with formation of the 4,5-diarylamino type **8** being followed by ring opening by acid, since, as indicated earlier, this reaction proceeds readily at room temperature in the same solvent as that usually employed for preparation of the Stenhouse salts.

The observed complete deuterium retention at C5 of **8b** excluded what had been an initial postulate we had made concerning this reaction; namely that it proceeded through an open chain intermediate where ring closure



occurred, as suggested by the experiments of Blatt and Gross,[47] by intramolecular reaction of the active methylene group with the anil to form **8b**. This sequence would lead to **8b** with a maximum of 50% D incorporation at C5. The observed complete retention of the deuterium label rules out this possibility.

The formation of 2,4-diarylaminocyclopent-2-enones **7** from Stenhouse salts when treated with sodium hydroxide as first observed by McGowan[19] fits simply into the mechanism proposed above. Abstraction of the hydroxyl proton from the Stenhouse salt leads directly to the postulated intermediate (II).

Reactions of Stenhouse salts under acid conditions

A number of Stenhouse salts derived from simple amines had not been reported previously and in attempting to prepare the unknown salt from *p*-nitroaniline the components were mixed in alcohol containing concentrated hydrochloric acid and the red-violet solution gently warmed. After cooling, instead of the purple salt, a yellow solid separated. The Stenhouse salt was subsequently prepared by mixing the cold reagents and keeping the reaction mixture chilled. The yellow solid was identified as N-*p*-nitrophenylpyrrole-2-aldehyde **9a** and investigation of the literature indicated that we had "re-discovered" a preparation reported by Yanovskaya[48] and Petit and Pallaud.[49] The latter workers claimed that the reaction only proceeded with *m*- or *p*-nitro substituted amines. The formation of the transient violet colour during the preparation of the product **9a** suggested that the usually sparingly soluble Stenhouse salt was being rapidly decomposed. Treatment of the isomeric *m*-nitro Stenouse salt under similar conditions gave the corresponding aldehyde **9b** in fair yield and subsequently it was found that a wide variety of Stenhouse salts reacted similarly to form the N-arylpyrrole-2-aldehyde in varying yields (see Table 1). It is,

Table 1. Yields of products isolated from the acid hydrolysis of Stenhouse salts **3**

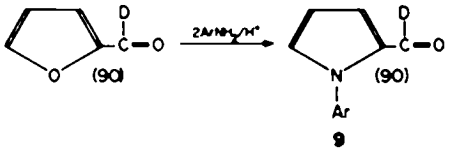
3	**9**	Products	**10**
p-$NO_2C_6H_4$	80%		none
3-NO_2,4-ClC_6H_3	26*		not isolated
m-$NO_2C_6H_4$	37*		17
4-CH_3,3-NO_2	33**		16**
p-ClC_6H_4	18		not isolated
p-$CH_3C_6H_4$	11		60
C_6H_5	12		58

* The actual yields are probably higher than shown. Considerable loss (up to 30%) occurred when the solutions were decolourised with charcoal.

** With no acid added.

of course, unnecessary to isolate the Stenhouse salt, as it suffices simply to mix furfuraldehyde and the amine with hydrochloric acid, warm and then extract. The yields of pyrrole aldehyde **9** are not large in many cases, but the reaction is a rapid one-step process and, where the amine is cheap, provides a simpler approach to N-arylpyrrole-2-aldehydes than those reported previously.[50,51]

When the Stenhouse salt **3d** was warmed in methanol in the absence of added acid a crystalline solid was isolated which was shown to be the corresponding anil of the pyrrole aldehyde, which on hydrolysis with dilute acid readily formed the aldehyde **9c**. As the various deuterated furfuraldehydes were available these were converted into the Stenhouse salts and thence to the corresponding pyrrole aldedhyes **9**. In each case the deuterium atom was quantitatively retained and was in the same relative position as in the starting furfuraldehyde.



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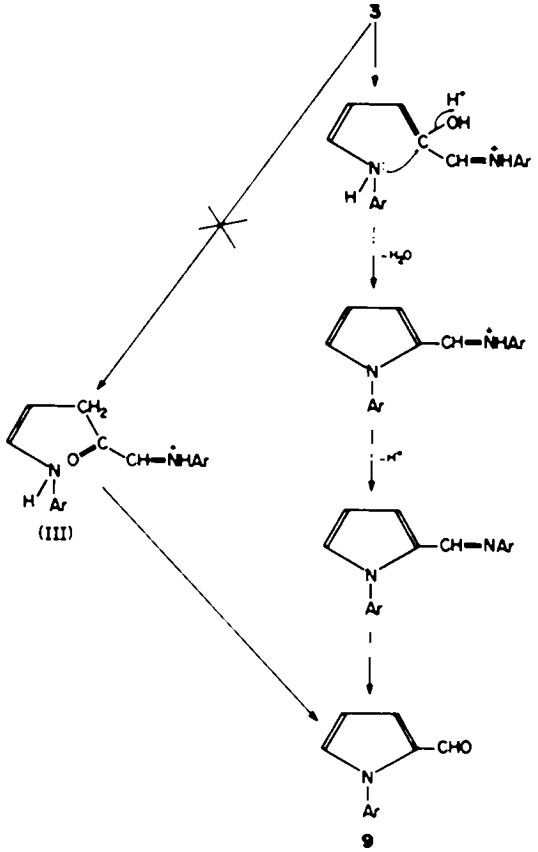
The suggested mechanism of formation of the N-phenylpyrrole aldehydes is shown in Scheme 3.



Scheme 3.

As before the essentially complete retention of deuterium during the conversion of the Stenhouse salts into the aldehydes **9** excludes the formation of a ketonised intermediate such as III. It has been long known[6,7,14,16] that the heating of Stenhouse salts under acid conditions yields N-aryl-3-hydroxypyridinium salts. The conditions used by Koelsch and Carney[16] are similar to those used above for the formation of the N-arylpyrrole-2-aldehydes **9** and consequently after isolation of the aldehydes the mother liquors were concentrated and diluted with acetone. In most cases a creamy insoluble solid separated which after purification proved to be the N-aryl-3-hydroxypyridinium salt **10**. Under ordinary conditions at 60 MHz the ABMN signals of the pyridinium ring protons could not be solved by a first order analysis. When the Stenhouse salt **3e** derived from furfuraldehyde-αD was employed, a product was obtained having 90% deuterium incorporation at C2 of the pyridinium ring as judged from the chemical shifts and coupling constants of the signals in the simplified PMR spectrum.

It is of interest that the integrity of the deuteration pattern is maintained in the Stenhouse salts derived from specifically labelled furfuraldehydes. The resonance stabilised salt **3** has an unsymmetrical locating group in the hydroxyl which preserves the deuterium relationship with respect to the individual amine residues.

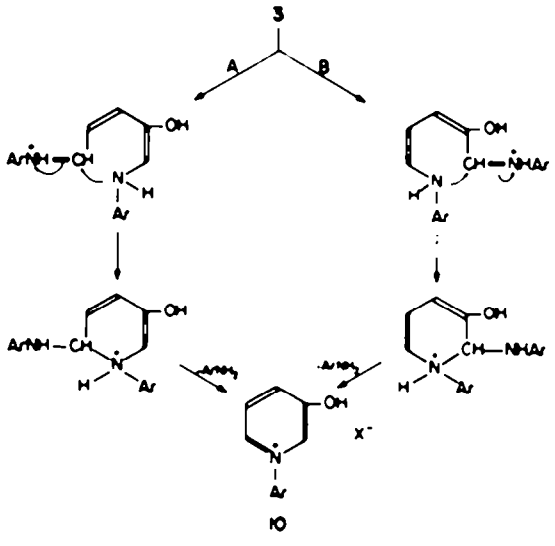
Formation of both 3-hydroxypyridinium salts **10** and N-arylpyrrole-2-aldehydes **9** from the Stenhouse salts **3** occurs concurrently under aqueous acid conditions, with the proportion of the compounds isolated varying with the amine present. It is tempting to assume that the pyridinium salts are formed in a manner similar to that described for the formation of N-phenylpyridinium chloride from 5-anilino-N-phenyl-2,4-pentadienylideniminium chloride.[52,53] This reaction has been shown to occur in quantitative yield for various aryl substituted derivatives at approximately the same rate, in different solvents, in the presence of acid or base, and is considered to proceed via an electrocyclic process of the conjugate base of the salt cation.[52,53]

It seems unlikely that a similar suggestion for the cyclisation of Stenhouse salts **3** is feasible as upon treatment with base deprotonation occurs at the hydroxy group with subsequent reaction to form **7** or **8** while under neutral conditions reversion to furfuraldehyde anil occurs while even under acid conditions the Stenhouse salt **3c** appeared to form no detectable amount of the pyridinium salt **10c**.

Any attempt to formulate a reasonable mechanism must consider the suggestion that the function of the acid is to keep the 2-hydroxy group in the enolic form, which remains unchanged while a nucleophilic intramolecular addition takes place between either of the nitrogen lone pairs and the $CH{=}NH^+$ of the protonated anil as in Scheme 4.

Incorporation of deuterium into the product when furfuraldehyde-αD was used indicated labelling at C2 of the 3-hydroxy-pyridinium salt **10** in agreement with the proposed mechanism. The reaction has been carried out in hot acetic acid,[14] methanol[16] and nitrobenzene[22] as well as in hot aqueous ethanol, conditions which could readily bring about the number of *trans-cis* interconversions necessary for the addition to proceed.

The same 3-hydroxypyridinium salt **10** is formed regardless of which path is followed in Scheme 4. It should be noted that any attempt to use two different aryl substituents in compounds of structure **3** to see if either Path A or B dominates the cyclisation, must include precautions to prevent amine exchange in the anil[54] occurring before cyclisation takes place.



Scheme 4.

Reversibility of Stenhouse salt formation

In an attempt to isolate the anil of N-phenylpyrrole-2-aldehyde **9d** the Stenhouse salt **3a** was boiled with aqueous methanol and the cooled reaction mixture then extracted with light petroleum. Somewhat surprisingly no N-phenylpyrrole-2-aldehyde was isolated, the product being an oil from which aniline and N-furfurylidene aniline (in 22% yield) were obtained. From the mother liquors a quantity of N-phenyl-3-hydroxy-pyridinium chloride was isolated (26% yield). It is apparent that the ring opening of furfuraldehyde in the presence of aniline and acid to form the Stenhouse salt is a reversible process under suitable conditions. Reversal to the furan system liberates acid in the presence of which transformation of some of the unreacted Stenhouse salt to pyridinium salt **10a** occurs. This reversibility was confirmed by the examination of the behaviour of the Stenhouse salt **11** derived from N-methylaniline. Here the formation of the N-substituted pyrrole-2-aldehyde **9** or the N-aryl-3-hydroxypyridinium salt **10** is not possible. Heating the Stenhouse salt in aqueous alcoholic solution gave an ether soluble gum consisting of N-methylaniline and furfuraldehyde while from the aqueous residue N-methylanilinium bromide was obtained.

Reactions of Stenhouse salts with nucleophiles

When it was established that treatment of the Stenhouse salts with sodium hydroxide yielded compounds of type **7** the removal of the acidic proton of **3a** was attempted under milder conditions by treatment with aliphatic amines. Methylamine gave an oil shown from its PMR spectrum to be 2-anilino-4-methylaminocyclopent-2-enone **12a** and subsequently crystalline solids of similar structure (**12b** and **12c** respectively), were obtained using piperidine and morpholine while use of piperazine gave the related bis-derivative. Treatment of the Stenhouse salt with sodiodimethylmalonate also gave a similar product **12d**.

Subsequently reinvestigation[9] of the reaction of Stenhouse salts with sodium sulphite[14] showed that here again a product of similar structure **12e** was formed.

In all the above examples it is considered that the first step is the removal of proton from the hydroxyl of the Stenhouse salt followed by cyclisation to form the 4,5-dianilino compound **8** as in Scheme 2. The excess nucleophile then adds to the unhindered C=C of the α,β-unsaturated carbonyl system to form the trisubstituted cyclopentanone which then eliminates a molecule of aniline to form the 2-anilino-4-substituted cyclopent-2-enone system **12**, in a process similar to that suggested earlier for the conversion of **8** into **7**.

Reaction of 2,4-dianilinocyclopent-2-enone with acid

McGowan[10] stated that treatment of the substances now assigned structure **7** with mineral acid regenerated the Stenhouse salt. In our experience the formation of Stenhouse salts occurred only when compounds of type **8** were treated with strong acids. UV spectroscopic investigation of the colour formed when concentrated hydrochloric acid was added to the dianilino compound **7a** in alcohol revealed that initially a broad weak band absorbing at λ_{max} 528 nm appeared (cf λ_{max} 519 nm ϵ 72,000 for the Stenhouse salt **3a**). On standing, a deep brown colour appeared. The broadness of the absorption suggests that no single chromophore is present and certainly that no simple reversion to Stenhouse salt occurs. When a solution of the Stenhouse salt **3a** was diluted in spectroscopic ethanol (carefully purified), the absorption at λ_{max} 519 nm was almost entirely replaced by absorption in the UV region at λ_{max} 245 and 289 nm. Immediate addition of one drop of concentrated hydrochloric acid to the solution regenerated the absorption typical of the Stenhouse salt. If the solution was allowed to stand for some hours before re-acidification then very little absorption around λ_{max} 519 nm was apparent. The absorptions observed at λ_{max} 245 and 289 nm together with the immediate regeneration of the Stenhouse salt suggest that initially the 4,5-dianilino compound **8d** is formed in solution and that this subsequently slowly transforms to the more stable **7a** isomer.

Secondary amine and furfuraldehyde

An initial attempt to prepare the N-methyl substituted Stenhouse salt **11** using the method of Hafner and Asmus[11] was unsuccessful. Reaction of N-methylaniline with furfural was then examined, either with the neat reagents or in alcohol solution. Purification of the product by molecular distillation gave a product the PMR spectrum of which showed that it possessed the 4,5-type structure **13**. The cyclic enone was very sensitive to acids and readily formed the orange coloured N-methyl Stenhouse salt when treated with hydrochloric or hydrobromic acid.

In view of the fairly ready conversion of the 4,5-diarylamino compounds **8** into the 2,4-type **7** attempts were made to transform the 4,5-di-N-methylanilino compound **13** into the corresponding 2,4-type derivative **14a** but these were unsuccessful. Heating the compound with a small amount of free N-methylaniline in the presence of a weak acid catalyst gave no conversion to the 2,4-type. Similarly heating with aniline gave no displacement to form the expected compound **14b**. On the other hand when the Stenhouse salt **11** was heated with methanolic sodium carbonate solution the expected 4,5-N-methylanilino derivative **13** was obtained admixed with 4-methoxy-2-(N-methylanilino)-cyclopent-2-enone **14c**. Treatment of **13** subsequently with sodium methoxide in methanol gave the methoxy compound **14c** in good yield. Similar products **14d** and **e** were obtained when piperidine and cyanide ion reacted with **13** although in the latter case further reaction occurred.

The failure to effect conversion of the 4,5-di-N-methylanilino compound **13** into the 2,4-di-N-methylanilino type **14** was surprising. Examination of space-filling molecular models (Courtauld type) indicated a considerably greater degree of steric hindrance of the C=C bond when the N-methyl derivative **13** was compared with the NH derivative **7**, so that the explanation of the failure to effect conversion is probably a steric one where the bulky, weak nucleophile, N-methylaniline, is unable to add to the conjugated enone system while the smaller, more powerful nucleophiles, such as methoxide and cyanide ions add quite readily.

The product derived from reaction of cyanide ion with **13** was assigned formula $C_{25}H_{23}N_3O_2$ and still contained two M-methylanilino groups. The IR spectrum indicated that the part structure 2-(N-methylanilino)-cyclopent-2-enone was present. While no IR band for CN was observed such absorption is often very weak[38] if a tertiary cyanide group is present and the mass spectrum provided evidence for the presence of the CN group. Interpretation of the PMR spectrum (see Fig. 3) allowed formula **15** to be assigned to this product.

The genesis of **15** is outlined in Scheme 5.

The stabilised anion (IV) is considered to displace cyanide ion from **14e** to yield the final product.

Properties of the 2,4-diarylaminocyclopent-2-enone system

The 2,4-diarylaminocyclopent-2-enone system appeared to be a potentially reactive system worthy of investigation. As a β-anilino ketone, fairly ready elimination of aniline was expected to occur with the possible formation of a stabilised substituted cyclopentadienone **16**. It was realised relatively early that elimination was not facile, as the 5,5-dideutero derivative of **7a** could be isolated in fair yield by treatment of the parent with sodium deuteroxide in dioxan at 100°.[37] Nevertheless heating of **7a** with either aqueous acid or base led to the loss of aniline, but no isolation of a substituted cyclopentadienone or its dimer was achieved. In the case of **7d** refluxing in ethanol alone gave a new product which, from analysis and comparison of its PMR spectrum with that of the starting material, had undergone replacement of the 4-anilino group with the formation of 2-*p*-chloranilino-4-ethoxycyclopent-2-enone. At first this product was interpreted as having been formed by the addition of ethanol to the unhindered double bond of the transiently formed cyclopentadienone **16b** and attempts were made to trap any such intermediate by refluxing the 2,4-diarylamino type **7** in methanol containing maleic anhydride. In no case was any adduct isolated, the products formed in excellent yield being the corresponding 2-arylamino-4-methoxy-cyclopent-2-enones **12** and the substituted maleanilic acid.

In several experiments carried out without addition of maleic anhydride, prolonged reflux periods were employed in an attempt to improve the yield of the ethoxy compound. From these reactions [starting particularly with **7d** and **7e**] up to 20% yield of sparingly soluble products were obtained. These substances were isomers of formula $C_{28}H_{22}Cl_2N_2O_2$ and thus had the requisite

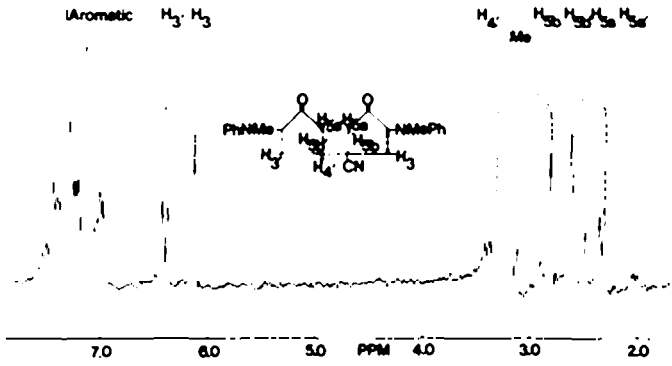
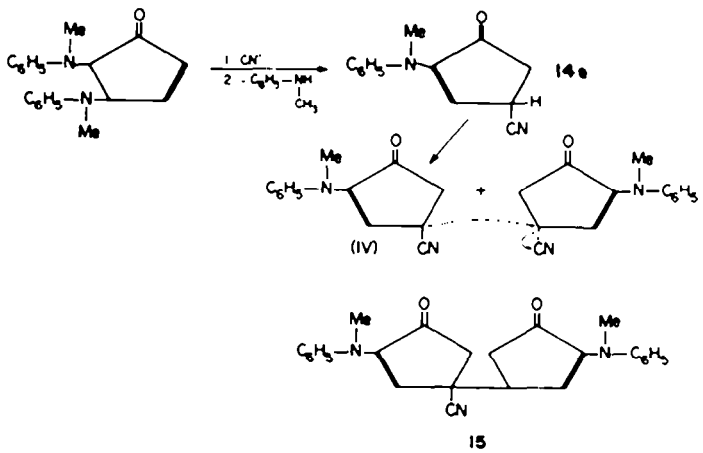


Fig. 3.



Scheme 5.

composition to have been formed from a Diels–Alder type reaction of one molecule of cyclopentadienone **6b** or **c** with one molecule of starting product **7d** or **e**. The IR spectrum of the *m*-chloro "adduct" showed carbonyl absorption of cyclopentanone type, and from the mass spectrum and the analysis three *m*-chloroanilino residues are then most likely and this was confirmed by the occurrence of absorption for eighteen aromatic carbon atoms in the ^{13}C NMR spectrum. The PMR spectrum at 60 MHz was quite complex but the 220 MHz spectrum was much simpler, though still not readily interpretable (Fig. 4). Synthesis of 2,4-di-*m*-chloroanilinocyclopent-2-enone **7e** from furfuraldehyde-5D gave the 3-deuterated product (with *ca.* 90% deuterium incorporation) and conversion of this into the "adduct" gave a product containing 2 deuterium atoms. The "dideutero adduct" gave a considerably simplified 220 MHz spectrum which enabled the assignments indicated in Fig. 4 and Scheme 7 to be made. The relationships so deduced clearly eliminated the possibility that the "adduct" originated from the transient formation of 2-*m*-chloroanilinocyclopentadienone which underwent a Diels–Alder reaction with unchanged **7e**, followed by intramolecular cyclisation (Scheme 6). In this possibility there are only eight alicyclic type protons and only one $\rangle CH\text{–}CH_2\text{–}CO$-system is present, whereas two such AB patterns typical of methylene groups appear in the observed spectrum, and the introduction of the two deuterium atoms (at the asterisked carbons) would not lead to the observed simplifications. The structure suggested for the "adduct" and its mode of formation is outlined in Scheme 7.

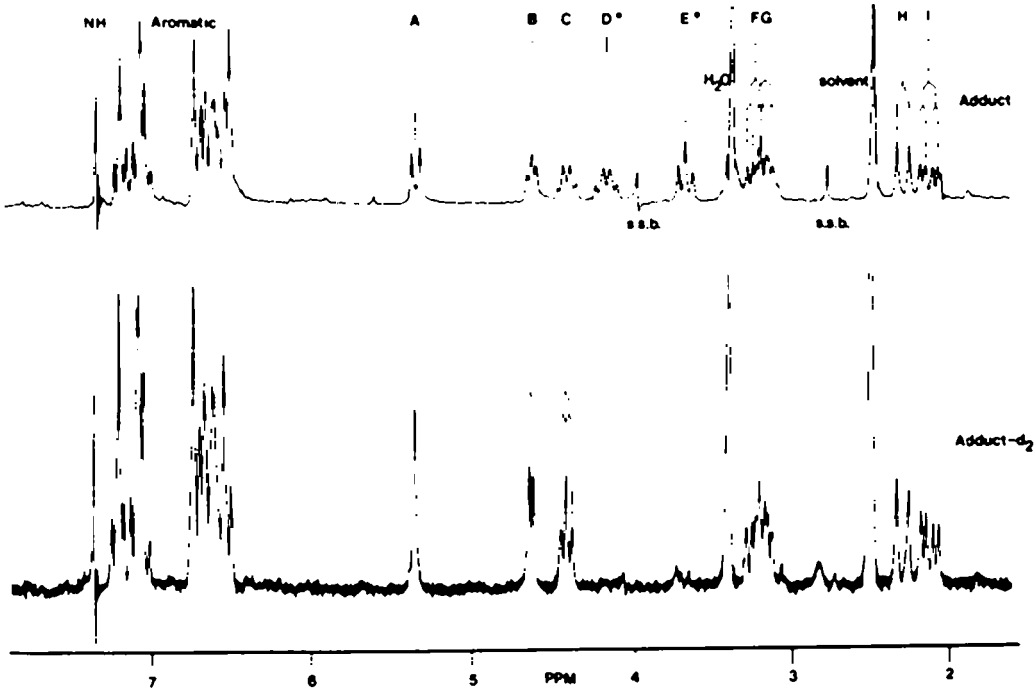
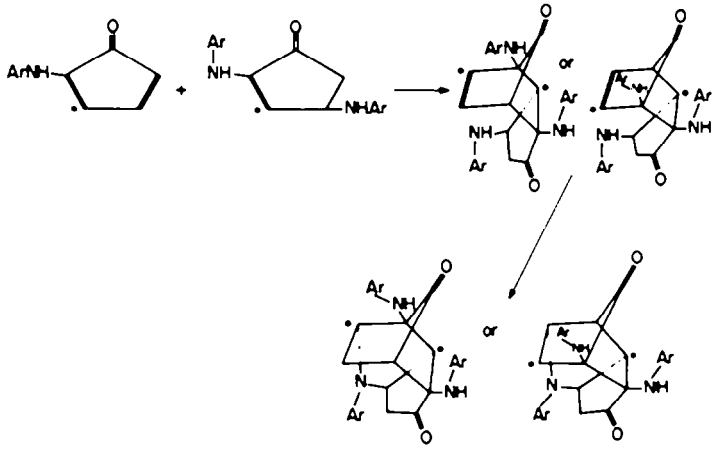
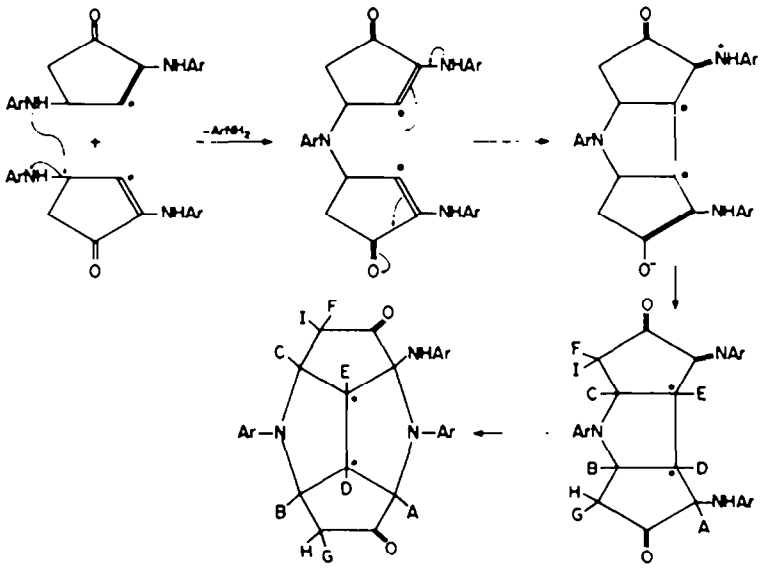


Fig. 4.

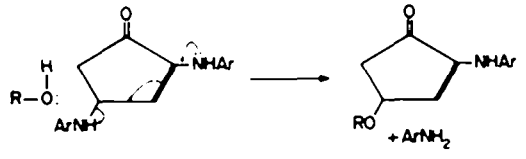


Scheme 6.



Scheme 7.

In summary, no evidence for the existence of 2-arylaminocyclopentadienone was obtained. The isolation of solvolysis products from **7a, d** and **e** and the formation of the condensation product from the action of cyanide upon **13**, together with the postulated step in the formation of the *m*-chloro "adduct" above are considered to result from a nucleophilic displacement of the arylamino or other group brought about by participation of the 2-arylamino group as indicated.



Compounds of type **7** possess an enamine structure, albeit one derived from a primary amine, and this type is usually more stable as the tautomeric anil.[59] In the cyclopentanone system, however, the enamine structure is evidently the more stable as might be expected from analogy with the corresponding 1,2-diones.[60] The non-acylation of the C2 NH group commented on earlier could be attributed to its functioning as part of an enamine system. The normal PMR chemical shift position of a proton attached to C=C of a simple enamine is *ca.* δ4.5.[61] Proton H3 of **7a** absorbs at δ6.6 which falls in the range assigned by Matter *et al.*[62,63] for the β-proton of such a substituted α,β-unsaturated ketone. Numerous unsuccessful attempts were made to alkylate or acylate the enamine system of **7a**.

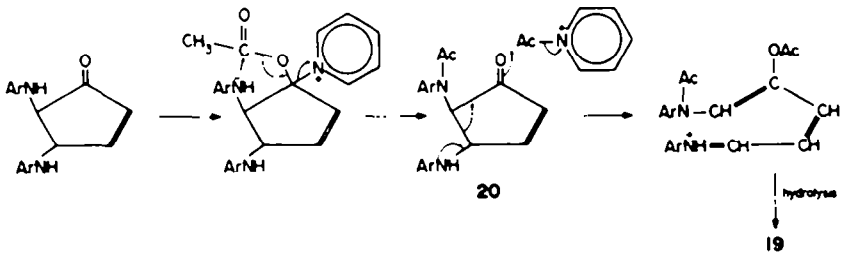
In approaches to the synthesis of the 4-arylaminocyclopent-2-enone system, bromination of 2-anilinocyclopent-2-enone was attempted using N-bromosuccinimide (with benzoyl peroxide as catalyst). A monobromo product was readily isolated which was, from its spectral properties, the 3-bromo **17a** rather than the desired 4-bromo-isomer **17b**. A similar reaction occurred in the absence of a radical initiator and compound **7a** with N.B.S. gave a 60% yield of the 3-bromoderivative **17c**. No evidence of an intermediate addition product such as has been isolated in the reaction of some substituted enol ethers[64] or with substituted aldoenamines[65] with N.B.S. could be detected even when reaction was carried out at $-40°$. Bromination with molecular bromine yielded the same product and it is probable that in this reaction **7a** and the related 2-anilinocyclopent-2-enones are showing normal enamine function[66] with bromine and that elimination of proton occurs to form the substitution product.

Reactions of Stenhouse salts under acetylation conditions

Aschan and Schwalbe[11] first observed that Stenhouse salts when acetylated with acetic anhydride–acetic acid–sodium acetate formed a mixture of colourless acetylated aldehydes which they considered to be the N,O-diacetyl compound **18a** together with the two possible monoacetyl derivatives.

Subsequently McGowan[67] treated the salts **3a, e, f** with acetic anhydride in pyridine and isolated in each case only a single product to which he also assigned structure **18a, b, c**. Repetition[68] of the work of Aschan and Schwalbe showed that most probably only two compounds were formed which were both diacetyl derivatives, and of which one was identical with that obtained by McGowan from **3a**. The PMR spectrum of the common product showed it to have the structure **19a** isomeric with that originally proposed. The second diacetyl compound isolated with the use of acetic anhydride-sodium acetate was shown to have the structure **18a**.

It was of considerable interest that the pyridine-acetic anhydride conditions yielded only a single product[67,68] whereas the expected mixture was obtained with acetic anhydride-acetic acid in the presence of sodium acetate.[68] It is suggested that the formation of the single product **19** occurs as follows. Dissolution of the Stenhouse salt **3a** in pyridine has been observed[69] to yield a solution, the PMR signals of which indicate that **8d** is formed. If N-acetylpyridinium ion then adds to the carbonyl group of **8d** as suggested by French and Adams,[69] Cohen and Song[70] and Kuhn and Teller[71] then the intermediate formed could reasonably undergo acyl migration and collapse to form the N-acetyl compound **20**. This could then ring-open in the presence of further N-acetylpyridinium ion to form a diacetyl protonated anil which on hydrolysis during work up would yield the observed diacetyl aldehyde **19a**.



Presumably the acetate ion also causes cyclisation to **8a** but in this case acetylation occurs at either nitrogen non-selectively and ring opening occurs via protonation to give both possible N-acetyl enols which are acetylated and eventually hydrolysed.

The above acetylated dienals, particularly **19**, are readily available and appear to be useful intermediates for synthesis. They contain a masked keto group which is alkali labile and an aldehyde group which can be protected as the acid labile acetal under mildly acidic conditions without loss of the enolic acetate group.[72] Mineral acids lead to fragmentation of the parent with elimination of acetanilide.[72] In an early attempt[73] to synthesise 2,4-dianilinocyclopent-2-enone the dienal **19a** was treated with methanolic sodium methoxide in expectation of obtaining 5-(N-acetylanilino)-4-oxopent-2-enal. The product isolated (also obtained in better yield by the use of sodium bicarbonate) was 2-anilino-4-methoxycyclopent-2-enone **12f** identical with the material obtained by solvolysis of 2,4-dianilinocyclopent-2-enone in methanol containing maleic anhydride. Two points are of interest, firstly the very ready ring closure of the open chain keto aldehyde and secondly the hydrolysis under very mild conditions of the N-acetyl group.

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