TETRAHEDRON REPORT NUMBER 26

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

K. G. LEWIS

Organic Chemistry Department, University of New England, Armidale, N.S.W. 2351, Australia

and

C. E. MULQUINEY Armidale College of Advanced Education, Armidale, N.S.W. 2350, Australia

(Received in the UK for publication 5 June 1976)

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 Mühlhausen⁶ and Borsche, Leditschke and Lange⁷ from a variety of primary and secondary amines. Schiff⁵ reported that tertiary amines such as dimethylaniline gave no formation of coloured salts under such conditions. Fischer⁸ and Renshaw and Naylor⁹ showed that with dimethylaniline a diphenylfurylmethane leuco base was formed which after subsequent oxidation yielded an analogue of Malachite green. Schiff⁵ 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 Mühlhausen⁶ on the other hand, preferred an open chain representation 2 which was based on analogy with the formula proposed by Zincke¹⁰ 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 Hathaway¹⁴ put forward evidence in support of the triphenylmethane type structure 1 but the evidence was added to by Williams and Wilson¹⁵ and reinterpreted by them in terms of the hydroxyglutaconic aldehyde dianil formula 2 of Zincke.⁶ Koelsch and Carney¹⁶ 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 studies¹⁸ 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

Stenhouse² 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 McGowan¹⁹ eventually isolated a creamy coloured solid (C17H16N2O) for which he proposed the possible structures 4a, b mainly upon chemical and UV spectral evidence. Subsequently the structure was revised²⁰ 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 reported²⁰ 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 Smets²¹ 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 Peters²² 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 McGowan¹⁹ 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 $\delta 4.67$ to 6.12), indicated which of the two NH groups formed the stable acetyl derivative. A di-



Aspects of the formation and use of Stenhouse salts and related compounds



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 hydrol-

ysed (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 extended²⁷ 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 Smets²¹ had included m-nitroaniline in their examination, and they reported that from this amine three isomeric products were obtained depending on the condi-

tions 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 $\delta 4.0$ 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 Smets²¹ 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 8a³⁰ to be assigned (Fig. 2). Similar results were obtained with the isomeric products derived from the o-



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 survey²⁹ 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 3,5dinitroanilines). In only the one case, that of mnitroaniline, 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 used²¹ 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 2,4diarylaminocyclopent-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 study²⁹ 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 observed³¹ 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 δ H4 values are very close) shows a decrease in J_{H3-H4} (from ca. 2.9 to 1.9 Hz) and an increase in J_{H4-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 2.3.4triarylaminocyclopentanone, 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-2enones 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 reported³³ 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 Niznik³⁶ involving of furyl-lithium the reaction with 1.1.3.3tetramethylbutylisonitrile 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}







The figures in parentheses represent percentage deuterium incorporation.

deuterated aldehydes were employed again with the mnitroaniline. 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 methanols⁴² and similar precursors such as furfuryl

Scheme 1.

acrylic acid43 and related furfurylidene ketones44,45 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



K. G. LEWIS and C. E. MULQUINEY



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 4,5diarylamino 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 McGowan¹⁹ 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-pnitrophenylpyrrole-2-aldehyde 9a and investigation of the literature indicated that we had "re-discovered" a preparation reported by Yanovskaya⁴⁸ 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-arvlpyrrole-2-aldehyde in varying yields (see Table 1). It is,

3	<u>9</u>	Products	<u>10</u>
<u>p-N0</u> 2 ^C 6 ^H 4	80%		none
3-NO2,4-C1C6H3	26*		not isolated
<u>m</u> − ^{NO} 2 ^C 6 ^H 4	37*		17
4-CH3, 3-NO2	33**		16**
₽- ^{C1C} 6 ^H 4	18		not isolated
₽ ^{-CH} 3 ^C 6 ^H 4	11		60
^C 6 ^H 5	12		58

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

* 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-2aldehydes 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.



The suggested mechanism of formation of the Nphenylpyrrole aldehydes is shown in 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 Carney¹⁶ 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-3hydroxypyridinium 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- α D 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 Narylpyrrole-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 5-anilino-N-phenyl-2,4-pentadienylchloride from ideniminium 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- α D 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 methanol¹⁶ and nitrobenzene²² 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 anil⁵⁴ occurring before cyclisation takes place.



Reversibility of Stenhouse salt formation

In an attempt to isolate the anil of N-phenylpyrrole-2aldehyde 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-3hydroxypyridinium 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 Nmethylanilinium 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 reinvestigation⁵⁵ of the reaction of Stenhouse salts with sodium sulphite⁵⁶ 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

McGowan¹⁹ 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 Asmus⁵⁷ 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 4,5diarylamino 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-Nmethylanilino 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-Nmethylanilino compound 13 into the 2,4-di-Nmethylanilino 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 $C_{23}H_{23}N_3O_2$ and still contained two M-methylanilino groups. The IR spectrum indicated that the part structure 2-(N-methylanilino)-cyclopent-2enone was present. While no IR band for CN was observed such absorption is often very weak³⁸ 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°.27 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-4ethoxycyclopent-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-methoxycyclopent-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 $C_{28}H_{22}Cl_3N_3O_2$ and thus had the requisite



Scheme 5.

composition to have been formed from a Diels-Alder type reaction of one molecule of cyclopentadienone 16b 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 ¹³C 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-2enone 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 $CH-CH_2$ -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.



472

Scheme 6.





In summary, no evidence for the existence of 2arylaminocyclopentadienone 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 nonacylation 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*. $\delta 4.5$.⁶¹ Proton H3 of 7a absorbs at $\delta 6.6$ 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 4arylaminocyclopent-2-enone system, bromination of 2anilinocyclopent-2-enone was attempted using Nbromosuccinimide (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 ethers⁶⁴ or with substituted aldoenamines⁶⁵ 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 function⁶⁶ with bromine and that elimination of proton occurs to form the substitution product.

Reactions of Stenhouse salts under acetylation conditions

Aschan and Schwalbe¹³ first observed that Stenhouse salts when acetylated with acetic anhydride-acetic acidsodium 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 McGowan⁶⁷ 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**. Repetition⁶⁸ 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 observed²⁹ to yield a solution, the PMR signals of which indicate that 8d is formed. If Nacetylpyridinium ion then adds to the carbonyl group of 8d as suggested by French and Adams,⁶⁹ Cohen and Song⁷⁰ and Kuhn and Teller⁷¹ 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 Nacetylpyridinium 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 attempt⁷³ 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 sodium bicarbonate) was 2-anilino-4of 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.

REFERENCES

- ¹J. Stenhouse, Liebigs Ann. 74, 278 (1850).
- ²J. Stenhouse, Ibid. 156, 197 (1870).
- ³H. Schiff, Ibid. 201, 355 (1880).
- ⁴H. Schiff, Ber. Dtsch. Chem. Ges. 19, 2153 (1886).
- ⁵H. Schiff, Liebigs Ann. 239, 349 (1887).
- ⁶T. Zincke and G. Mühlhausen, Ber. Dtsch. Chem. Ges. 38, 3824 (1905).
- ⁷W. Borsche, H. Leditschke and K. Lange, Ibid. 71, 957 (1938).
- ⁸O. Fischer, Liebigs Ann. 206, 141 (1883).
- ⁹R. R. Renshaw and N. M. Naylor, J. Am. Chem. Soc. 44, 862 (1922).
- ¹⁰T. Zincke, Liebigs Ann. 333, 296 (1904).
- ¹¹W. König, J. Prakt. Chem. 72, 555 (1905).
- ¹²W. Dieckmann and L. Beck, *Ber. Dtsch. Chem. Ges.* **38**, 4123 (1905).
- ¹³O. Aschan and A. Schwalbe, *Ibid.* 67, 1830 (1934).
- ¹⁴E. R. Riegel and M. Hathaway, J. Am. Chem. Soc. 63, 1835 (1941).
- ¹⁵G. Williams and C. L. Wilson, J. Chem. Soc. 506 (1942).
- ¹⁶C. F. Koelsch and J. J. Carney, J. Am. Chem. Soc. 72, 2285 (1950).
- ¹⁷W. M. Foley, G. E. Sanford and H. McKennis, *Ibid.* 74, 5489 (1952).
- ¹⁸G. Scheibe, W. Seiffert, G. Hohlneicher, C. Jutz and H. J. Springer, *Tetrahedron Letters* 5053 (1966).
- ¹⁹J. C. McGowan, J. Chem. Soc. 777 (1949).
- ²⁰J. C. McGowan, *Ibid.* 4032 (1954).
- ²¹J. Rombaut and G. Smets, Bull Soc. Chim. Belg. 58, 421 (1949).
- ²²A. P. Dunlop and F. N. Peters, *The Furans*, p. 662. Reinhold, New York (1953).
- ²³M. S. Barvinok, V. S. Kuprik, V. V. Mazurek and G. I. Semenov, *Zh. obshch. Khim.* **31**, 632 (1961).

- ²⁴M. S. Barvinok, A. P. Platonov, V. S. Kuprik and B. N. Sverdlova, USSR Pat. 164, 285 (1964) (Chem. Abstr. 62, 527 (1965)).
- ²⁵M. S. Barvinok, A. P. Platonov, V. S. Kuprik and I. S. Bukhareva, *Zh. Org. Khim.* 3, 1107 (1967).
- ²⁶K. G. Lewis and C. E. Mulquiney, Chem. Ind. 1249 (1968).
- ²⁷K. G. Lewis and C. E. Mulquiney, Aust. J. Chem. 23, 2315 (1970).
 ²⁸C. E. Mulquiney, M.Sc. Thesis, University of New England (1968).
- ²⁹C. E. Mulquiney, Ph.D. Thesis, University of New England (1971).
- ³⁰K. G. Lewis and C. E. Mulquiney, Chem. Ind. 128 (1971).
- ³¹C. H. DePuy, C. E. Lyons and L. B. Rodewald, J. Chem. Engng Data 11, 102 (1966).
- ³²D. Chadwick, A. C. Legon and D. J. Millen, J. Chem. Soc. Chem. Commun. 1130 (1969).
- ³³S. F. Thames and H. C. Odom, J. Het. Chem. 3, 490 (1966).
- ³⁴T. Hase, Acta Chem. Scand. 24, 2263 (1970).
- ³⁵D. J. Chadwick, J. Chambers, H. E. Hargreaves, G. D. Meakins and R. L. Snowden, J. Chem. Soc. Perkin I, 2327 (1973).
- ³⁶H. M. Walborsky and G. E. Niznik, J. Am. Chem. Soc. 91, 7778 (1969).
- ³⁷D. J. Bennett, G. W. Kirby and V. A. Moss, *J. Chem. Soc.* (C), 2049 (1970).
- ³⁸Ref. No. 22, p. 295.
- ³⁹N. Clauson-Kaas and J. T. Nielsen, Acta Chem. Scand. 9, 475 (1955).
- ⁴⁰K. G. Lewis, J. Chem. Soc. 531 (1957).
- ⁴¹L. Birkofer and R. Dutz, Liebigs Ann. 608, 7 (1957).
- ⁴²M. I. Ushakov and V. F. Kucherov, J. Gen. Chem. USSR 14, 1080 (1944).
- 43W. Markwald, Ber. Dtsch. Chem. Ges. 20, 2811 (1887).
- 44E. A. Kehrer and E. Hofacker, Liebigs Ann. 294, 165 (1897).
- ⁴⁵E. A. Kehrer and P. Igler, *Ber. Dtsch. Chem. Ges.* 32, 1176 (1899).
- ⁴⁶D. A. Isacescu, I. Gavat, C. Stoicescu and M. Sterescu, Bull. Soc. Chim. Fr. 2171 (1967).
- ⁴⁷A. H. Blatt and N. Gross, J. Org. Chem. 29, 3306 (1964).
- ⁴⁸L. A. Yanovskaya, Synthesen Organischer Verbindungen 1, 120 (1950); Chem. Abstr. 47, 8005 (1953).
- 49 R. Petit and R. Pallaud, C.R. Acad. Sci. Paris 258, 230 (1964).
- ⁵⁰N. Elming and N. Clauson-Kaas, Acta Chem. Scand. 6, 867 (1952).
- ⁵¹C. F. Candy, R. A. Jones and P. H. Wright, J. Chem. Soc. (C), 2563 (1970).
- ⁵²E. N. Marvell, G. Caple and I. Shahidi, J. Am. Chem. Soc. 92, 5641 (1970).
- 53E. N. Marvell and I. Shahidi, Ibid. 92, 5646 (1970).
- ⁵⁴B. A. Porai-Koshits and A. L. Remisov, Sbornik Statei Obshchei Khim. 2, 1570, 1577 (1953); Chem. Abstr. 49, 5367 (1955).
- ⁵⁵K. G. Lewis, Aust. J. Chem. 26, 893 (1973).
- ⁵⁶J. C. McGowan and F. M. Page, Chem. Ind. 1648 (1957).
- ⁵⁷K. Hafner and K-D. Asmus, Liebigs Ann. 671, 31 (1964).
 - ⁵⁸L. J. Bellamy, Advances in Infrared Group Frequencies, p. 74. Methuen, London (1968).
 - 59A. G. Cook, Enamines, p. 2. Marcel Dekker, New York (1969).
 - ⁶⁰C. W. N. Cumper, G. B. Leton and A. I. Vogel, J. Chem. Soc. 2067 (1965).
 - ⁶¹P. W. Hickmott and H. Suschitzky, Chem. Ind. 1188 (1970).
 - ⁶²U. E. Matter, C. Pascual, E. Pretsch, A. Pross, N. Simon and S. Sternhell, *Tetrahedron* 25, 691 (1969).

⁶³U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon and S. Sternhell, *Ibid.* 25, 2023 (1969). ⁴⁴K. Schank and W. Pack, *Chem. Ber.* 102, 1892 (1969).

- 65J. J. Riehl and F. Jung, C.R. Acad. Sci. Paris 270, 2009 (1970).
- ⁶⁶J. Szmuszkovicz, Advances in Organic Chemistry. Methods and Results (Edited by R. A. Raphael, E. C. Taylor and H. Wynberg), Vol. 4, p. 1. Interscience, New York (1963).
- ⁶⁷J. C. McGowan, *Chem. Ind.* 523 (1956). ⁶⁸A. P. Dillon and K. G. Lewis, *Tetrahedron* 25, 2035 (1969).
- 69H. E. French and R. Adams, J. Am. Chem. Soc. 43, 651 (1921).
- ⁷⁰T. Cohen and I. H. Song, J. Am. Chem. Soc. **37**, 074 (1721).
 ⁷⁰T. Cohen and I. H. Song, J. Am. Chem. Soc. **87**, 3780 (1965).
 ⁷¹R. Kuhn and E. Teller, Liebigs Ann. 715, 106 (1968).
 ⁷²K. G. Lewis, unpublished results.

- ⁷³K. G. Lewis and C. E. Mulquiney, unpublished results.