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FORMYLATION AND ACYLATION OF ORGANIC COMPOUNDS WITH SUBSTITUTED AMIDES OF CARBOXYLIC ACIDS

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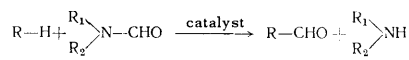
I. INTRODUCTION

The formylation of organic compounds with substituted formamides is one of the most widely used methods for the preparation of aromatic and heterocyclic aldehydes.

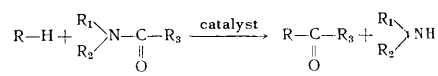
An aldehyde group can be introduced into various aromatic and heterocyclic rings by one or other of the following reactions: Gattermann[1-8], Gattermann-Koch[3-5], Karrer[6], Reimer-Tiemann[7], Duff[8,9], and some others. Although worked out in detail, they all have a rather narrow field of application. Thus. the Gattermann-Koch reaction can only be used for hydrocarbons and their halogen derivatives, the Gattermann reaction does not proceed with heterocyclic compounds (except pyrrole derivatives) and amines, and the Duff reaction is only applicable to aromatic amines and phenols. In view of the limitations of the classical synthetic methods, the new general method for preparing aromatic and heterocyclic aldehydes, using substituted formamides, is of considerable interest.

The formamide method for introducing aldehyde groups has a number of advantages over other methods of direct formylation: it can be used for preparing some dialdehydes, unsaturated aldehydes, and aromatic aminoaldehydes, and is applicable to various oxygen-, nitrogen-, sulphur-, and selenium-containing heterocyclic compounds notwithstanding their acid sensitive nature. In contrast to the Gattermann and Gattermann-Koch methods, the formylating agents used are not toxic, and the catalysts do not have dealkylating properties. The accessibility of formylating agents, the mild reaction conditions, and high yields of aldehydes make this method even more valuable.

Formylation of organic compounds with substituted formamides can be represented in its general form by the following equation:



Formylation is a particular case of the more general reaction of acylation by means of substituted acid amides:



Formylations and other acylations of organic compounds with substituted carboxylic amides were first described in the patent literature. In 1924 Fischer and his collabora-

tors[10] found that, on heating *N*-methylacetanilide with phosphorus oxychloride, a migration occurred of the acetyl group from the amino group of one ring into another aromatic ring, in the *ortho*-position to an existing substituent. Vilsmeier and Haack[11] continued the study of this reaction, and, by reacting *N*-methylformanilide with methylaniline in the presence of phosphorus oxychloride, obtained *p*-methylaminobenzaldehyde. In this way they established, in principle, the possibility of introducing an aldehyde group into an aromatic ring by reaction with a substituted formamide.

Further studies showed the formamide method to be convenient for introducing aldehyde groups into polynuclear aromatic hydrocarbons, aromatic amines, phenols, naphthols and their ethers, compounds with several functional groups, arylethylenes, and heterocyclic and some other compounds.

By this method it was possible to prepare many aldehydes otherwise difficult to obtain, for instance, indole-3-aldehyde, anthracene-9-aldehyde, picolinic aldehyde, and the aldehydes in the thiophene, selenophene, and carbazole series.

Acylation with substituted acid amides is dealt with mainly in the patent literature, and has not yet been applied to such a field of organic chemistry as has formylation. It has, nonetheless, possibilities for the synthesis of aromatic and heterocyclic ketones, especially those which cannot be obtained by the Friedel-Crafts reaction.

In this review we have undertaken to bring together the mass of disconnected information available in the literature about formylation and acylation of organic compounds by means of substituted carboxylic amides. The early work in this field has already been reviewed in the monographs by Vorozhtsov[12], Fieser and Fieser[13], and Houben-Weil[14], and also in the short surveys by Ferguson[15] and Van Dormael[16].

II. FORMYLATION OF VARIOUS ORGANIC COMPOUNDS

1. Reaction Conditions

Formamide and its *N*-alkyl(aryl) derivatives can be used for introducing an aldehyde group into organic compounds. The most widely used derivative is *N*-methylformanilide, as it can easily be prepared by boiling methylaniline with formic acid[17], and gives high yields of aldehydes. It has, however, lately been successfully superseded by *N*-dimethylformamide, which is a cheap industrial product[18,19].

Compared with methylformanilide, dimethylformamide requires harsher reaction conditions and as a rule gives somewhat lower yields of aldehydes[20]. On the other hand, it has a lower molecular weight and, being easily accessible, it can be used in considerable excess; it is also a good solvent and therefore improves the homogeneity of the reaction mixture.

The formylating action of diethylformamide is similar to that of dimethylformamide, while ethylformanilide acts similarly to methylformanilide[21]. Diphenylformamide has also been used in formylations[22]. Unsubstituted formamide is inactive under ordinary reaction conditions, but it yields aldehydes if $AlCl_3$ is used as a catalyst instead of phosphorus oxychloride[15,16,23,24]. It is possible that in this case a different mechanism underlies the reaction. Formyl derivatives of piperidine[25], indoline[26], and tetrahydroquinoline[27] can also be used to introduce an aldehyde group into aromatic and heterocyclic nuclei.

By using *N*-substituted methylformanilide vinylogues of the general formula

$$C_6H_5-N(CH_3)-(CH=CH)_n-CHO,\quad (n=1,\ 2)$$

polyenal groups can be attached to aromatic compounds[28].

Phosphorus oxychloride is the most generally used condensing agent for formylations and acylations. PCl_5, $POBr_3$, oxalyl chloride, phosgene, and thionyl chloride are used much less frequently. Their action cannot be attributed to the formation of hydrogen chloride in the reaction mixture, as is borne out by the failure of dimethylformamide to formylate indole in the presence of hydrogen chloride[29].

Formylation is usually carried out by keeping the reaction mixture at 0°–40°, but sometimes heating for a short time at 100° is required. Formylation of acid sensitive heterocyclic compounds can be carried out in solution in toluene, dichloroethane, chlorobenzene, *o*-dichlorobenzene, chloroform, tetrahydrofuran, etc.

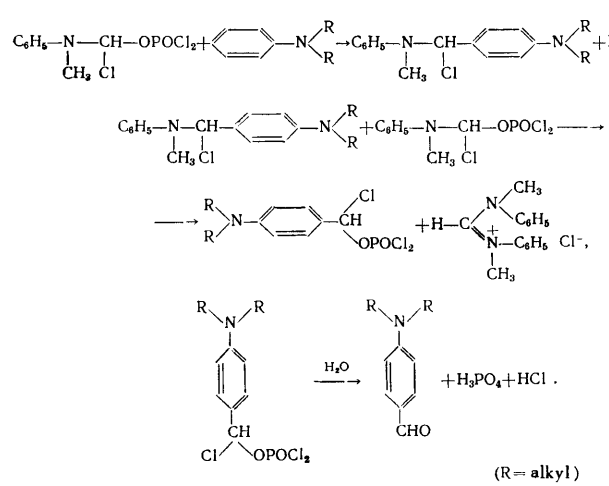
2. Reaction Mechanism

Vilsmeier and Haack[11] attempted to explain the formylation mechanism in their first paper devoted to the introduction of an aldehyde group into the nuclei of aromatic amines by the reaction with methylformanilide and phosphorus oxychloride. They thought that methylformanilide, on standing at room temperature with phosphorus oxychloride, formed product (I):

$$C_6H_5-N(CH_3)-CHO + POCl_3 \rightarrow C_6H_5-N(CH_3)-CH(Cl)-OPOCl_2.$$
(I)

The formation of such an intermediate was confirmed in a later paper[30]. It was established that by prolonged heating at 70° this product yielded *p*-methylaminobenzaldehyde and *N*,*N*'-diphenyl-*N*,*N*'-dimethylformamidinium chloride.

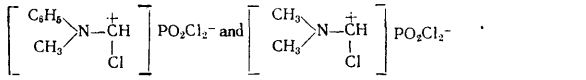
In the opinion of the authors the analogous condensation of methylformanilide with dialkylanilines proceeds in the following manner:



(R = alkyl)

The mechanism of the formylation of phenol and naphthol ethers is considered to be similar to the one above.

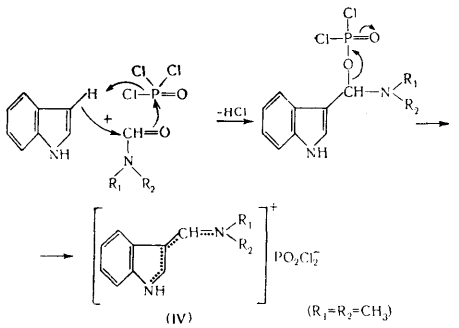
Lorenz and Wizinger[31], as well as Treibs and his collaborators[32] disputed Vilsmeier's mechanism, and ascribed a carbonium salt structure (II) and (III) to the crystalline reaction products from phosphorus oxychloride and the formylating agents:



(II) (III)

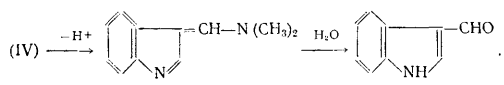
In their opinion such salts unite with the compound to be formylated, and form the products which upon decomposition by alkali yield aldehydes.

Smith[29] made a thorough study of the formylations of indole and pyrrole by means of dimethylformamide in the presence of $POCl_3$ and concluded that the reaction proceeds via the formation of intermediate quaternary ammonium salts (IV):

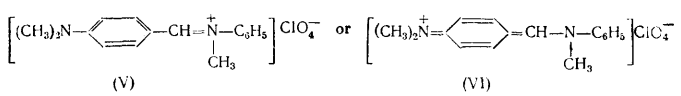


(IV) ($R_1=R_2=CH_3$)

The presence of compound (IV) in the reaction mixture was confirmed spectroscopically. This compound is completely stable in neutral and hydrochloric acid media, but loses a proton in the presence of alkali yielding 3-(dimethylaminomethylene)indolenine, which is subsequently hydrolysed quantitatively by boiling water to indole-3-aldehyde.



The intermediate formation of salt (IV) in all cases accords well with the fact that by using only catalytic quantities of $POCl_3$ very small yields of aldehydes are obtained. For complete formylation, it is necessary to use phosphorus oxychloride in quantity equivalent to that of the corresponding amide. The structure of (IV) was confirmed by spectroscopic study of the coloured reaction product from dimethylaniline, methylformanilide, and $POCl_3$.[28] This has a salt-like structure and can be isolated as a perchlorate.



(V) (VI)

By hydrolysis of the salt with dilute alkali, high yields of *p*-dimethylaminobenzaldehyde are obtained.

The formation of intermediate salts of types (IV)–(VI) is also surmised in formylations of pyrrole[34], azulene[35], and a series of other compounds. It is emphasised, however, that the role of the condensing agents lies mainly in increasing the electrophilic properties of the carbonyl carbon atom in amides.

Certain authors think that the formylation with methylformanilide is a purely ionic reaction involving the elimination of the formylium cation[33].

3. Formylation of Aromatic Hydrocarbons

Monocyclic aromatic hydrocarbons — benzene, toluene, and their homologues — do not react with *N*-alkylformanilides in the presence of the usual catalysts even at high temperatures, and can therefore be used in formylations as inert solvents.

Naphthalene and its homologues do not react, whereas anthracene, pyrene, acenaphthene, perylene, and other reactive polynuclear hydrocarbons are easy to formylate and give good yields of aldehydes. The introduction of an aldehyde group into anthracene by its reaction with methylformanilide and phosphorus oxychloride was first described in patents[36,37]. Wood and Bost[38], as well as Fieser and Hartwell[39] tested the patent data, and obtained anthracene-9-aldehyde in 92% yield. A well developed method for the preparation of this compound was described in a symposium[40]. 9-Methylanthracene[41] and anthrone[20,36] react similarly with methylformanilide. 2-Chloroanthrone and 1,5-dichloroanthracene are formylated in position 9, and simultaneously undergo chlorination by $POCl_3$ in position 10.[36]

Anthracene is more reactive than benzanthracenes. The reaction of methylformanilide with 1,2-benzanthracene is more difficult than with anthracene, whereas 1,2,5,6-dibenzanthracene does not react even after heating for 24 h, at 155°, in a sealed tube. This is explained by increased steric hindrance.

The formylation of acenaphthene and 3-methylacenaphthene gives good yields of aldehyde mixtures[41]. Acenaphthylene reacts easily with dimethylformamide in toluene solution at 100° giving 9-formylacenaphthylene, whereas under the same conditions fluoranthene does not yield an aldehyde[42]. Buu-Hoï and Lavit[42] explain the difference in the chemical behaviour of these hydrocarbons, on the basis of Thiele's theory, by the higher free valency of acenaphthene, and the position of substitution, by the maximum electron density at that point.

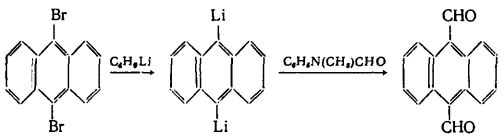
Volman et al.[43] described the preparation of pyrene-3-aldehyde by the reaction of pyrene with methylformanilide and phosphorus oxychloride. Under the same conditions dimethylformamide yields pyrene-1-aldehyde[44]. The use of *o*-dichlorobenzene as solvent is advantageous, as is shown in the formylations of benzo-[45], dibenzo-[46,47], and naphthopyrenes[48], and their homologues[46-48].

Buu-Hoï and his collaborators reported the formylations of perylene[49] and naphthacene[50] rings. As the aldehyde group is easily reducible to methyl (for instance by the Kishner method), this method may be used in the synthesis of the homologues of polynuclear hydrocarbons.

Fieser and Jones[41] showed that formylations by methylformanilide were considerably less suitable for aromatic hydrocarbons than was indicated in earlier patents. They did not succeed in obtaining the aldehydes from α-methylnaphthalene, hydrindene, phenanthrene, and chrysene by carrying out the formylation between 20° and 150°.

Attempts to prepare dialdehydes of aromatic hydrocarbons, for instance anthracene, were also unsuccessful, owing to the strong deactivating effect of the aldehyde group

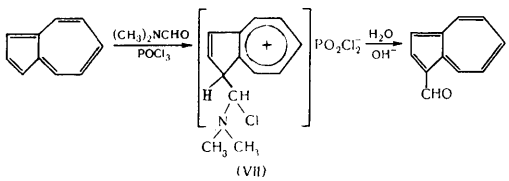
already introduced into the nucleus. If, however, the nucleophilic character of positions 9 and 10 in anthracene is enhanced by substituting the corresponding hydrogen atoms with an alkali metal, e.g. lithium, and the resulting organometallic compound is treated with methylformanilide, 9,10-dialdehyde can be obtained in about 50% yield[51]:



The mechanism of the organometallic synthesis is, naturally, completely different from the one above.

Naphthacene dialdehyde can be prepared in the usual way; 5-formyl- and 5,11-diformylnaphthacene are formed simultaneously[50].

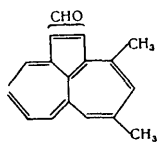
Azulene and its homologues are highly reactive to formylation. In the presence of catalysts ($POCl_3$, PCl_5, $COCl_2$, $SOCl_2$) they react with dimethylformamide yielding 1-aldehydes and 1,3-dialdehydes[34,35,52,53]. At an intermediate stage of this reaction salts of type (VII) are formed; these are hydrolysed in the presence of alkalis giving azulene aldehydes in 90–95% yield[35]:



(VII)

If the position 1 in azulene is substituted, the formyl group occupies position 3.[32]

Hafner and Schneider[54] described the formylation of 2,4-dimethyl(cyclopentadieno-1',5',4' : 1,11,10)heptalene with dimethylformamide. It is assumed that, as in the case of azulene, the aldehyde group substitutes the hydrogen atom in position 2' or 3' of the five-membered ring:



A number of workers have studied the introduction of the formyl group into the ferrocene nucleus[55–58]. The highest yield of ferrocene aldehyde (77.6%) was obtained by adding ferrocene to double the theoretical amount of a previously prepared mixture of methylformanilide and phosphorus oxychloride; the reaction mixture was left for three days, and the aldehyde isolated in the usual manner[58]:

$$(C_5H_5)_2Fe \xrightarrow[POCl_3]{C_6H_5N(CH_3)CHO} C_5H_5FeC_5H_4CHO.$$

The mild formylation conditions indicate the enhanced reactivity of ferrocene as compared with that of benzene.

Owing to the deactivation of the aldehyde group already present in the aromatic nucleus, it was for a long time impossible to introduce another such group into the ferrocene molecule even by using a considerable excess of formylating agents. Recently, however, a patent[59] described the preparation of diformylferrocene, isolated as a brownish-red oil, in small yield. The reaction was carried out at a high temperature. The acylation of ferrocene was reviewed in a paper by Nesmeyanov and Perevalova[60].

Data on the formylation of aromatic hydrocarbons are given in Table 1.

4. Formylation of Phenols, Naphthols, and Their Derivatives

Wood and Bost[38] extended the formylation by means of dimethylformanilide to ethers derived from β-naphthol.

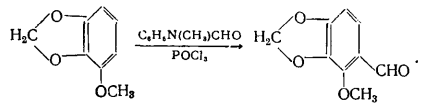
According to data published in patents[23] and journals, formylation can be applied to ethers derived from phenol[63,65], thiophenol[63], dihydric phenols[25,26,66], α- and β-naphthols[69,70], thionaphthol[72], hydroxytetralines[36,63], and their derivatives. Of special interest is the preparation of substituted hydroxyanthracene aldehydes by the formylation of 1,2- and 2,6-dimethoxyanthracenes[36].

In the preparation of alkoxyaldehydes the formyl group primarily enters the position *para* to the alkoxy group, but if that position is already occupied (for instance by a methyl group) the substitution can take place in the *o*-position, with considerably smaller yields of aldehydes.

Ethers derived from phenol (anisole and phenetole[36,63]), thymol[71], and the cresols[65] are easily formylated by different formylating agents, even after short heating of the components on a water bath in the presence of $POCl_3$, and give the corresponding alkoxybenzaldehydes in good yields.

Akabori and Senoh[25] described the preparation of veratraldehyde and 2,4-dimethoxybenzaldehyde, in which *N*-formylpiperidine was used as a formylating agent. These aldehydes were later also prepared by means of dimethylformamide[63], and methylformanilide[26].

Brownell and Weston[66] synthesised croweacin aldehyde from 1-methoxy-2,3-methylenedioxybenzene:



Ethers from α- and β-naphthols are usually formylated under milder conditions than phenolic ethers, giving higher yields of aldehydes. Buu-Hoï and his colleagues prepared a large number of alkoxy- and dialkoxynaphthalene aldehydes by formylation of the corresponding ethers with dimethylformamide[69,73–77]. Some of these aldehydes are starting materials in the synthesis of drugs used for protection against radiation sickness and for arresting the growth of sarcoma tumours. The aldehyde group was also introduced into diphenyl ether[63] and 2-hydroxynaphthalene-3-carboxylic acid[36].

All attempts to introduce two aldehyde groups into the aromatic ring of phenol and naphthol ethers failed. Negative results were also obtained in formylations of *p*-terphenyl[78], 4-chloro-2-naphthol[79], and some alkylanisoles[63].

Owing to the mild reaction conditions, formylation by means of substituted formamides can be used for introducing the aldehyde group into the nuclei of phenol[63], resorcinol[64], β-naphthol[23], and di-, tri-, and tetramethylphenols[35,65]. *p*-Hydroxybenzaldehyde was obtained in small yield, but in other cases the respective yields of aldehydes were no worse than in the Gattermann reaction. Formylation data for phenols, naphthols, the corresponding

TABLE 1. Formylation of aromatic hydrocarbons

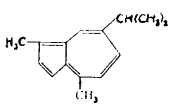
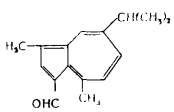
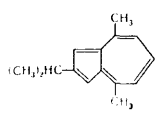
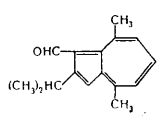
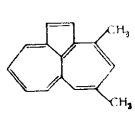
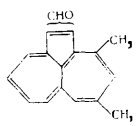
Starting material	Product	Formylating agent	Reaction conditions	Yield %	Reference
C_{10}					
Azulene	Azulene-1-aldehyde	MFA*	$POCl_3$, 24 h, 20° or 1 h, 70°	85	32
"	"	DMFA**	$POCl_3$, 5-10 min, in the cold	90-95	32, 35
"	Azulene-1,3-dialdehyde	"	$POCl_3$, 45 min, 70°	43	32
Ferrocene	Ferrocenealdehyde	MFA	$POCl_3$, 72 h, 20°-25°	77.6	57
"	"	"	$POCl_3$, 3 h, 20°	66-70	55, 56
"	Ferrocenealdehyde and bisformylferrocene	"	$POCl_3$, 15 h, 20°, or 2 h, 50°-55°	55	58
"	Ferrocenealdehyde	DMFA	$POCl_3$, 3 h, 20°	23	55
C_{11}					
1-Methylazulene	1-Methylazulene-3-aldehyde	DMFA	$POCl_3$, 5-10 min, in the cold	90-95	32, 35
C_{12}					
Acenaphthylene	Acenaphthylene-9-aldehyde	DMFA	$POCl_3$, toluene, 10 min, 100°	11-13	42
Acenaphthene	Acenaphthene-3-aldehyde	MFA	$POCl_3$, 6 days, 20°-25°	85	41
"	"	DMFA	$POCl_3$, xylene, 6 h, 100°	85	44
4,7-Dimethylazulene	4,7-Dimethylazulene-1-aldehyde	"	$POCl_3$, 5-30 min, in the cold	91	32
4,8-Dimethylazulene	4,8-Dimethylazulene-1-aldehyde	"	"	94	32
C_{13}					
3-Methylacenaphthene	A mixture of aldehydes	MFA	$POCl_3$, 6 days, 20°-25°	68	41
4,6,8-Trimethylazulene	4,6,8-Trimethylazulene-1-aldehyde	DMFA	$POCl_3$, 5-30 min, in the cold	90-95	32, 35
1,4,7-Trimethylazulene	1,4,7-Trimethylazulene-3-aldehyde	"	"	96	32
2,4,8-Trimethylazulene	2,4,8-Trimethylazulene-1-aldehyde	"	"	88	32
C_{14}					
Anthracene	Anthracene-9-aldehyde	MFA	$POCl_3$, *o*-dichlorobenzene, 20 min, 90°-95°	77-92	36-40
"	"	DMFA	$POCl_3$, 1-2 h, 100°	63	20
1,2-Benzazulene	1,2-Benzazulene-3-aldehyde	"	$POCl_3$, 5-30 min, in the cold	91	32
Anthrone	Anthrone-9-aldehyde	MFA	$POCl_3$, 1-2 h, 100°	-	20, 36
1,5-Dichloroanthracene	1,5,10-Trichloroanthracene-9-aldehyde	"	"	-	36
2-Chloroanthrone	2,10-Dichloroanthracene-9-aldehyde	"	"	-	36
C_{15}					
9-Methylanthracene	9-Methylanthracene-10-aldehyde	MFA	$POCl_3$, 45 min, 100°	84	41
Guaiazulene	Guaiazulene-3-aldehyde	MFA or DMFA	$POCl_3$, 5-30 min, in the cold	90-95	32, 35, 52
					
Isoguaiazulene	Isoguaiazulene-1-aldehyde	MFA or DMFA	$POCl_3$, 5-30 min, in the cold	88-98	32, 52
"	Isoguaiazulene-1,3-dialdehyde	"	"	96	32
Vetivazulene	Vetivazulene-1-aldehyde	"	"	up to 98	32, 52
					
2,4-Dimethyl-6-isopropylazulene	2,4-Dimethyl-6-isopropylazulene-1-aldehyde	MFA or DMFA	$POCl_3$, 5-30 min, in the cold	90	32
C_{16}					
Pyrene	Pyrene-3-aldehyde	MFA or DMFA	$POCl_3$, *o*-dichlorobenzene, 2-6 h, 100°	53	43, 44
2,4-Dimethylcyclopentadieno-(1',5',4':1,11,10)heptalene	2,4-Dimethyl-2'(or 3')-formylcyclopentadieno-(1',5',4':1,11,10)heptalene	DMFA	$POCl_3$, benzene, 1 h, 20°	57	54
					

TABLE 1 (contd.)

Starting material	Product	Formylating agent	Reaction conditions	Yield %	Reference
2-Methylguaiazulene	1,2,4-Trimethyl-2-isopropylazulene-3--aldehyde	DMFA	$POCl_3$, 5-30 min, in the cold	92	32
1-Methylvetivazulene	1,4,8-Trimethyl-2-isopropylazulene-3--aldehyde	"	"	72	32
C_{17}					
3-Methylpyrene	A mixture of aldehydes	DMFA	$POCl_3$, 6 days, 20°-25°	73	41
4-Methylpyrene	4-Methylpyrene-8-aldehyde	"	$POCl_3$, *o*-dichlorobenzene, 100°	80	61
2,3-Cyclopentenoanthracene	2,3-Cyclopenteno-9-anthraldehyde	"	$POCl_3$, toluene, 2 h, 100°	71	62
C_{18}					
1,2-Benzanthracene	1,2-Benzanthracene-10-aldehyde	DMFA	$POCl_3$, *o*-dichlorobenzene, 2 h, 95°-100°	64	39
Naphthacene	Naphthacene-5-aldehyde and naphthacene-5,11-dialdehyde	"	$POCl_3$, chlorobenzene, 6 h, 100°	-	50
C_{20}					
Perylene	Perylene-3-aldehyde	MFA	$POCl_3$, *o*-dichlorobenzene, 30 min, 95°-100°	63	49
Benzo[*cd*]pyrene	Benzo[*cd*]pyrene-3-aldehyde	"	"	90	45
C_{21}					
3-Methylperylene	3-Methylperylene-10-aldehyde	MFA	$POCl_3$, *o*-dichlorobenzene, 30 min, 95°-100°	54	49
C_{23}					
3,4,9,10-Dibenzopyrene	3,4,9,10-Dibenzopyrene-5-aldehyde	MFA	$POCl_3$, *o*-dichlorobenzene, 30 min, 95°-100°	57	50
C_{24}					
Naphtho[2,3-*a*]pyrene	Naphtho[2,3-*a*]pyrene-6-aldehyde	MFA	$POCl_3$, *o*-dichlorobenzene, 4 h, 95°-100°	51	48
"	Naphtho[2,3-*a*]pyrene-7-aldehyde	"	"	-	48
Dibenzo[*a,h*]pyrene	Dibenzo[*a,h*]pyrene-3-aldehyde	"	"	81	46
5-Methyl-dibenzo[*cd,l*]pyrene	5-Methyl-dibenzo[*cd,l*]pyrene-8-aldehyde	"	"	46	49
C_{25}					
6-Methylnaphtho[2,3-*a*]pyrene	6-Methylnaphtho[2,3-*a*]pyrene-7-aldehyde	MFA	$POCl_3$, *o*-dichlorobenzene, 4 h, 95°-100°	30	48
7-Methyldibenzo[*a,h*]pyrene	7-Methyldibenzo[*a,h*]pyrene-14-aldehyde	"	"	77	46
C_{26}					
Naphtho[2,3-*a*]naphthacene	Naptho[2,3-*a*]naphthacene-9-aldehyde	MFA	$POCl_3$, *o*-dichlorobenzene, 4 h, 95°-100°	22	50

* Methylformanilide.

** Dimethylformamide.

TABLE 2. Formylation of phenols, naphthols, and their derivatives

Starting material	Product	Formylating agent	Reaction conditions	Yield %	Reference
C_6					
Phenol	4-Hydroxybenzaldehyde	DMFA*	$POCl_3$, boiling for 2 h, 20°	low	63
Resorcinol	2,4-Dihydroxybenzaldehyde	"	"	46	64
C_7					
Anisole	Anisaldehyde	DMFA	$POCl_3$, boiling for 15 h	70	63
"	"	MFA**	$POCl_3$, 1 h, 100°	good	36
2-Chloroanisole	3-Chloro-4-methoxy-benzaldehyde	"	$POCl_3$, boiling for 15 h	3	15
Thioanisole	4-Methylthiobenzaldehyde	DMFA	$POCl_3$, boiling for 24 h	low	63

TABLE 2 (contd.)

Starting material	Product	Formylating agent	Reaction conditions	Yield %	Reference
C_8					
2,5-Dimethylphenol	4-Hydroxy-2,6-dimethylbenzaldehyde	MFA	$POCl_3$, 1 h, 100°	-	36
o-Tolyl methyl ether	4-Methoxy-3-methylbenzaldehyde	DMFA	$POCl_3$, 20°-25°	70	65
m-Tolyl methyl ether	4-Methoxy-2-methylbenzaldehyde	"	"	72	65
Phenetole	4-Ethoxybenzaldehyde	"	$POCl_3$, boiling for 15 h	70	63
Veratrole	Veratraldehyde	"	$POCl_3$, boiling for 6 h	30-40	63
"	"	MFA	$POCl_3$, room temperature	38	26
"	"	*N*-formylpiperidine	$POCl_3$, 100°	40	25
1,3-Dimethoxybenzene	2,4-Dimethoxybenzaldehyde	"	$POCl_3$, 20°-25°, then 100°	30	25
"	"	MFA	$POCl_3$, 20°-25°	85	26
1,4-Dimethoxybenzene	2,5-Dimethoxybenzaldehyde	"	"	16	26
1-Methoxy-2,3-methylenedioxybenzene	Croweacin aldehyde	"	$POCl_3$, 2 h, 100°	46	66
C_9					
3,4,5-Trimethylphenol	6-Hydroxy-2,3,4-trimethylbenzaldehyde	DMFA	$POCl_3$, 20°-25°	70	65
2,4,5-Trimethylphenol	6-Hydroxy-2,3,5-trimethylbenzaldehyde	"	"	66	65
1-Methoxy-2,5-dimethylbenzene	4-Methoxy-2,5-dimethylbenzaldehyde	"	"	72	65
1-Methoxy-2,3-dimethylbenzene	4-Methoxy-2,3-dimethylbenzaldehyde	"	"	70	67
1,2-Dimethoxy-4-methylbenzene	3,4-Dimethody-2-methylbenzaldehyde	"	$POCl_3$, boiling	35-40	63
4-Chloro-3,5-dimethylanisole	4-Chloro-3,5-dimethylanisaldehyde	MFA	$POCl_3$, 12 h, 105°	-	68
C_{10}					
2-Naphthol	2-Hydroxy-1-naphthaldehyde	MFA	$POCl_3$, 1 h, 100°	-	23, 36
2,3,4,5-Tetramethylphenol	6-Hydroxy-2,3,4,5-tetramethylbenzaldehyde	DMFA	$POCl_3$, 20°-25°	68	65
2,7-Dihydroxynaphthalene	2,7-Dihydroxy-1-naphthaldehyde	MFA	$POCl_3$, 1 h, 100°	-	36
4,8-Dihydroxynaphthalene	4,8-Dihydroxy-1-naphthaldehyde	"	"	-	36
C_{11}					
1-Methoxynaphthalene	4-Methoxy-1-naphthaldehyde	DMFA	$POCl_3$, 3 h, 95°-100°	90	69
2-Methoxynaphthalene	2-Methoxy-1-naphthaldehyde	"	"	90	69, 70
6-Methoxytetralin	6-Methoxytetralin-7-aldehyde	MFA	$POCl_3$, boiling	79	63
1-Methoxytetralin	1-Methoxytetralin-4-aldehyde	"	"	-	36
2-Methoxytetralin	2-Methoxytetralin-1-aldehyde	"	"	-	36
1-Methyl-3-methoxy-4-isopropylbenzene	3-Isopropyl-4-methoxy-6-methylbenzaldehyde	DMFA	$POCl_3$, 4 h, 30°	33-35	11
1-Methyl-2-methoxy-4-isopropylbenzene	4-Methoxy-3-methyl-6-isopropylbenzaldehyde	"	$POCl_3$, 10 h, boiling	76	63
2-Hydroxy-3-carboxynaphthalene	2-Hydroxy-3-carboxy-1-naphthaldehyde	MFA	$POCl_3$, 1 h, 100°	-	36
2-Methylthionaphthalene	2-Methylthio-1-naphthaldehyde	"	$POCl_3$, 6 h, 95-100°	35	72
C_{12}					
Phenyl ether	4-Phenoxybenzaldehyde	DMFA	$POCl_3$, boiling for 24 h	low	63
1-Methoxy-4-methylnaphthalene	1-Methoxy-4-methyl-2-naphthaldehyde	"	$POCl_3$, 3 h, 100°	22	69
2-Ethoxynaphthalene	2-Ethoxy-1-naphthaldehyde	"	$POCl_3$, 6 h, 95°-100°	74-84	36
6-Methyl-2-methoxynapthalene	2-Methoxy-6-methyl-1-naphthaldehyde	"	$POCl_3$, boiling for 5 h	86	40, 115, 73
1-Methyl-3-methoxy-4-t-butylbenzene	4-Methoxy-3-t-butyl-6-methylbenzaldehyde	"	$POCl_3$, boiling for 7 h	90	63
2,3-Dimethoxynaphthalene	2,3-Dimethoxy-1-naphthaldehyde	"	$POCl_3$, 20°-25°	23.5	74
2,7-Dimethoxynaphthalene	2,7-Dimethoxy-1-naphthaldehyde	"	$POCl_3$, 30 min, 100°	82	69
2,6-Dimethoxynaphthalene	2,6-Dimethoxy-1-naphthaldehyde	"	$POCl_3$, 3 h, 95°-100°	80	69
1,8-Dimethoxynaphthalene	4,5-Dimethoxy-1-naphthaldehyde	"	$POCl_3$, boiling in toluene	83	76
1,4-Dimethoxynaphthalene	1,4-Dimethoxy-2-naphthaldehyde	"	"	42	75
1,3-Dimethoxy-4-t-butylbenzene ether	4,6-Dimethoxy-3-t-butylbenzaldehyde	"	$POCl_3$, 6 h, 100°	79	63
C_{13}					
2-Methoxydiphenyl	4-Methoxy-3-phenylbenzaldehyde	DMFA	$POCl_3$, 90°-95°	-	63
2-Methoxy-6-ethylnaphthalene	2-Methoxy-6-ethylnaphthaldehyde	"	$POCl_3$, boiling for 5 h	98	77
2,7-Dimethoxy-1-methylnaphthalene	2,7-Dimethoxy-8-methylnaphthaldehyde	"	toluene, 9 h, 95°-100°	70	69
2,6-Dimethoxy-1-methylnaphthalene	2,6-Dimethoxy-5-methylnaphthalene-1-aldehyde	"	"	40.5	75
C_{16}					
1,2-Dimethoxyanthracene	1,2-Dimethoxy-10-chloroanthracene-9-aldehyde	MFA	toluene, 1 h, 100°	-	36
2,6-Dimethoxyanthracene	2,6-Dimethoxy-10-chloroanthracene-9-aldehyde	"	"	-	36

* Dimethylformamide.

** Methylformanilide.

ethers, and other derivatives are given in Table 2.

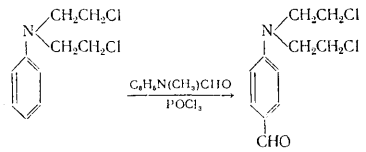
5. Formylation of Aromatic Amines

The formylation of the nucleus in aromatic amines[11] was the first example of the synthesis of aldehydes by the reaction of organic compounds with substituted formamides described in the literature.

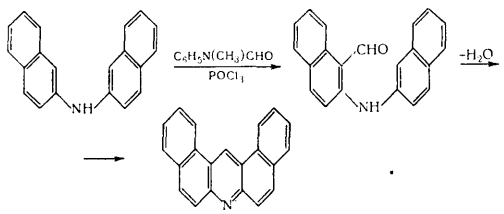
The conditions for the introduction of the aldehyde group into the nucleus of secondary and tertiary aromatic and aliphatic-aromatic amines are now well understood and the reaction is used for formylating *N*-alkyl- and *N*,*N*-dialkylanilines[11,20,80,81], toluidines[11], phenylene diamines[81], α- and β-naphthylamines[11,81], as well as diarylamines[82], and triarylamines[81,83].

Methylformanilide easily formylates dimethylaniline at 0°–10° giving 50% *p*-dimethylaminobenzaldehyde[11]. With dimethylformamide, the yield is somewhat increased, but the reaction proceeds only on heating[20].

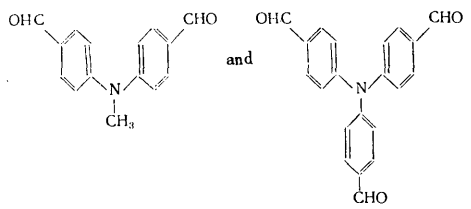
Cases have been described of the introduction of an aldehyde group into the *p*-position of secondary aliphatic-aromatic amines containing highly branched substituents, for instance diisopropylmethylaniline and isohexylaniline[84,85]. Anker and Cook[86] similarly obtained 4-(bis-β-chloroethylamino)-benzaldehyde and its derivatives:



In the nucleus of aromatic amines the formyl group usually enters the position *para* to the amino group. Recently, however, Buu-Hoï, Roger, and Hubert-Habart[87] have synthesised angular benzacridines by reacting appropriate secondary arylamines with methylformanilide. In such cases the formyl group takes up *o*-position with respect to the amino group. The aldehydes formed are thereafter easily transformed into acridines[88]:



Products containing several formyl groups were obtained by heating *N*-methyldiphenylamine and triphenylamine with dimethylformamide and $POCl_3$ (or $SOCl_2$). This reaction was described in patents[81,83]:



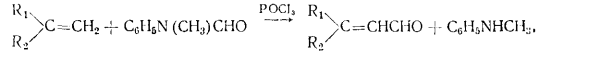
These aldehydes were used in the preparation of new styryl dyes.

The reaction of dimethylformamide with primary aromatic amines yields *N*-formanilides[89].

Data on the formylation of the aromatic ring in amines are given in Table 3.

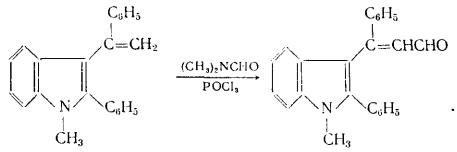
6. Preparation of Unsaturated Aldehydes and Dialdehydes

The formamide method is the only direct formylation by which α,β-unsaturated aldehydes can be prepared from substituted ethylenes[91,92]. The reaction proceeds easily without heating by mixing the unsaturated compound with methylformanilide and $POCl_3$ in solution in carbon tetrachloride, according to the equation



where R_1 = H, alkyl, arylmethyl, or a heterocyclic radical; R_2 = aryl.

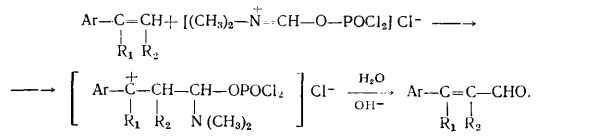
Unsymmetrical diarylacroleins[92], which are of interest as starting materials for the synthesis of polymethine dyes, were prepared in this way. The formylation of styrene and its derivatives is carried out by heating with dimethylformamide in the presence of $POCl_3$.[93] Unsaturated aldehydes containing the indole ring can be prepared similarly.



This method is of especial value for the synthesis of β-substituted cinnamaldehydes, which are not readily available and whose preparation by other methods is extremely complicated[94,95].

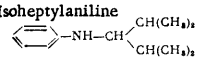
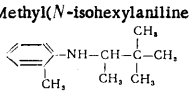
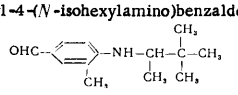
The authors assume that in the reaction dimethylformamide and phosphorus oxychloride form a complex salt of the following structure:

The cation subsequently reacts with the double bond in the substituted arylethylene and yields a product which is hydrolysed in alkaline solution to give unsaturated aldehyde:



Jutz[28] developed a new method for the preparation of unsaturated aldehydes by the direct introduction of the polyenal group into organic compounds. The acylating agents in this reaction are methylformanilide vinylogues: 3-(*N*-methylanilino)acrolein and 1-(*N*-methylanilino)penta-1,3-diene-5-al; the reaction is carried out with cooling in chloroform or tetrahydrofuran solution, and $POCl_3$ is used as

TABLE 3. Formylation of aromatic amines

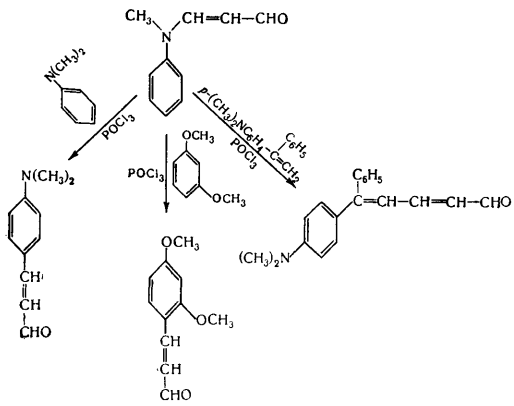
Starting material	Product	Formylating agent	Reaction conditions	Yield %	Reference
C_7					
N-Methylaniline	*p*-(Methylamino)benzaldehyde	MFA* or DMFA**	$POCl_3$, 70°	26	11
C_8					
N,*N*-Dimethylaniline	*p*-(Dimethylamino)benzaldehyde	MFA	$POCl_3$, 0°-10°	50	11, 80
"	"	DMFA	$POCl_3$, 2 h, 90°-95°	71	20, 81
C_9					
N,*N*-Dimethyl-*m*-toluidine	2-Methyl-4-(dimethylamino)benzaldehyde	DMFA	$POCl_3$, 50°	low	11
N-Methyl-*N*-(β-chloroethyl)aniline	*p*-[*N*-Methyl-*N*-(β-chloroethylamino)] benzaldehyde	"	$POCl_3$, benzene, 4 h, 30°-35°	32	86
$C_6H_5N(CH_3)CH_2CH_2Cl$	p-$OHCC_6H_4N(CH_3)CH_2CH_2Cl$				
C_{10}					
N,*N*-Diethylaniline	*p*-(Diethylamino)benzaldehyde	DMFA	$POCl_3$, 70°	-	11, 81
N,*N*,*N*',*N*'-Tetramethyl-*m*-phenylenediamine	An aldehyde, CHO position not indicated	"	$POCl_3$, 1.5 h, 95°	-	81
N-Ethyl-*N*-(β-chloroethyl) aniline	*p*-[Ethyl(β-chloroethyl) amino]benzaldehyde	MFA	$POCl_3$, benzene, 4.5 h, 30°-35°	42	86
N,*N*-Bis(β-chloroethyl)aniline	*p*-[Bis-(β-chloroethyl)amino]benzaldehyde	"	"	70	86
$C_6H_5N(CH_2CH_2Cl)_2$	p-$OHC-C_6H_4N(CH_2CH_2Cl)_2$				
C_{11}					
o-Methyl-*N*,*N*-diethylaniline	3-Methyl-4-(diethylamino)benzaldehyde	DMFA	$POCl_3$, 1.5 h, 95°	-	81
m-Methyl-*N*,*N*-diethylaniline	2-Methyl-4-(diethylamino)benzaldehyde	"	"	-	81
C_{12}					
N,*N*-Dimethyl-α-naphthylamine	4-(Dimethylamino)-1-naphthaldehyde	MFA	$POCl_3$, 50°	low	11
N-Isohexylaniline	*p*-(Isohexylamino)benzaldehyde	"	$POCl_3$, benzene, 15 h, 10°	-	84, 85
$C_6H_5N(H)-CH(CH_3)-C(CH_3)_3$	p-$OHC-C_6H_4-N(H)-CH(CH_3)-C(CH_3)_3$				
C_{13}					
N-Methyldiphenylamine	*N*-Methylbis(4-formylphenyl)amine	DMFA	$POCl_3$, 1.5 h, 90°-95°	-	83
N-Isoheptylaniline	*p*-(*N*-Isoheptylamino)benzaldehyde	MFA	$POCl_3$, benzene, 15 h, 10°	-	84, 85
					
o-Methyl(*N*-isohexylaniline	3-Methyl-4-(*N*-isohexylamino)benzaldehyde	MFA	$POCl_3$, benzene, 15 h, 10°	-	84, 85
					
C_{14}					
N-Methyl-*N*-benzylaniline	*p*-(*N*-Methyl-*N*-benzylamino)benzaldehyde	MFA	$POCl_3$, benzene, 20°	82	11
N,*N*-Diethyl-1-naphthylamine	4-(*N*,*N*-Diethylamino)-1-naphthaldehyde	DMFA	$POCl_3$, 1.5 h, 95°-100°	-	81
N,*N*-Diethyl-2-naphthylamine	6-(*N*,*N*-Diethylamino)-2-naphthaldehyde	"	"	-	81
N,*N*,*N*',*N*'-Tetraethyl-*m*-phenylenediamine	An aldehyde, position of CHO group not indicated	"	"	-	81
C_{16}					
N-Phenyl-2-naphthylamine	2-Phenylamino-1-naphthaldehyde	MFA	$POCl_3$, 100°	48***	82
o-(Diethylamino)diphenyl	3-Phenyl-4-(diethylamino)benzaldehyde	DMFA	$POCl_3$, 1.5 h, 95°-100°	-	81
N,*N*'-Dimethyl-*N*,*N*'-diphenylethylenediamine	*N*,*N*'-Dimethyl-*N*,*N*'-di(*p*-formylphenyl) ethylenediamine	"	"	70	81, 90
$C_6H_5N(CH_3)-CH_2-CH_2-N(CH_3)C_6H_5$	$OHCC_6H_4N(CH_3)-CH_2-CH_2-N(CH_3)C_6H_4CHO$				
C_{18}					
Triphenylamine	Tris (*p*-formylphenyl)amine	DMFA	$POCl_3$, 1.5 h, 95°-100°	-	81, 83
N,*N*'-Diethyl-*N*,*N*'-diphenylethylenediamine	*N*,*N*'-Diethyl-*N*,*N*'-di(*p*-formylphenyl)-ethylenediamine	"	$POCl_3$, or $SOCl_2$, in the cold	-	90
$C_6H_5N(C_2H_5)-CH_2CH_2N(C_2H_5)C_6H_5$	$OHCC_6H_4N(C_2H_5)-CH_2CH_2N(C_2H_5)C_6H_4CHO$				
C_{20}					
2-Dinaphthylamine	2-Naphthylamino-1-naphthaldehyde	MFA	$POCl_3$, 100°	-	82
N,*N*-Dibenzylaniline	*p*-Dibenzylaminobenzaldehyde	"	$POCl_3$, 40°-50°	-	11

* Methylformanilide.

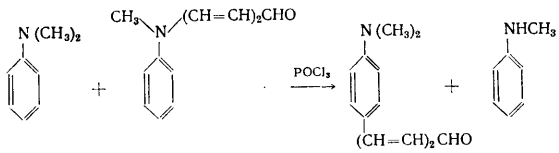
** Diethylformamide.

*** The yield was calculated from the benzacridine formed on cyclisation.

condensing agent:

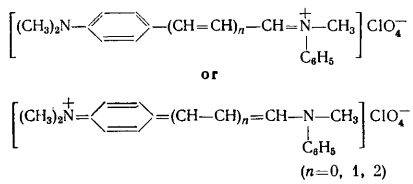


The penta-1,3-dienal radical (−CH = CH − CH = CH − CHO) can be introduced directly into the *p*-position of dimethylaniline in the following manner:



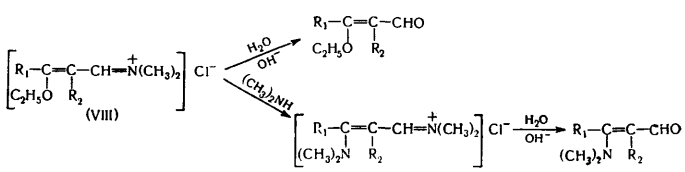
The introduction of polyenal chains into the aromatic nucleus can also be applied, as shown recently[54,96], to azulenic hydrocarbons. These reactions are a convincing example of the principle of vinylogy.

The intermediate products in this reaction are deeply coloured compounds, which can be isolated in the form of perchlorates:



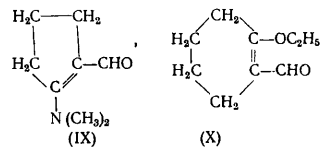
The Jutz method has obviously a wide applicability and may prove even more useful in the future.

Arnold and Zemlicka[97] studied the formylation of the diethylketals of acetone, acetophenone, propiophenone, cyclopentanone, and cyclohexanone by means of dimethylformamide in the presence of phosgene solution in dichloroethane. It is assumed that in the course of the reaction an intermediate quaternary salt (VIII) is formed, whose decomposition follows a different pattern according to the nature of the ketone and other reagents.

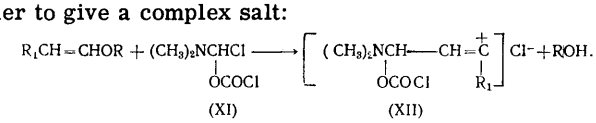


It is also highly probable that the cation of the salt (VIII) is formed as a result of the elimination of alcohol from the ketal molecule. The vinyl ether formed is subsequently formylated according to the mechanism given above.

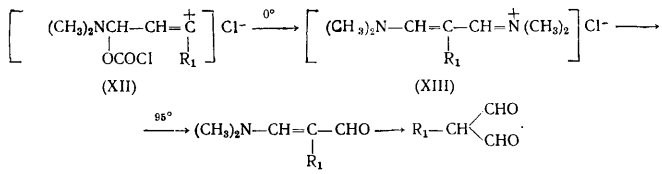
Using this method, the authors prepared various β-ethoxy(dimethylamino)acroleins in good yields. From diethylketals of cyclopentanone and cyclohexanone, 2-dimethylaminocyclopenten-1-aldehyde (IX) and 2-ethoxycyclohexan-1-aldehyde (X) are formed, respectively:



Arnold and Sorm[98]* developed a general method for the preparation of dialdehydes of the type $R-CH(CHO)_2$, by the formylation of vinyl ethers, acetals, and α-chloro-ethers with dimethylformamide and a solution of phosgene in dichloroethane. It is assumed that in the course of the reaction an intermediate product (XI) is formed from dimethylformamide and phosgene, which unites with vinyl ether to give a complex salt:



The decomposition of the complex by potassium carbonate solution at 0° results in quaternary salts, which, on further hydrolysis with aqueous alkali, are transformed into dialdehydes, according to the following scheme:



Such a reaction mechanism is confirmed to some extent by the separation and identification of the intermediate products (XI)−(XIII). The reaction of acetals and chloro-ethers with dimethylformamide apparently also proceeds via the formation of vinyl ethers. Dialdehydes of the general formula $R-CH-(CHO)_2$ were prepared by the Arnold and Sorm method, where R = H, CH_3, C_2H_5, iso-C_3H_7, C_4H_9, C_5H_{11}, C_6H_5, $C_6H_5CH_2$ (Table 4).

7. Formylation of Heterocyclic Compounds

Formylation by means of dimethylformamide and methylformanilide has lately been used with success for the preparation of a series of heterocyclic aldehydes. The application of this method to heterocyclic compounds is of special interest, as the Gattermann-Koch and Reimer-Tiemann reactions often give poor results owing to the acid sensitive character of certain heterocyclic compounds.

Heterocyclic aldehydes can be conveniently obtained by periodate oxidation of the carbon−carbon sugar derivatives with heterocyclic aglucones[99-102].

Indole-3-aldehyde was the first heterocyclic aldehyde (not counting those dealt with in patents) to be synthesised by the formanilide method[103]. This compound is the starting

* The mechanism given here is not that suggested by Arnold and Sorm, for details of which see the original paper. (Ed. of Translation.)

TABLE 4. Unsaturated aldehydes prepared by the formamide method

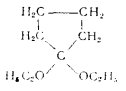
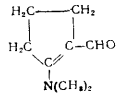
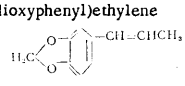
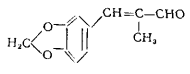
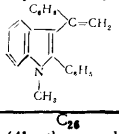
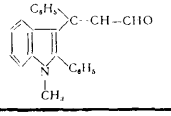
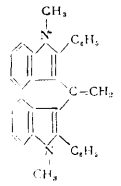
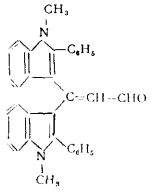
Starting material	Product	Formylating agent	Reaction conditions	Yield %	Reference
C_7					
Acetone diethylketal $CH_3C(OC_2H_5)_2CH_3$	β-dimethylaminocrotonaldehyde $CH_3-C(=CH-CHO)-N(CH_3)_2$	DMFA*	$COCl_2$, dichloroethane, 3 h, 40°	46	97
C_8					
Styrene	Cinnamaldehyde	DMFA	$POCl_3$, 1 h, 75°-80°	41	93
"	"	"	$POCl_3$, dichloroethane, boiling, 15 min	38	93
"	"	MFA**	$POCl_3$, CCl_4, 20°-25°	-	91
1,3-Dimethoxybenzene	2,4-Dimethoxycinnamaldehyde	MAPr***	$POCl_3$, $CHCl_3$, 1.5 h, 35°	90	28
Dimethylaniline	*p*-(Dimethylamino)cinnamaldehyde	"	"	70-80	28
"	1-[*p*-(Dimethylamino)phenyl]penta-1,3-dien-5-al $(CH_3)_2N-C_6H_4-(CH=CH)_2CHO$	MAPd****	"	18-20	28
Diethyl succinate	Diethyl 2-formylsuccinate	DMFA	NaH, ethanol	-	22
C_9					
4-Methylstyrene	*p*-Methylcinnamaldehyde	DMFA	$POCl_3$, dichloroethane, 40 min, 5°, or 15 min [boiling? (Ed. of Translation)]	46	93
1-Methyl-1-phenylethylene	β Phenylcrotonaldehyde	"	$POCl_3$, boiling for 1 h, 75°-80°	52	93
Cyclopentanone diethylketal 	2-Dimethylaminocyclopenten-1-aldehyde 	"	$COCl_2$, dichloroethane, 3 h, 40°	47.6	97
Pinacolone diethylketal	β-Butyl-β-ethoxyacrolein	DMFA	$COCl_2$, dichlorethane, 3 h, 40°	82	97
C_{10}					
Azulene	1-(Azulenyl-1')prop-1-en-3-al	MAPr	$POCl_3$, 20°-25°	good	96
"	1-(Azulenyl-1')penta-1,3-dien-5-al	MAPd	"	"	96
1-Methyl-1-(*p*-methylphenyl)-ethylene	β-(4'-Methylphenyl)crotonaldehyde	DMFA	$POCl_3$, 1 h, 75°-80°	64	93
1-Methyl-2-(*p*-methoxyphenyl)-ethylene	α-Methyl-β-(4'-methoxyphenyl)acrolein	"	"	68	93
1-Methyl-2-(methylene-3',4'-dioxyphenyl)ethylene 	α-Methyl-β-(methylene-3',4'-dioxyphenyl)-acrolein 	"	"	27	93
Cyclohexanone diethylketal	2-Ethoxycyclohexen-1-aldehyde	DMFA	$COCl_2$, dichloroethane, 3 h, 40°	59	97
Diethylaniline	4-Dimethylaminocinnamaldehyde	MAPr	$POCl_3$, $CHCl_3$, 1.5 h, 35°	84	28
C_{12}					
1-Methyl-1-(*p*-isopropylphenyl)-ethylene	β-(*p*-Isopropylphenyl)crotonaldehyde	DMFA	$POCl_3$, dichloroethane, 15 min boiling	34	93
Acetophenone diethylketal	β-Chlorocinnamaldehyde and β-dimethylaminocinnamaldehyde	"	$COCl_2$, dichloroethane, 3 h, 40°	5.8 and 25.7	97
C_{13}					
Propiophenone diethylketal	α-Methyl-β-ethoxy-β-phenylacrolein	DMFA	$COCl_2$, dichloroethane, 3 h, 40°	92	97
C_{14}					
1,1-Bis(*p*-hydroxyphenyl)ethylene	β,β-Bis(*p*-hydroxyphenyl)acrolein	MFA	$POCl_3$, CCl_4, 20°	-	91
1,1-Bis(*p*-chlorophenyl)ethylene	β,β-Bis(*p*'-chlorophenyl)acrolein	"	"	-	91
C_{15}					
Guaiazulene	1-(Guaiazulenyl-3')prop-1-en-3-al	MAPr	$POCl_3$, $CHCl_3$, 1.5 h, 35°	good	96
"	1-(Guaiazulenyl-3')penta-1,3-dien-5-al	MAPd	"	-	96
C_{16}					
1-Phenyl-1-(*p*-dimethylamino-phenyl)-ethylene	1-Phenyl-1-(*p*-dimethylaminophenyl)-penta-1,3-dien-5-al	MAPd	$POCl_3$, $CHCl_3$, 1.5 h, 35°	94	28
1,1-Bis-(*p*-methylaminophenyl)-ethylene	β,β-Bis(*p*-dimethylaminophenyl) acrolein	MFA	$POCl_3$, CCl_4, room temperature	-	91

TABLE 4. (contd.)

Starting material	Product	Formylating agent	Reaction conditions	Yield %	Reference
C_{23} 1-Phenyl-1-(1'-methyl-2'-phenylindol-3'-yl)ethylene	β-Phenyl-β-(1-methylphenylindolyl-3')-acrolein	MFA	$POCl_3$, CCl_4, room temperature	-	91
1-(*p*-Chlorophenyl)-1-(1'-methyl-2'-phenylindol-3'-yl)ethylene 	β-(*p*-Chlorophenyl)-β-(1'-methyl-2'-phenylindol-3'-yl)acrolein 	MFA	$POCl_3$, CCl_4, room temperature	-	91
C_{26} 1,1-Bis(4'-ethoxynaphth-1'-yl)-ethylene	β,β-Bis(4-ethoxynaphth-1-yl)acrolein	MFA		-	91
C_{32} 1,1-Bis(1'-methyl-2'-phenyl-indolyl-3')ethylene 	2,2-Bis(1'-methyl-2'-phenylindolyl-3')-acrolein 	MFA	$POCl_3$, CCl_4, room temperature	-	91

* Dimethylformamide.

** Methylformanilide.

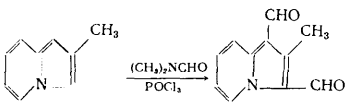
*** 2-Phenylmethylaminoacrolein.

**** 5-Phenylmethylaminopenta-1, 3-dien-5-al.

material in the synthesis of racemic tryptophan. It can be prepared by direct formylation of indole or its potassium salt in 53–72% yield[103,104], or by formylation of 2-ethoxycarbonyl indole; in the latter case the aldehyde separates in quantitative yield after saponification and decarboxylation[103]. In some later work dimethylformamide is given preference over methylformanilide, as it can serve at the same time as a solvent[29,105]. This last method, which gives quantitative yields, is considered the best for the preparation of indole-3-aldehyde.

Pyrrole reacts with dimethylformamide even in the cold, forming 83% of pyrrole-2-aldehyde[29]. Other aldehydes of the pyrrole series are obtained in the like manner[106].

Holland and Nayler[107] established that the formylation of 2-methylpyrrocoline by this method yields a product with two aldehyde groups in the nucleus:



Buu-Hoi and Hoan[108] extended the formylation by methylformanilide to carbazoles, and described the preparation of a series of *N*-alkylcarbazole-3-aldehydes. Kucherova et al.[109] found that the formylation of *N*-substituted 1,2,3,4-tetrahydrocarbazoles, in contrast to that of *N*-alkylcarbazoles, yields 7-aldehydes.

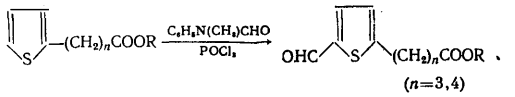
Of special interest is the first direct formylation of the pyridine ring by methylformanilide[110], in which an α-aldehyde, but not the β-isomer, was obtained. Quinoline does not react at all, whereas *N*-methyl-1,2,3,4-tetrahydroquinoline is formylated yielding 46% of the 6-aldehyde[111]. Attempts to formylate pyrazole and *N*-benzoylpyrazole were not successful[112,113], but nevertheless Finar and Lord recently carried out the formylation of 1-methyl-, 1-phenyl-, and 1-*m*-nitrophenylpyrazoles, and some other derivatives, with dimethylformamide, and obtained 4-aldehydes[114].

The formylation of oxygen-containing acid sensitive heterocycles by means of dimethylformamide has recently been reported to be successful. The formylation of furan and its homologues with dimethylformamide in the presence of $POCl_3$ is worthy of mention[115]. Yields of α-aldehydes are 50–70%. Harsher reaction conditions are required for the introduction of an aldehyde group into a benzofuran ring, and the yields are lower than in the case of furan and its derivatives[116,117]. A 7-methoxy substituent has a beneficial effect, whereas a chlorine atom in position 5 inhibits the formylation[116]. 2-Methoxydibenzofuran[118], 5-ethylnaphtho[2,1-*b*]furan[116], and phenanthro[3,2-*a*]dibenzofuran[119] have also been formylated. The formylation of certain hydroxycoumarins[120] and 1,4-dioxane[121] has been studied.

The formylation of thiophene and its derivatives has been studied in detail by a number of workers. King and Nord[122,123] found that at 90°–100° the aldehyde group enters the α-position. If both α-positions are occupied, the formyl group is attached in the β-position, so that even 2,3,5-trimethylthiophene forms an aldehyde in satisfactory yield. The formylation of thiophene with dimethylformamide can also be carried out at higher temperatures[20,124,125], but Weston and Michaelis[21] found that on increasing the reaction time to 16–18 h, the reaction is completed even at room temperature. As expected, attempts at further formylation of thiophene aldehyde to obtain dialdehydes, proved unsuccessful.

The formylation of alkyl-[20,21,122-128] and aryl-[129] thiophenes has been the most thoroughly studied synthesis of heterocyclic aldehydes by means of substituted formamides. In the formylation of 5-bromothiophene an exchange of halogen atoms takes place between that compound and $POCl_3$, giving rise to 5-chlorothiophene-2-aldehyde. 5-Bromothiophene-2-aldehyde is obtained if $POBr_3$ is used in the reaction instead of $POCl_3$.[123]

Gol'dfarb and his colleagues described the preparation of new aldehydes derived from thiophene and bis(2-thienyl)-methane, which were subsequently used for the synthesis of aliphatic alcohols[128,130-132]. Esters of thiophene-2-carboxylic acids are formylated in a similar manner[133,134]:



Weston and Michaelis[21] also described the introduction of an aldehyde group into thionaphthene ring. Their results in the preparation of thionaphthene-3-aldehyde were recently confirmed by Gnaisas[135]. In contrast to thionaphthene, 4,5,6,7-tetrahydrothionaphthene yields a 2-aldehyde[136].

The first report on the formylation of the selenophene ring in 3,5-diarylselenophenes was published in 1954[129]. Yur'ev and his associates obtained high yields of selenophene-2-aldehyde and its homologues by this method[137-139].

Cauquil and Casadevall[140] developed a method for the preparation of phenothiazine aldehydes. On formylating unsubstituted phenothiazine or *N*-acylphenothiazine, the *N*-formyl derivatives are formed, whereas *N*-alkylphenothiazines yield phenothiazine-3-aldehydes. If the positions 3 and 4 are occupied, no formylation takes place.

Data available in the literature on the formylation of heterocyclic compounds with substituted formamides are collected in Table 5.

TABLE 5. Formylation of heterocyclic compounds

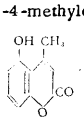
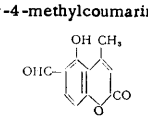
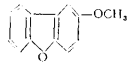
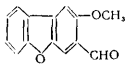
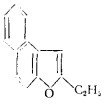
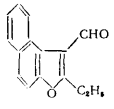
Starting material	Product	Formylating agent	Reaction conditions	Yield %	Reference
	1. Oxygen-containing heterocycles				
C_4					
Furan	Furfural	DMFA*	$POCl_3$, 30 min, 100°	64	115
1,4-Dioxane	1,4-Dioxane-2-aldehyde	MFA**	$POCl_3$, heat	37	121
C_5					
2-Methylfuran	5-Methylfurfural	DMFA	$POCl_3$, 30 min, 100°	76	115
C_6					
2-Ethylfuran	5-Ethylfurfural	DMFA	$POCl_3$, 30 min, 100°	50	115
2,5-Dimethylfuran	No aldehyde is formed	"	"	-	115
C_8					
Benzofuran	Benzofuran-2-aldehyde	DMFA	$POCl_3$, boiling for 6-7 h	37.7	116
C_9					
2-Methylbenzofuran	2-Methylbenzofuran-3-aldehyde	DMFA	$POCl_3$, boiling for 11 h	75	116
C_{10}					
2-Ethylbenzofuran	2-Ethylbenzofuran-3-aldehyde	DMFA	$POCl_3$, boiling for 11 h	66	116
2-Ethyl-5-chlorobenzofuran	2-Ethyl-5-chlorobenzofuran-3-aldehyde	"	"	6	116
5-Hydroxy-4-methylcoumarin	5-Hydroxy-4-methylcoumarin-6-aldehyde	MFA	"	low	120
					
2,7-Dihydroxy-4-methylcoumarin	7,9-Dihydroxy-4-methylcoumarin-8-aldehyde	MFA	$POCl_3$, boiling for 11 h	good	121
C_{11}					
2-Ethyl-7-methoxybenzofuran	2-Ethyl-7-methoxybenzofuran-3-aldehyde	DMFA	$POCl_3$, boiling for 11 h	76	116
4,7-Dimethyl-5-hydroxycoumarin	4,7-Dimethyl-5-hydroxycoumarin-8-aldehyde and 4,7-dimethyl-5-hydroxycoumarin-6-aldehyde	MFA	"	- -	120 120

TABLE 5. (contd.)

Starting material	Product	Formylating agent	Reaction conditions	Yield %	Reference
C_{12}					
5,7-Dimethoxy-4-methylcoumarin	5,7-Dimethoxy-4-methylcoumarin-6-aldehyde and 5,7-dimethoxy-4-methylcoumarin-8-aldehyde	MFA	$POCl_3$, boiling for 11 h	low "	121 121
C_{13}					
2-Methoxybenzofuran 	2-Methoxybenzofuran-3-aldehyde 	DMFA	$POCl_3$, 6 h, 95°-100°	25	118
5,6,7-Trimethoxy-4-methylcoumarin	5,6,7-Trimethoxy-4-methylcoumarin-8-aldehyde	MFA	$POCl_3$, 6 h, 95°-100°	low	120
C_{14}					
2-Phenylbenzofuran	2-Phenylbenzofuran-3-aldehyde	DMFA	$POCl_3$, 8 h	good	117
5-Ethyl-(2',1':2,3)napthofuran 	5-Ethyl-(2',1':2,3)naphthofuran-4-aldehyde 	"	$POCl_3$, toluene, boiling for 11 h	49.5	116
C_{15}					
2-Benzylbenzofuran	2-Benzylfuran-3-aldehyde	DMFA	$POCl_3$, 8 h	good	117
3-Benzylbenzofuran	3-Benzylbenzofuran-2-aldehyde	"	"	"	117
C_{16}					
2,5-Diphenylfuran	2,5-Diphenylfuran-3-aldehyde	DMFA	$POCl_3$, 3 h, 100°	40	115
3-Benzyl-6-methoxybenzofuran	3-Benzyl-6-methoxybenzofuran-2-aldehyde	"	$POCl_3$, 8 h	good	117
C_{18}					
3-(3',4'-Dimethoxybenzyl)-6-methoxybenzofuran	3-(3',4'-Dimethoxybenzyl)-6-methoxy-benzofuran-2-aldehyde	DMFA	$POCl_3$, 8 h	good	117

2. Sulphur- and selenium-containing heterocycles

C_4					
Thiophene	Thiophene-2-aldehyde	MFA	$POCl_3$, 20°-25°	75-77	122,141,142
Thiophene	Thiophene-2-aldehyde	DMFA	$POCl_3$, 1-2 h, 90°-95°	77	20,124,125
2-Chlorothiophene	5-Chlorothiophene-2-aldehyde	MFA or DMFA	$POCl_3$, 90°-95°	43-59	20,21,122
2-Bromothiophene	5-Bromothiophene-2-aldehyde	"	$POCl_3$, *o*-dichlorobenzene, 18 h, 20°	up to 70	21, 123
3-Bromothiophene	3-Bromothiophene-2-aldehyde	DMFA	$POCl_3$, boiling, 4.5 h	69	143
Selenophene	Selenophene-2-aldehyde	MFA	$POCl_3$, 65°	70	137
C_5					
2-Methylthiophene	5-Methylthiophene-2-aldehyde	MFA or DMFA	$POCl_3$, heat	66-81	20,122,124
3-Methylthiophene	3-Methylthiophene-2-aldehyde	"	$POCl_3$ or $SOCl_2$, heat	68-83	20,122,126
3-Methylselenophene	3-Methylselenophene-2-aldehyde	DMFA	$POCl_3$, 1 h, 50°-70°	72	138
C_6					
2-Ethylthiophene	5-Ethylthiophene-2-aldehyde	MFA	$POCl_3$, 100°	75-80	122
2,3-Dimethylthiophene	4,5-Dimethylthiophene-2-aldehyde	"	"	84.5	123
2,5-Dimethylthiophene	2,5-Dimethylthiophene-3-aldehyde	"	"	20	21,144
2-Acetamidothiophene	5-Acetamidothiophene-2-aldehyde	DMFA	$POCl_3$, 15 h, 95°	43	20,144,145
2,3-Dimethylselenophene	2,3-Dimethylselenophene-5-aldehyde	"	$POCl_3$, 65°	66	139
3,4-Dimethylselenophene	3,4-Dimethylselenophene-2-aldehyde	"	"	94	139
C_7					
2,3,5-Trimethylthiophene	2,3,5-Trimethylthiophene-4-aldehyde	MFA	$POCl_3$, 100°	38	123
2-Propylthiophene	5-Propylthiophene-2-aldehyde	"	"	77-85	122,127
2,3,4-Trimethylselenophene	2,3,4-Trimethylselenophene-5-aldehyde	DMFA	$POCl_3$, 65°	77	139
C_8					
2-n-Butylthiophene	5-n-Butylthiophene-2-aldehyde	MFA	$POCl_3$, 3 h, 25°-35°	80	128
2-t-Butylthiophene	5-t-Butylthiophene-2-aldehyde	"	"	76-99	20,21,128

TABLE 5. (contd.)

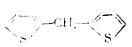
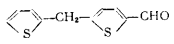
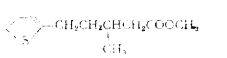
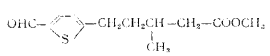
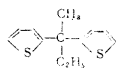
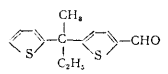
Starting material	Product	Formylating agent	Reaction conditions	Yield %	Reference
Thionaphthene	Thionaphthene-3-aldehyde	MFA	$POCl_3$, 16 h, 25°-35°	9	21, 135
4, 5, 6, 7-Tetrahydrothionaphthene	4, 5, 6, 7-Tetrahydrothionaphthene-2-aldehyde	"	$POCl_3$, heat	-	136
5-(β-acetoxyethyl)thiophene	5-(β-acetoxyethyl)thiophene-2-aldehyde	"	"	-	21, 130
C_9					
2-Methyl-5-t-butylthiophene	2-Methyl-5-t-butylthiophene-3-(or 4)-aldehyde	MFA	$POCl_3$, 3 h, 55°-65°	30.5	128
Bis(2-thienyl)methane	1-(2'-Thenyl)thiophene-5-aldehyde	"	$POCl_3$, 25°-35°	48	131
					
C_{10}					
2-Phenylthiophene	5-Phenylthiophene-2-aldehyde	MFA	$POCl_3$, toluene, 5 h	80	129
2-*m*-Chlorophenylthiophene	5-*m*-Chlorophenylthiophene-2-aldehyde	"	"	70	129
6-Ethoxythionaphthene	6-Ethoxythionaphthene-3-aldehyde	"	$POCl_3$, heating at 100°	-	36
2-(γ-Ethoxycarbonylpropyl)thiophene	5-(γ-Ethoxycarbonylpropyl)thiophene-2-aldehyde	"	$POCl_3$, 20°-25°	83	133, 134
2-(δ-Methoxycarbonylbutyl)thiophene	5-(δ-Methoxybutyl)thiophene-2-aldehyde	"	"	94	134
5-Methyl-2-(then-2-yl)thiophene	5-(5'-methyl-then-2'-yl)thiophene-2-aldehyde	"	$POCl_3$, 3 h, 55°-60°	44	128
C_{11}					
2-*m*-Tolylthiophene	5-*m*-Tolylthiophene-2-aldehyde	MFA	$POCl_3$, toluene, 5 h, 100°	77	129
2-(δ-Ethoxycarbonylbutyl)thiophene	5-(δ-Ethoxycarbonylbutyl)thiophene-2-aldehyde	"	$POCl_3$, 25°-35°	75-83	134
2-(γ-Methyl-δ-methoxycarbonylbutyl)thiophene	5-(γ-Methyl-δ-methoxycarbonylbutyl)-thiophene-2-aldehyde	"	"	84	134
					
C_{12}					
2, 5-Di-t-butylthiophene	2, 5-Di-t-butylthiophene-3-aldehyde	MFA	$POCl_3$, 3 h, 55°-60°	36	128
2, 2-Bis(2'-thienyl)butane	2-(2'-Thienyl)-2-(5'-formylthien-2'-yl)butane	"	$POCl_3$, 25°-35°	64	132
					
C_{16}					
2, 4-Diphenylthiophene	3, 5-Diphenylthiophene-2-aldehyde	MFA	$POCl_3$, toluene, 100°	-	129
2, 4-Diphenylselenophene	3, 5-Diphenylselenophene-2-aldehyde	"	$POCl_3$, toluene, 5 h, 100°	83.5	129
C_{18}					
2, 4-Di-*p*-tolylthiophene	3, 5-Di-*p*-tolylthiophene-2-aldehyde	MFA	$POCl_3$, 100°, toluene	82	129
2, 4-Di-*p*-tolylselenophene	3, 5-Di-*p*-tolylselenophene-2-aldehyde	"	"	83	129
2, 4-Di-*p*-anisylselenophene	3, 5-Di-*p*-anisylselenophene-2-aldehyde	"	"	69	129
	3. Nitrogen-containing heterocycles				
C_4					
Pyrrole	Pyrrole-2-aldehyde	DMFA	$POCl_3$, dichloroethane, 30 min, 30°-40°	39-89	29, 34, 146
1-Methylpyrazole	1-Methylpyrazole-4-aldehyde	"	$POCl_3$, 1.5 h, 95°-100°	33	112
C_5					
Pyradine	Picolinic aldehyde	MFA	$POCl_3$, 100°	low	110
N-Methylpyrrole	*N*-Methylpyrrole-2-aldehyde	DMFA	$POCl_3$, dichloroethane, 30°-40°	79-90	34
C_8					
Indole	Indole-3-aldehyde	DMFA	$POCl_3$, DMFA, 30°-35°	95.5	29
"	"	MFA	$POCl_3$, dichloroethane, 100°	53.5	103
"	"	*N*-Formylindoline	$POCl_3$, trichloroethane, boiling, 30 min	25	26
Potassium indole	"	DMFA	$POCl_3$, 30°-35°, DMFA	72	104

TABLE 5. (contd.)

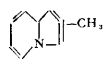
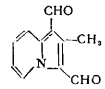
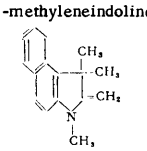
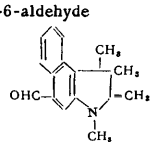
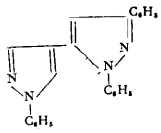
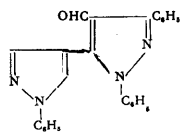
Starting material	Product	Formylating agent	Reaction conditions	Yield %	Reference
C_9					
2-Methylpyrrocoline 	1,3-Diformyl-2-methylpyrrocoline 	DMFA	$POCl_3$, 15 min, 50°-60°	28	107
2,4-Dimethyl-5-ethoxycarbonylpyrrole	2,4-Dimethyl-3-formyl-5-ethoxycarbonylpyrrole	DMFA	$POCl_3$, boiling, 2 h	96	106
1-Phenylpyrazole	1-Phenylpyrazole-4-aldehyde	"	$POCl_3$, DMFA, 4 h, 95°-100°	76	112
1-(*m*-Nitrophenyl)pyrazole	1-(*m*-Nitrophenyl)pyrazole-4-aldehyde	"	"	9	114
C_{10}					
N-Methyl-1,2,3,4-tetrahydroquinoline	*N*-Methyl-1,2,3,4-tetrahydroquinoline-6-aldehyde	MFA	$POCl_3$, benzene, 10-12 h, 20°	46	111
C_{11}					
2-Ethoxycarbonylindole	2-Ethoxycarbonylindole-3-aldehyde	MFA	$POCl_3$, dichloroethane, boiling, 1 h	99.5	103
5-Bromo-2-ethoxycarbonylindole	5-Bromo-2-ethoxycarbonylindole-3-aldehyde	DMFA	"	42	105
C_{12}					
1,2,3,4-Tetrahydrocarbazole	*N*-Formyl-1,2,3,4-tetrahydrocarbazole	DMFA	$POCl_3$, 8 h, 95°-100°	65	109
1,3,3-Trimethyl-2-methyleneindoline	1,3,3-Trimethyl-2-methyleneindoline-6-aldehyde	MFA	$POCl_3$, benzene, 5°-15°	80	142
C_{13}					
N-Methylcarbazole	*N*-Methylcarbazole-3-aldehyde	MFA	$POCl_3$, *o*-dichlorobenzene, 6 h, 100°	61	27
N-Methyl-1,2,3,4-tetrahydrocarbazole	-Methyl-1,2,3,4-tetrahydrocarbazole-*N*-7-aldehyde	DMFA	$POCl_3$, 8 h, 95°-100°	34	109
N-Methyl-6-nitrocarbazole	*N*-Methyl-6-nitrocarbazole-3-aldehyde	MFA	$POCl_3$, *o*-dichlorobenzene, 6 h, 100°	80	108
N-Methyl-6-bromocarbazole	*N*-Methyl-6-bromocarbazole-3-aldehyde	"	"	85	108
C_{14}					
N-Ethylcarbazole	*N*-Ethylcarbazole-3-aldehyde	MFA	$POCl_3$, 100°	-	36
2-Methyl-4-phenyl-5-ethoxycarbonylpyrrole	2-Methyl-4-phenyl-5-ethoxycarbonylpyrrole-3-aldehyde	DMFA	$POCl_3$, boiling, 2 h	97	106
C_{15}					
5-Benzyloxyindole	5-Benzyloxyindole-3-aldehyde	DMFA	$POCl_3$, 45 min, 35°	75	147
C_{16}					
N-Butylcarbazole	-Butylcarbazole-3-aldehyde	MFA	$POCl_3$, *o*-dichlorobenzene, boiling	81	108
4,5-Benzo-1,3,3-trimethyl-*N*-2-methyleneindoline 	4,5-Benzo-1,3,3-trimethyl-2-methyleneindoline-6-aldehyde 	"	$POCl_3$, benzene, 5°-15°	-	148
1,4-Diphenylpiperazine	1,4-Bis(4'-formylphenyl)piperazine	DMFA	$POCl_3$, 1.5 h, 95°-100°	-	81
N-Butyl-6-nitrocarbazole	*N*-Butyl-6-nitrocarbazole-3-aldehyde	MFA	$POCl_3$, *o*-dichlorobenzene, 6 h, 100°	85	108
N-Butyl-6-bromocarbazole	*N*-Butyl-6-bromocarbazole-3-aldehyde	"	"	90	108
C_{17}					
N-Isopentylcarbazole	-Isopentylcarbazole-3-aldehyde	MFA	$POCl_3$, *o*-dichlorobenzene, 6 h, 100°	85	108
N-Butyl-6-methylcarbazole	*N*-Butyl-6-methylcarbazole-3-aldehyde	"	"	85	108
-Isopentyl-6-nitrocarbazole	*N*-Isopentyl-6-nitrocarbazole-3-aldehyde	"	"	85	108
C_{19}					
N-Benzyl-1,2,3,4-tetrahydrocarbazole	*N*-Benzyl-1,2,3,4-tetrahydrocarbazole-*N*-7-aldehyde	DMFA	$POCl_3$, 8 h, 95°	36	109

TABLE 5.(contd.)

Starting Material	Product	Formylating agent	Reaction conditions	Yield %	Reference
C_{24} 1,3,1'-Triphenyl-5,4'-bipyrazole 	1,3,1'-Triphenyl-5,4'-bipyrazole-4--aldehyde 	DMFA	$POCl_3$, DMFA, 4 h, 95°-100°	83	114

4. Heterocycles with more than one hetero-atom

C_{10} 4-Phenylmorpholine	*p*-(4-Morpholinyl)benzaldehyde	DMFA	$POCl_3$, 1-2 h, 95°-100°	2	81
C_{13} 10-Methylphenothiazine	10-Methylphenothiazine-3-aldehyde	MFA	$POCl_3$, 4 h, 100°	88	140
C_{14} 10-Ethylphenothiazine	10-Ethylphenothiazine-3-aldehyde	MFA	$POCl_3$, 4 h, 100°	82.5	140
3,10-Dimethylphenothiazine	3,10-Dimethylphenothiazine-7-aldehyde	"	"	42	140
C_{15} 3-Methyl-10-ethylpheno-thiazine	3-Methyl-10-ethylphenothiazine-7--aldehyde	MFA	$POCl_3$, 4 h, 100°	72	140
10-Phenylphenothiazine	10-Phenylphenothiazine-3-aldehyde	"	"	63	108

* Dimethylformamide.

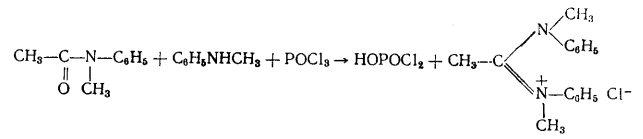
** Methylformanilide.

III. ACYLATION OF ORGANIC COMPOUNDS

Although discovered before formylation, other acylations of the various types of organic compounds with substituted carboxylic amides has been studied much less thoroughly than their formylation.

In 1896 Friedel[149] studied the reaction between *N*-methylacetanilide and $POCl_3$, which ensued upon heating the reactants at 120°. He continued the heating as long as HCl was evolved, and then, by treating the melt with soda solution, he obtained a dye, to which, upon analysis, he ascribed the formula $C_{22}H_{20}N_2Cl_2$. The structure of that dye remained unknown until Fischer and his colleagues[10] established that in the Friedel reaction, under the action of $POCl_3$, the acetyl group of one molecule of methylacetanilide was split off and attached to the nucleus of another such molecule, in the *o*-position with respect to the *N*-acetylamino group. The *o*-acetamidoacetophenone, which was thereby formed, was subsequently transformed into a cyanine dye.

Methylaniline formed in this reaction condenses easily in the presence of $POCl_3$ with unreacted methylacetanilide yielding *N*,*N*'-diphenyl-*N*,*N*'-dimethylacetamidinium chloride. This accords with the usual scheme for the formation of amidines from arylamides and secondary aliphatic--aromatic amines under the action of phosphorus halides[150]:



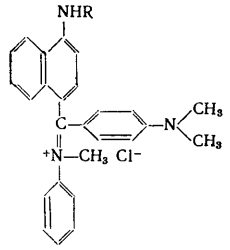
The amidine formed is presumed[11] to be even more capable of acylating the aromatic ring than the initial methylacetanilide.

Fischer's work proved the migration of the acetyl group from one molecule of aryl-*N*-alkylacetamide into the aromatic ring of another, and provided an explanation for the mechanism of a series of similar transformations, described in the patent literature[151-156].

By heating benzanilide with dimethylaniline and $POCl_3$ at 120°, 4-dimethylaminobenzophenone anil is formed[150]. Diethylaniline behaves similarly in this reaction.

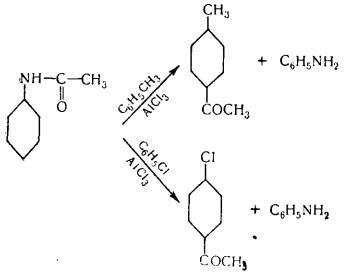
Noelting[152,153] patented the reaction for the introduction of the *p*-dimethylaminobenzyl group into the nucleus of *N*-methyl-α-naphthylamine, *N*-ethyl-α-naphthylamine, and *N*-phenyl-α-naphthylamine, by means of *N*-methyl-*p*-di-

methylaminobenzanilide in dimethylaniline solution. Here the reaction products are dyes similar in their properties to auramine:

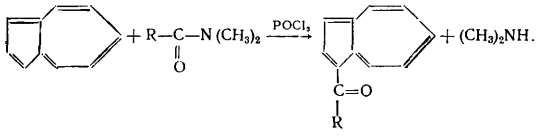


where R = CH_3, C_2H_5, C_6H_5.

The uses of benzoyl-*m*-xylidine[148], *N*-methylbenzanilide[154,155], *m*-methoxybenzanilide[155], and α-naphthanilide[156] as acylating agents have been reported in patents. Acetanilide in the presence of $AlCl_3$ is also capable of acylating the benzene ring in toluene and chlorobenzene[157,158].



This reaction proceeds via the intermediate formation of acetyl chloride, followed by a Friedel-Crafts ketone synthesis, i.e. as in the case of the molecular rearrangement of anilides[159]. The more reactive aromatic hydrocarbons react with substituted amides even under ordinary conditions. Hafner and Bernhard[160] developed a very elegant method for the preparation of azulenic ketones by acylation of azulene with different *N*,*N*-dimethylcarboxamides. The reaction is carried out in the presence of $POCl_3$, by boiling for 4 h in tetrahydrofuran solution.



1-Acetylazulene, 1-benzoylazulene, 1-lauroylazulene, and ω-ethoxycarbonylhexyl(1-azulyl)ketone were prepared by this method.

1. I. V. Machinskaya, "Reaktsii i Metody Issledovaniya Organicheskikh Soedinenii" (Reactions and Methods for the Study of Organic Compounds), Vol. 7, Goskhimizdat, 1958, p. 309.
2. H. Fischer, H. Berg, and A. Schormuller, Annalen, 480, 153 (1930).
3. C. Thomas, "Anhydrous Aluminium Chloride in Organic Chemistry" (Translated into Russian), Inostr. Lit., 1949, p. 595.
4. N. Crounse, "Organic Reactions", 1949, Vol. 5, p. 290.
5. I. V. Machinskaya, "Reaktsii i Metody Issledovaniya Organicheskikh Soedinenii" (Reactions and Methods for the Study of Organic Compounds), Vol. 7, Goskhimizdat, 1958, p. 279.
6. P. Karrer, Helv. Chim. Acta, 2, 89 (1919).
7. K. Reimer and F. Tiemann, Ber., 9, 824 (1876).
8. J. C. Duff, J. Chem. Soc., 547 (1941).
9. J. C. Duff, J. Chem. Soc., 276 (1945).
10. O. Fischer, A. Müller, and A. Vilsmeier, J. prakt. Chem., 109, (2), 69 (1924).
11. A. Vilsmeier and A. Haack, Ber., 60, 119 (1927).
12. N. N. Vorozhtsov, "Osnovy Sinteza Promezhutochnykh Produktov i Krasitelei" (Principles of the Synthesis of Intermediate Products and Dyes). Goskhimizdat, 1955, p. 712.
13. L. Fieser and M. Fieser, "Organic Chemistry" (Translated into Russian), Inostr. Lit., 1949.
14. I. Houben-Weil, "Methoden der organischen Chemie", G. Tieme, Stuttgart, 1954, Band III (1).
15. L. N. Ferguson, Chem. Rev., 38, 227 (1946).
16. A. Van Dormael, Ind. chim. belge, 16, 433 (1951).
17. "Organic Syntheses" (Translated into Russian), Inostr. Lit., Vol. 3, 1952 p. 320.
18. J. Werner and H. Trimborn, Chem. Ztg., 78, 682 (1954).
19. G. Hara, J. Soc. Organ. Synth. Chem. Japan, 16, 144 (1958).
20. E. Compaigne and W. L. Archer, J. Amer. Chem. Soc., 75, 989 (1953).
21. A. W. Weston and R. J. Michaelis, J. Amer. Chem. Soc., 72, 1422 (1950).
22. E. van Heyningen, J. Amer. Chem. Soc., 80, 5470 (1958).
23. G. Kalischer, H. Scheyer, and K. Keller, German Pat. 514415; Frdl., 17, 564.
24. G. Kalischer and K. Keller, German Pat. 519806, quoted in Ref. 15.
25. S. Akabori and J. Senoh, Chem. Soc. Japan, 14, 166 (1939).
26. A. H. Sommers, R. J. Michaelis, and A. W. Weston, J. Amer. Chem. Soc., 74, 5546 (1952).
27. A. N. Kost and A. G. Yudin, "Materialy Soveshchaniya po Khimii, Tekhnologii i Primeneniyu Proizvodnykh Piridina i Khinolina, Riga, 1957" (Communications at the Conference on the Chemistry, Technology, and Application of Pyridine and Quinoline Derivatives, Riga, 1957) (in print).
28. C. Jutz, Chem. Ber., 91, 850 (1958).
29. G. F. Smith, J. Chem. Soc., 3842 (1954).
30. A. Vilsmeir, Chem. Ztg., 75, 133 (1951).
31. H. Lorenz and R. Wizinger, Helv. Chim. Acta., 28, 600 (1945).
32. W. Treibs, H. J. Neupert, and J. Hiebsch, Chem. Ber., 92, 141 (1959).
33. G. Cauquil and A. Casadevall, Compt. rend., 236, 1569 (1953).
34. R. M. Silverstein, E. Ryskiewicz, C. Willard, and R. C. Koehler, J. Org. Chem., 20, 668 (1955).
35. K. Hafner and C. Bernhard, Angew. Chem., 69, 533 (1957).
36. French Pat., Chem. Zentr., 1, 2825 (1929).
37. German Pat. 519444, Frdl., 17, 565; Chem. Abs., 25, 2734 (1931).
38. J. H. Wood and R. W. Bost, J. Amer. Chem. Soc., 59, 1721 (1937).
39. L. F. Fieser and J. L. Hartwell, J. Amer. Chem. Soc., 60, 2555 (1938).
40. "Organic Syntheses" (Translated into Russian), Inostr. Lit., Vol. 3, 1952, p. 74.
41. L. F. Fieser and J. E. Jones, J. Amer. Chem. Soc., 64, 1666 (1942).
42. N. P. Buu-Hoï and D. Lavit, Rec. Trav. chim., 77, 724 (1958).
43. H. Volman, H. Becker, M. Corell, and H. Streeck, Annalen, 1, 531 (1937).
44. G. Saint-Ruf, N. P. Buu-Hoï, and P. Jacquignon, J. Chem. Soc., 48 (1958).
45. L. F. Fieser and E. B. Herschberg, J. Amer. Chem. Soc., 60, 2542 (1938).
46. N. P. Buu-Hoï and D. Lavit, Rec. Trav. chim., 76, 321

(1957).
47. N. P. Buu-Hoï and D. Lavit, Rec. Trav. chim., 75, 1194 (1956).
48. N. P. Buu-Hoï, D. Lavit, and P. Jacquignon, Rec. Trav. chim., 77, 462 (1958).
49. N. P. Buu-Hoï and C. T. Long, Rec. Trav. chim., 75, 1221 (1956).
50. N. P. Buu-Hoï and D. Lavit, Rec. Trav. chim., 76, 419 (1957).
51. G. Rio and B. Sillion, Compt. rend., 244, 623 (1957).
52. W. Treibs, I. Hiebsch, and H. I. Neupert, Naturwiss., 44, 352 (1957).
53. K. Hafner, Angew. Chem., 70, 419 (1958).
54. K. Hafner and J. Schneider, Annalen, 624, 37 (1959).
55. G. D. Bromund, J. M. Osgerby, and P. L. Pauson, Chem. and Ind., 209 (1957).
56. P. J. Graham, G. W. Parschall, M. L. Peterson, and G. M. Whitman, J. Amer. Chem. Soc., 79, 3416 (1957).
57. M. Rosenblum, Chem. and Ind., 72 (1957).
58. C. D. Broadhead, J. M. Osgerby, P. L. Pauson, and R. V. Lindsay, J. Chem. Soc., 650 (1958).
59. U. S. Pat. 2 849 469 (1958); Chem. Abs., 53, 4298 (1959).
60. A. N. Nesmeyanov and E. G. Perevalova, Uspekhi Khim., 27, 3 (1958).
61. W. Treibs and G. Möbius, Annalen, 619, 122 (1958).
62. N. P. Buu-Hoï and D. Lavit, Rec. Trav. chim., 77, 467 (1958).
63. N. P. Buu-Hoï, N. D. Xyong, M. Sy, G. Lejenne, and N. B. Tien, Bull. Soc. chim. France, 1594 (1955).
64. M. Bisagni, N. P. Buu-Hoï, and R. Roger, J. Chem. Soc., 3693 (1955).
65. N. P. Buu-Hoï, G. Lejenne, and M. Sy, Compt. rend., 240, 2241 (1955).
66. W. B. Brownell and A. W. Weston, J. Amer. Chem. Soc., 73, 4971 (1951).
67. G. Lejenne, N. P. Buu-Hoï, M. Sy, and A. Cheutin, Bull. Soc. chim. France, 1073 (1957).
68. J. P. Brown and E. B. McCall, J. Chem. Soc., 3875 (1957).
69. N. P. Buu-Hoï and D. Lavit, J. Chem. Soc., 2776 (1955).
70. N. P. Buu-Hoï, N. Hoan, and M. R. Knenissi, J. Chem. Soc., 2307 (1951).
71. R. Roger, P. Demerseman, and A. Cheutin, Bull. Soc. chim. France, 304 (1957).
72. N. P. Buu-Hoï, N. Hoan, and D. Lavit, J. Chem. Soc., 485 (1953).
73. N. P. Buu-Hoï, D. Lavit, and J. Collard, J. Org. Chem., 23, 542 (1958).
74. N. P. Buu-Hoï and D. Lavit, J. Org. Chem., 21, 21 (1956).
75. N. P. Buu-Hoï and D. Lavit, J. Chem. Soc., 1743 (1956).
76. N. P. Buu-Hoï and D. Lavit, J. Chem. Soc., 2412 (1956).
77. N. P. Buu-Hoï and D. Lavit, J. Org. Chem., 22, 912 (1957).
78. G. R. Ames and W. Davey, J. Chem. Soc., 3480 (1957).
79. H. Burton, J. Chem. Soc., 280 (1945).
80. German Pat. 547 101; Frdl., 18, 2973.
81. U. K. Pat. 607 980 (1948); Chem. Abs., 43, 2232 (1949).
82. N. P. Buu-Hoï, P. Jacquignon, and C. T. Long, J. Chem. Soc., 505 (1957).
83. U. S. Pat. 2 558 285 (1951); Chem. Abs., 46, 1041 (1952).
84. French Pat. 860 456; Chem. Zentr., 1, 2710 (1940).
85. W. Richter, German Pat. 706 437; Chem. Abs., 36, 1946 (1942).
86. R. M. Anker and A. H. Cook, J. Chem. Soc., 489 (1944).
87. N. P. Buu-Hoı, R. Roger, and M. Hubert-Habart, J. Chem. Soc., 3584 (1953).
88. F. Meyer and W. Freund, Ber., 55, 2049 (1922).
89. J. R. Pettit and E. G. Thomas, J. Org. Chem., 24, 895 (1959).
90. U. S. Pat. 2 437 370; Chem. Abs., 42, 5924 (1948).
91. French Pat. 839 359; Chem. Zentr., 11, 1774 (1939).
92. U. K. Pat. 504 125 (1939); Chem. Abs., 33, 7313 (1939).
93. C. J. Schmidle and P. G. Barnett, J. Amer. Chem. Soc., 78, 3209 (1956).
94. J. F. Areus and D. A. Van Dorp, Rec. Trav. chim., 67, 459, 973 (1948).
95. E. E. Royals and E. R. Covington, J. Amer. Chem. Soc., 77, 1697 (1955).
96. C. Jutz, Angew. Chem., 70, 270 (1958).
97. Z. Arnold and J. Zemlicka, Chem. Listy, 52, 458 (1958).
98. Z. Arnold and F. Sorm, Coll. Czech. Chem. Comm., 23, 452 (1958).
99. Yu. A. Zhdanov and G. N. Dorofeenko, Uspekhi Khim., 27, 179 (1958).
100. Yu. E. Zhdanov and G. N. Dorofeenko, Zhur. Obshch. Khim., 29, 2677 (1959).
101. H. Petering and D. Weisblat, J. Amer. Chem. Soc., 69, 2566 (1947).
102. R. M. Hann and C. S. Hudson, J. Amer. Chem. Soc., 69, 1050 (1947).
103. A. C. Shabica, E. E. Howr, J. B. Ziegler, and M. Tischler, J. Amer. Chem. Soc., 68, 1156 (1946).
104. A. T. Tyson and J. T. Shaw, J. Amer. Chem. Soc., 74, 2273 (1952).
105. G. Cavalini, F. Ravenna, and J. Grasso, Farmaco Ed. Scient, 13, 113 (1958).
106. E. Ju-Hwa-Chu and T. C. Chu, J. Org. Chem., 19, 266 (1954).
107. D. O. Holland and J. H. C. Nayler, J. Chem. Soc., 1504 (1955).
108. N. P. Buu-Hoï and N. Hoan, J. Amer. Chem. Soc., 73, 98 (1951).
109. N. F. Kucherova, V. P. Evdakov, and N. K. Kochetkov, Zhur. Obshch. Khim., 27, 1049 (1957).
110. Q. Mingoia and P. C. Ferreira, Anaic. fac. farm. odontol. Univ. San-Paulo, 11, 3 (1953); Chem. Abs., 49, 7566 (1955).
111. D. M. Brown and G. A. R. Kon, J. Chem. Soc., 2147 (1948).
112. I. L. Finar and G. H. Lord, J. Chem. Soc., 3314 (1957).
113. I. L. Finar and T. R. Hurlock, J. Chem. Soc., 3024 (1957).
114. I. L. Finar and G. H. Lord, J. Chem. Soc., 1819 (1959).
115. W. J. Traynelis, J. J. Miskel, and J. K. Sowa, J. Org. Chem., 22, 1269 (1957).
116. M. Bisagni, N. P. Buu-Hoï, and R. Roger, J. Chem. Soc., 3688 (1955).
117. J. R. Chatterjea, J. Indian Chem. Soc., 34, 347 (1957).
118. C. Routier, N. P. Buu-Hoï, and R. Roger, J. Chem. Soc., 4276 (1956).
119. N. P. Buu-Hoï and D. Lavit, J. Chem. Soc., 38 (1959).
120. R. M. Naik and V. M. Thakor, J. Org. Chem., 22, 1630 (1957).
121. E. A. Prill and W. R. Smith, Contrib. Boyce Thompson Inst., 18, 187 (1955).
122. W. J. King and F. F. Nord, J. Org. Chem., 13, 635 (1948).
123. W. J. King and F. F. Nord, J. Org. Chem., 14, 405, 638 (1949).
124. W. C. Emerson and T. M. Patrick, U. S. Pat. 2 581 009 (1952); Chem. Abs., 46, 9610 (1953).
125. D. J. Brockmeyer and F. C. Meyer, U. S. Pat. 2 746 220 (1956).
126. J. Lamy, D. Lavit, and N. P. Buu-Hoï, J. Chem. Soc., 4202 (1958).
127. N. P. Buu-Hoï, H. D. Xyong, R. Roger, and D. Lavit, J. Chem. Soc., 547 (1953).
128. Ya. L. Gol'dfarb and P. A. Konstantinov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 992 (1950).
129. P. Demerseman, N. P. Buu-Hoï, and R. Roger, J. Chem. Soc., 4193 (1954).

130. Ya. L. Gol'dfarb and M. B. Ibragimova, Dokl. Akad. Nauk SSSR, 113, 594 (1957).
131. Ya. L. Gol'dfarb and Ya. L. Danyushevskii, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 1361 (1956).
132. Ya. L. Gol'dfarb and P. A. Konstantinov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 121 (1959).
133. B. P. Fabrichnyi, N. F. Shalavina, and Ya. L. Gol'dfarb, Zhur. Obshch. Khim., 28, 2520 (1958).
134. Ya. L. Gol'dfarb, B. P. Fabrichnyi, and N. F. Shalavina, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 1276 (1956).
135. V. V. Gnaisas, J. Org. Chem., 22, 703 (1957).
136. N. P. Buu-Hoi and M. Kneinissi, Bull. Soc. chim. France, 359 (1958).
137. Yu. K. Yur'ev and N. N. Mezentsova, Zhur. Obshch. Khim., 27, 179 (1957).
138. Yu. K. Yur'ev, N. K. Sadovaya, and M. A. Gal'bershtam, Zhur. Obshch. Khim., 28, 620 (1958).
139. Yu. K. Yur'ev, N. K. Sadovaya, and M. A. Gal'bershtam, Zhur. Obshch. Khim., 29, 1970 (1959).
140. G. Cauquil and A. Casadevall, Compt. rend., 240, 538, 1784 (1955).
141. U.S. Pat. 2741622 (1956); Chem. Abs., 50, 16869 (1956).
142. A. W. Weston, U. S. Pat. 2601479 (1952); Chem. Abs., 47, 2214 (1953).
143. S. Nishimura, R. Motoyama, and E. Imoto, Bull. Univ. Osaka, 6A, 127 (1958); Chem. Abs., 53, 4248 (1959).
144. J. Cimmerman-Craig and D. Willis, Chem. and Ind., 797 (1953).
145. E. Compaigne, P. A. Monroe, B. Arnwine, and W. L. Archer, J. Amer. Chem. Soc., 75, 988 (1953).
146. R. M. Silverstein, E. E. Ryskiewicz, and S. W. Chaikin, J. Amer. Chem. Soc., 76, 1485 (1954).
147. A. F. S. Rash and W. R. Wrag, J. Chem. Soc., 3887 (1958).
148. N. Roh and G. Kochendoerfer, U. K. Pat. 506797; Chem. Zentr., 11, 3195 (1939).
149. M. Friedel, Bull. Soc. chim. France, 11/3, 1027 (1896).
150. A. Pictet, Ber., 23, 3015 (1890).
151. German Pat. 41451, Frdl., 1, 44.
152. E. Noelting, German Pat. 84655, Frdl., 4, 223.
153. E. Noelting, German Pat. 79390, Frdl., 4, 221.
154. German Pat. 42853, Frdl., 1, 598.
155. German Pat. 44077, Winther, 63.
156. German Pat. 6952, Winther, 64.
157. D. N. Kursanov, Zhur. Obshch. Khim., 13, 286 (1943).
158. J. F. J. Dippy and J. H. Wood, J. Chem. Soc., 2709 (1949).
159. B. I. Ardashev and V. I. Minkin, Uspekhi Khim., 28, 218 (1959).
160. K. Hafner and C. Bernhard, Annalen, 625, 108 (1959).

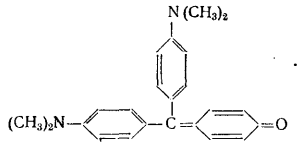
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INFLUENCE OF THE SOLVENT ON THE COLOUR OF DYES (SOLVATOCHROMISM)

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The colour of organic dyes always depends to a certain extent on the solvent. Acid and alkaline solvents change the colour of dyes by forming salts with them, but in most cases neutral solvents have little influence on the absorption of light by the dyestuff. There exists, however, a certain number of dyestuffs (or coloured substances) which change colour very markedly on passing from one completely neutral solvent to another. This has received the name "solvatochromism".

A classic example of solvatochromism is that exhibited by tetramethyldiaminofuchsone (I), prepared by Schlenk in 1909[1]:



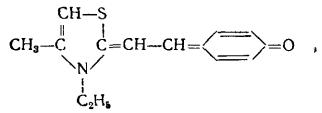
(I)

This dyestuff is yellow in benzene solution and red-violet in alcohol. Schlenk considered the change of colour as due to a change of molecular weight; the fuchsone giving a true solution in alcohol, but polymers being formed in benzene and the dyestuff dissolving as a colloid. This explanation of the solvatochromic effect in tetramethyldiaminofuchsone, as in other dyes, has since been shown to be false[2]; they dissolve, in organic solvents at least, to form monomolecular solutions.

Up to the 1940's, the solvatochromic effect was explained on the basis of the old views of the dyestuff molecule as one containing a stable system of valency bonds. Of various theories of this type by various workers[2,3,4], we shall consider only one – that of the formation of characteristically coloured complexes of the molecules with solvent molecules[2], since this type of theory is met even in later publications[5,6].

The attempt to explain solvatochromism in dyes by the formation of simple complexes with the solvent must be discarded mainly on the evidence of the study of the absorption spectra of such dyes in mixed solvents.

Kiprianov and Timoshenko[7] obtained the absorption curves of the dyestuff (II):



(II)

which shows a clear solvatochromic effect. These curves are shown in Fig. 1 (*A* in pyridine, *B* in water, and *C* in a

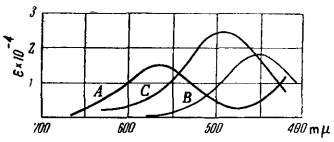


Fig. 1.

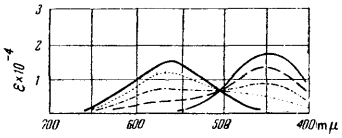


Fig. 2.