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CHEMICAL ADVANCES IN SYNTHESIS AND REACTIONS OF DIARYLUREAS

D.F.Kutepov

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I. INTRODUCTION

Urea (carbamide) and its derivatives have found wide application in the aniline dye industry and in the production of macromolecular compounds — plastics, synthetic resins, and rubber. They are of great importance also in the production of mineral fertilisers and feeding stuffs, and also in the preparation of chemical poisons for use in agriculture as insecticides, fungicides, and weed-killers.

Urea and its substituted derivatives are widely used in the synthesis of medicinal preparations, such as the complex aromatic urea derivative Germanin, which is more effective than any other trypanocidal preparations known hitherto.

Diphenylurea and its substituted derivatives are acquiring increasing importance every year. They form the starting materials for the synthesis of various chemical products.

Until recently, however, many questions of theoretical and practical significance concerning synthesis and reactions in the diarylurea series remained unanswered. The number of new compounds synthesised remained very inadequate, while known diarylureas and their derivatives were little studied.

With the evolution of chemical science and technology, it became necessary to investigate more thoroughly the reaction between aromatic amines and carbonyl chloride with the aim of obtaining diarylureas having various substituents both in the aromatic ring and attached to the nitrogen, and also to establish how the chemical, physicochemical, and other properties of the synthetic compounds varied with the nature and number of such substituents.

The synthesis of new compounds required a study of the chemistry of phosgenation processes, investigation both of the main reaction and of side-reactions, and study of the kinetics and mechanism of the reaction of carbonyl chloride with aromatic amines as a function of the reaction conditions.

Research workers have also been interested in the synthesis of diarylureas by the reaction of aromatic amines with aryl isocyanates. This method makes it possible to synthesise both symmetrical and unsymmetrical diarylureas as well as monoaryl- and arylalkyl-ureas.

Investigators have also studied the reaction of urea and diarylureas with aromatic amines at high temperatures, and this has led to the development of new methods for preparing diarylureas using urea as an acylating agent. Research on these lines led to the discovery of the reaction of transamidation, on the basis of which original methods have been worked out for preparing aromatic amines without the use of the acylating agents carbonyl chloride and urea.

In the course of the investigations it also became necessary to study and work out direct methods for synthesising substituted diarylureas by nitration, chlorination, and sulphonation of the initial diphenylurea. These reactions have been little studied until recently, while in individual cases the evidence was contradictory.

During recent years due attention has been paid to problems of the synthesis of aryl-, arylalkyl-, and diaryl--ureas, the study of their hydrolytic properties, and also the investigation of the various changes accompanying the interaction of diarylureas with aromatic amines.

The present paper discusses chemical progress in synthesis and in reactions in the diarylurea series.

II. SYNTHESIS OF DIARYLUREAS BY PHOSGENATION OF AROMATIC AMINES

The compound which has been studied most thoroughly in the diarylurea series is diphenylurea (carbanilide). It was first prepared by Hofmann [1] by passing carbonyl chloride into a saturated aqueous solution of aniline:

$$2C_6H_5NH_2 + COCl_2 \longrightarrow C_6H_5NHCONHC_6H_5 + 2HCl.$$

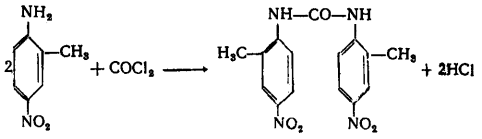
When distilled over phosphorus pentoxide, diphenylurea is partly decomposed into aniline and phenyl isocyanate:

$$C_6H_5NHCONHC_6H_5 \xrightarrow{P_2O_5} C_6H_5NH_2 + C_6H_5NCO.$$

Aromatic amines react readily with carbonyl chloride to form symmetrical diarylureas. This is a general reaction with primary and secondary amines.

A method has been described [2] for obtaining diphenylurea from aniline and carbonyl chloride in the presence of sodium carbonate in aqueous medium. Methods have also been worked out for obtaining diphenylurea by the phosgenation of aniline in aqueous medium, with the use of chalk, caustic alkali, or sodium bicarbonate to remove the hydrogen chloride formed [3].

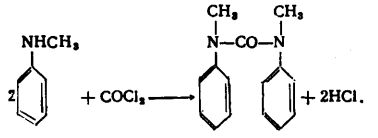
A large number of substituted diarylureas have now been prepared. Thus heating 2-methyl-4-nitroaniline with carbonyl chloride in toluene solution yields bis-2-methyl-4-nitrophenylurea [4]:



This method can be used with certain modifications to obtain the isomeric bismethylnitrophenylureas and bis-dimethylnitrophenylureas, as well as bis-4-nitrophenylurea [5,6].

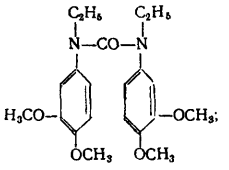
Phosgenation of the corresponding substituted anilines in an inert solvent in the presence of dimethylaniline yields bis-3-chloro-6-methoxy-4-nitrophenylurea and bis-2,5--dimethoxy-4-nitrophenylurea [7,8].

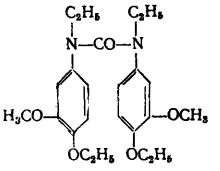
These methods can be recommended also for the preparation of other symmetrical halogeno, nitro, alkyl, and alkoxy derivatives of diarylureas. For example, symmetrical *NN'*-dimethyldiphenylurea (Centralite) is formed by the phosgenation of methylaniline:



Lastovskii[9] obtained the three isomeric (*o*-, *m*-, and *p*-) bisnitrophenylureas by phosgenation of the nitroanilines in nitrobenzene at 140°–150°.

Substituted diarylureas[10] have been synthesised by the phosgenation of methoxy- and ethoxy-anilines. For example, phosgenation of 3,4-$(CH_3O)_2C_6H_3NHC_2H_5$ and 3,4-$CH_3O.(C_2H_5O)C_6H_3NHC_2H_5$ yielded the respective diarylureas





A patent[11] describes the production of substituted diarylureas by the phosgenation of 4-nitro-, 4-acylamino-, and 4-sulphamoyl-2,5-dialkoxyanilines. All these compounds are intermediates in the synthesis of polyazo-dyes for colouring cellulose.

The synthesis of 1,3-bis-(4-dodecanoylsulphamoylnaphth-1-yl)urea by phosgenation of the amine $1,4\text{-}H_2NC_{10}H_6SO_2.NHCO[CH_2]_{10}CH_3$ has been described. The resulting urea derivative is used as a virus-inhibitor[12].

Considerable interest attaches to the synthesis of halogenated diarylureas. The chlorinated derivatives are very stable, and are obtained from the corresponding chlorinated anilines, methods for preparing which are well known. By varying these methods slightly to introduce chlorine into the ring in a specified position, the required chlorinated anilines were prepared. The latter were phosgenated in an organic solvent to yield di-, tetra-, and hexa-chlorodiphenylureas, and also the isomeric (*o*-, *m*-, and *p*-) bischlorophenylureas[13].

Phosgenation of 2,4-dichloroaniline in nitrobenzene at 100°, and in aqueous dichloroethane at 65°, yielded bis-2,4-dichlorophenylurea[14]. The isomeric bis-2,6-dichlorophenylurea was synthesised in a similar manner[15].

The three isomeric bistrichlorophenylureas (2,4,6-, 3,4,5-, and 2,4,5-) have been synthesised by reaction of the corresponding trichloroanilines with carbonyl chloride in dichloroethane or in nitrobenzene[13].

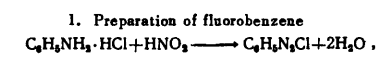
Phosgenation of tetrachloroaniline in nitrobenzene at 130° yields bis-2,3,5,6-tetrachlorophenylurea[14].

Apart from the above chlorinated diarylureas, the synthesis of bis-2,4,6-tribromophenylurea by the phosgenation of 2,4,6-tribromoaniline in nitrobenzene at 130° has been described[14].

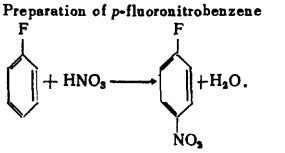
The synthesis of tetra- and hexa-fluorodiarylureas is of great interest, since the fluorine–carbon bond is more stable than those between carbon and the other halogens. Therefore the tetra- and hexa-fluorodiphenylureas possess the greatest chemical stability compared with the other halogenated diphenylureas.

The present author and his collaborators[20] have described multistage methods for preparing bis-2,4-difluoro- and bis-2,4,5-trifluoro-phenylureas. The synthesis of the latter compound, for example, comprises ten stages:

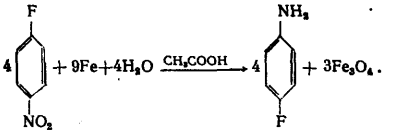
1. Preparation of fluorobenzene



2. Preparation of *p*-fluoronitrobenzene

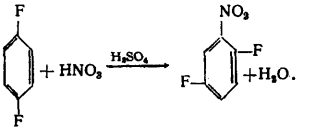


3. Preparation of *p*-fluoroaniline



4. Preparation of *p*-difluorobenzene
(by the method described in stage 1)

5. Preparation of 2,5-difluoronitrobenzene



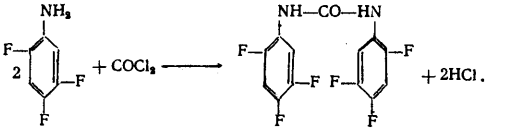
6. Preparation of 2,5-difluoroaniline
(by the method described in stage 3)

7. Preparation of 1,2,4-trifluorobenzene
(by the method described in stage 1)

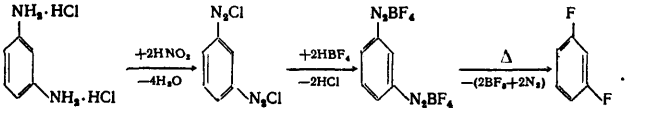
8. Preparation of 2,4,5-trifluoronitrobenzene
(by the method described in stage 5)

9. Preparation of 2,4,5-trifluoroaniline
(by the method described in stage 3)

10. 10. Preparation of bis-2,4,5-trifluorophenylurea



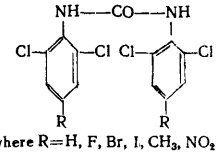
Bis-2,4-difluorophenylurea was synthesised in a similar manner but by a shorter reaction pathway, the starting material being *m*-phenylenediamine, which was converted into *m*-difluorobenzene. In this case we used Schiemann's method[18] to replace both amino-groups simultaneously by fluorine atoms[17]:



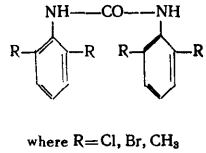
It is of interest to synthesise diarylureas containing both a halogeno and a polar group such as nitro in the ring; bis-2,6-dichloro-4- and bis-2,4-difluoro-6-nitrophenylurea have been prepared. Characteristically, reaction of dihalogenonitroanilines with carbonyl chloride does not lead to formation of the corresponding diarylureas either in aqueous dichloroethane in the presence of anhydrous sodium carbonate and an emulsifier or in nitrobenzene at

135°.[16] We were able to obtain bis-2,6-dichloro-4-nitrophenylurea only by phosgenation of 2,6-dichloro-4-nitroaniline in toluene solution in a sealed tube at 150°. Later an 80% yield of this compound was obtained by nitration of bis-2,6-dichlorophenylurea[15]. Bis-2,4-difluoro-6-nitrophenylurea is obtained in very low yield[16] by phosgenation of 2,4-difluoro-6-nitroaniline in trichlorobenzene in a sealed tube at 85°–90°, the initial difluoronitroaniline being obtained by nitration of 2,4-difluoroacetanilide with nitrosylsulphuric acid[19]. Thus derivatives of aniline containing both a halogeno- and a nitro-group in the ring react with carbonyl chloride much less readily than did those containing only halogens.

The syntheses have recently been described[15] of the substituted diarylureas represented by the formulae



where R=H, F, Br, I, CH_3, NO_2



where R=Cl, Br, CH_3

Apart from these compounds, bis-2,4-dichloro-6-fluorophenylurea has also been synthesised.

All these diarylureas are obtained comparatively easily by phosgenation of the corresponding anilines in an inert organic solvent with heating.

It has been found[15] that a carboxylic or a sulphonic acid group in position 4 has a still greater effect than the nitro-group in hindering the reaction of 2,6-dichloroanilines with carbonyl chloride. Thus substituted diarylureas could not be obtained by phosgenation of 4-amino-3,5-dichlorobenzoic or 4-amino-3,5-dichlorobenzenesulphonic acid. Such compounds can be synthesised by phosgenation of 2,6-dichloroaniline with subsequent introduction of the appropriate groups into the 4-positions of the bis-2,6-dichlorophenylurea.

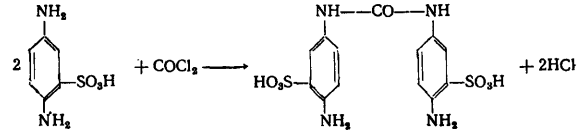
The phosgenation has been studied[3,20] of other aromatic amines as well, both in aqueous alkaline medium and in inert organic solvents. Almost quantitative yields of the corresponding diarylureas were obtained by phosgenation of aniline and *o*-anisidine in aqueous alkaline medium. However, the yield of bis-4-nitrophenylurea in the phosgenation of *p*-nitroaniline is very low (8.5%).

The high yields of diarylureas obtained in the phosgenation of aniline and *o*-anisidine are due to the ability of these amines to form emulsions with water, which ensure good contact between the amine and the carbonyl chloride.

On the other hand, the rate of phosgenation depends on the nature of the amine itself, increasing with increase in its basicity. The yields of diarylureas were in all cases considerably lower in the phosgenation of nitroanilines, whether in aqueous alkaline medium or in organic solvents, than in that of amines possessing more strongly basic properties (aniline, *o*-anisidine, *p*-anisidine, *o*-toluidine). Phosgenation of 2-methyl-4-nitroaniline in nitrobenzene gave a 79.6% yield of bis-2-methyl-4-nitrophenylurea.

The literature contains examples[21] of the phosgenation of aromatic amines containing various substituents in the ring. With *p*-aminobenzonitrile in 50% aqueous dioxane in the presence of anhydrous sodium carbonate at ordinary temperatures, for example, a 77% yield of bis-4-cyanophenylurea (m.p. 305°) was obtained.

Cases are known of the phosgenation of aromatic compounds containing substituents other than the amino-group which are able to react with carbonyl chloride. The presence of a second amino-group in the ring makes possible the formation of a large number of different substances, including polymers. The patent literature[22] refers to the possibility of obtaining diacyl derivatives of bis-4-aminophenylurea by phosgenation of substituted *N*-acylphenylene-1,4-diamines. In the phosgenation of 2,5-diaminobenzenesulphonic acid, it is the amino-group not *ortho* to the sulphonic acid group which reacts with the carbonyl chloride, resulting in the formation of bis-4-aminophenylurea-3,3′-disulphonic acid:[23]



Similarly, bis-4-amino-3,5-dichlorophenylurea is obtained from 2,6-dichlorophenylene-1,4-diamine[24].

Phosgenation of *p*-phenylenediamine in chloroform or in water in the presence of sodium acetate yields a polymer, a *p*-phenyleneurea derivative[25]. A similar phenomenon is observed in the phosgenation of *m*-phenylenediamine[26,27].

With aromatic *o*-diamines, carbonyl chloride forms heterocyclic urea derivatives[28–30]. Phosgenation of aromatic amines of the naphthalene series yields the corresponding diarylurea derivatives[31].

The patent literature[32–36] describes the preparation of urea derivatives by phosgenation of 1-aminonaphthalene-4-sulphonic acid, and also of urea derivatives based on 4-amino-5-hydroxynaphthalene-1,7-disulphonic acid and on *p*-nitrophenylcarbamoyl chloride.

Aminonaphthols having the amino- and hydroxy-groups *ortho* or *peri* relative to one another react with carbonyl chloride, in the presence of acceptors for hydrogen chloride, only at the amino-groups, the hydroxy-groups remaining unaffected[36].

Phosgenation of 6- and 8-amino-4-hydroxynaphthalene-2-sulphonic acids gave the corresponding urea derivatives.

Phosgenation in aqueous alkaline solution of metanilic and sulphanilic acids, with subsequent neutralisation of the reaction medium, yielded diphenylurea-3,3′-(and -4,4′-)disulphonic acids.

Thus it is possible to obtain various symmetrical diarylureas and their derivatives by phosgenation of aromatic amines.

III. CONDITIONS FOR AND MECHANISM OF THE PHOSGENATION OF AROMATIC AMINES

Symmetrical diarylureas and their substituted derivatives are synthesised by reaction of the corresponding aromatic amines with carbonyl chloride according to the equation

$$2RNH_2+COCl_2 \rightarrow RNHCONHR+2HCl.$$

Aromatic amines can be phosgenated either in an inert organic solvent or in aqueous medium[20]. In the former

case the reaction systems comprise a gas (carbonyl chloride) and a homogeneous liquid mixture (the amine dissolved in the organic solvent); in the latter case the reaction systems comprise a gas (carbonyl chloride) and a two-phase liquid system — an aqueous emulsion or suspension of the amine.

Sometimes the carbonyl chloride is passed through a suspension in the liquid of two solids, the amine and an inorganic base, the latter being used to combine with the hydrogen chloride.

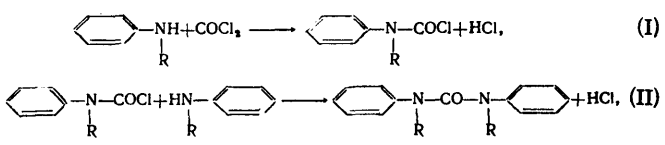
In the phosgenation of amines in aqueous medium, various bases (sodium carbonate, calcium carbonate, sodium acetate, magnesium oxide, zinc oxide, etc.) are employed to combine with the hydrogen chloride. If the reaction is carried out in organic solvents, organic bases, for example dimethylaniline and other amines, are most often employed as acceptors for the hydrogen chloride.

Processes involving phosgenation usually take place at a great rate, but in isolated cases such reactions may be relatively slow. The velocity of phosgenation has been found[20] to be affected by the temperature, the phase constitution of the reactant systems, and the removal of the resulting hydrogen chloride. Until recently inadequate attention has been paid in the literature to problems associated with the mechanism of the interaction of amines with carbonyl chloride. This applies especially to aniline derivatives containing alkyl and chloro-groups in the ring.

Several workers[37,38] have suggested that reaction between carbonyl chloride and amines takes place in stages. Addition of two molecules of the amine to the carbonyl chloride takes place first of all. Lastovskii[39], who holds this view, considers that dimethylaniline forms with carbonyl chloride the addition product $2[C_6H_5N(CH_3)_2].COCl_2$. He established that, when this product is heated, dimethyldiphenylurea and methyl chloride are formed:

$$2[C_6H_5N(CH_3)_2]\cdot COCl_2 \xrightarrow{\Delta} C_6H_5{-}N(CH_3){-}CO{-}N(CH_3){-}C_6H_5 + 2CH_3Cl.$$

This view is consistent with results obtained by Wahl[40], who studied the interaction of carbonyl chloride with dimethylaniline, diethylaniline, and dibutylaniline. Michler and Zimmermann[26,27] investigated the reaction of carbonyl chloride with secondary aromatic amines, and established that it takes place in two stages. A diarylcarbamoyl or an alkylarylcarbamoyl chloride is first formed, and this then reacts with the secondary amine to form the tetrasubstituted urea:



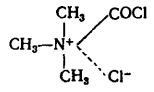
where R = alkyl or aryl.

Lastovskii concluded[39] from a study of the reaction between carbonyl chloride and secondary alkylarylamines in aqueous alkaline medium that at 10°–35° the alkylarylcarbamoyl chloride is formed, whereas at 100° it is mainly the dialkyldiarylurea which is obtained.

It is known[41,42] that reaction of dimethylaniline and diethylaniline with carbonyl chloride at 15°–50° leads to the formation of the *p*-dialkylaminobenzoyl chloride. At 100°–120° this condenses with dimethylaniline to form bis-4-dimethylaminobenzophenone (Michler's ketone).

Shilov and Dement'ev[43] observed that at 15°–20° dimethylaniline absorbs carbonyl chloride extremely readily, in amount considerably exceeding the theoretical amount for the formation of the ketone. Formation of *p*-dimethylaminobenzoyl chloride, however, occurs extraordinarily slowly. This fact points to the formation of addition compounds between carbonyl chloride and the tertiary amine, but these workers were unable to isolate such products. At higher temperatures (~200°) reaction between the starting materials leads to the formation of the dialkyldiarylurea.

Rudenko *et al.*[44] isolated an addition compound of carbonyl chloride and trimethylamine, to which they ascribed the structure



Such compounds are extremely unstable and have been little studied.

Until recently the mechanism of the reactions between carbonyl chloride and anilines which have been alkylated or halogenated in the ring remained obscure. This process is known to be extremely complicated, the first stage probably involving addition to the chloride of either one or two molecules of the aromatic amine, depending on the basic strength of the latter.

The carbonyl chloride molecule, being the complete acid chloride of carbonic acid, possesses highly electrophilic properties, which are due to the presence of the electronegative chlorine and oxygen atoms in its molecule. Therefore in the phosgenation an aromatic amine, possessing nucleophilic properties, reacts with the electrophilic molecule of carbonyl chloride, forming a new donor–acceptor C–N bond.

Since the partial positive charge on the carbon atom in the carbonyl chloride molecule is constant, it can be concluded that the rate of phosgenation of amines under the same conditions will depend on the nucleophilic properties of the aromatic amine.

The basic properties of aromatic amines are known to depend on the number and nature of the ring substituents. If the benzene ring of the amine contains electronegative substituents (atoms or groups), the amine will be feebly basic, *i.e.* it will have weak nucleophilic properties. As such properties become less marked, such aromatic amines react with carbonyl chloride with considerable difficulty. In order to obtain reasonable yields of the diarylureas, phosgenation must then be carried out in organic solvents at elevated temperatures, and sometimes under pressure as well. Aromatic amines possessing strongly basic properties react readily with carbonyl chloride, and the yields of the diarylureas are almost quantitative.

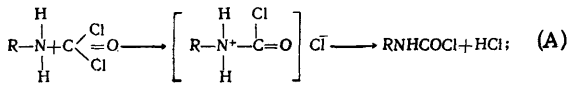
All the above points have been fully confirmed in the present author's investigations[45]. Thus aniline, the toluidines, *o*-anisidine, and other aromatic amines having strong nucleophilic properties react easily with carbonyl chloride in aqueous medium to form diarylureas in high yields. And conversely, aromatic amines having weak

nucleophilic properties, such as those containing halogeno-, nitro-, etc., substituents, have considerably greater difficulty in reacting with carbonyl chloride, and require more severe conditions.

The results obtained for the phosgenation of aromatic amines as a function of their nucleophilic properties are given in Table 1.[45]

Nevertheless, the rate of phosgenation of arylamines also depends on the structure of the amines, on their solubility in water and in inert organic solvents, and on the nature of the solvent in which reaction is taking place[20]. Phosgenation of 2,4,6-trichloroaniline goes better in 1,2,4--trichlorobenzene than in chlorobenzene under otherwise identical conditions[14], the optimum temperatures for the reaction in the two solvents being 120° and 110° respectively.

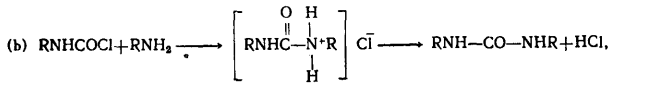
In an investigation of the mechanism of the reaction between 2,4,5-trichloroaniline and carbonyl chloride[46], 2,4,5--trichlorophenylcarbamoyl chloride and 2,4,5-trichlorophenyl isocyanate were identified as intermediate products. From a theoretical consideration of the data obtained, it can be concluded that the mechanism of the phosgenation of the trichloroaniline under conditions involving the formation of the bistrichlorophenylurea is as follows[47]:



(A)



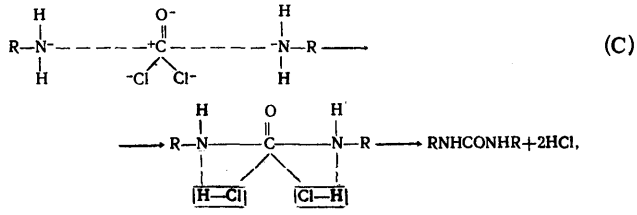
(B)



where R = $C_6H_2Cl_3$.

The first stage involves the addition of a molecule of the aromatic amine to the carbonyl chloride with formation of a transition complex of the quaternary ammonium base type, which is extremely unstable, decomposing with elimination of hydrogen chloride to form trichlorophenylcarbamoyl chloride. The second stage involves two main reactions taking place simultaneously. On the one hand, the trichlorophenylcarbamoyl chloride under the influence of heat splits off hydrogen chloride to form the trichlorophenyl isocyanate, which adds on trichloroaniline at its double bond, being thus converted into the bistrichlorophenylurea. In the other simultaneous reaction, the trichlorophenylcarbamoyl chloride reacts directly with the trichloroaniline, the reaction involving an onium type of transition complex as in the first stage of the process. The complex decomposes with elimination of hydrogen chloride and formation of the bistrichlorophenylurea. The symmetrical diarylurea produced in the reaction is weakly basic, does not form onium compounds with mineral or organic acids, and is stable.

In view of the highly electrophilic properties of carbonyl chloride, it can also be supposed that the latter can simultaneously add on two molecules of an aromatic amine with subsequent elimination of two molecules of hydrogen chloride and formation of the diarylurea, the mechanism of the process being as follows[47]:

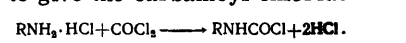


(C)

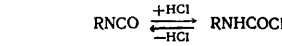
where R = $C_6H_2Cl_3$.

Similar considerations have been put forward also in papers by other workers[37-39]. In the present author's view the above mechanism (C) is most likely with aromatic amines having highly nucleophilic properties.

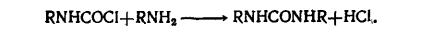
The reaction of aromatic amines with carbonyl chloride is extremely complicated, the main process being accompanied by side-reactions. Phosgenation of aromatic amines involves the evolution of hydrogen chloride, which combines rapidly with the amine to form a salt. The resulting hydrochloride of the amine undergoes decomposition when heated to its dissociation temperature, as a result of which the free base is formed, which can react with carbonyl chloride to give the carbamoyl chloride[48-50]:



The carbamoyl chloride, on being heated or recrystallised from hot carbon tetrachloride, readily loses hydrogen chloride, being converted into the aryl isocyanate. This reaction is reversible: when dry hydrogen chloride is passed into the isocyanate, the carbamoyl chloride is formed[51-61].

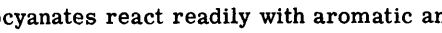


Arylcarbamoyl chlorides even at low temperatures react with primary aromatic amines to form diarylureas:

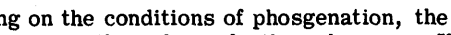


This reaction takes place readily also with secondary amines[26,27].

Aryl isocyanates react readily with aromatic amines to form diarylureas:



Depending on the conditions of phosgenation, the aryl isocyanates can easily undergo further changes. If water is present in the reaction medium, the isocyanate reacts with it to form the diarylurea[62]:



The process is slow, pyridine having a catalytic effect and accelerating the reaction[59].

TABLE 1.

Amine	Conditions of phosgenation, °C	Yield of diarylurea, %	Amine	Conditions of phosgenation, °C	Yield of diarylurea, %
$C_6H_5NH_2$	A, 20	99.4	2-CH_3-4-$NO_2C_6H_3NH_2$	B, 40	79.6
2-$CH_3OC_6H_4NH_2$	A, 25	98.8	2-$ClC_6H_4NH_2$	A, 30	87.6
4-$CH_3OC_6H_4NH_2$	B, 40	94.1	3-$ClC_6H_4NH_2$	A, 30	85.3
2-$CH_3C_6H_4NH_2$	B, 40	95.2	4-$ClC_6H_4NH_2$	A, 30	92.5
2-$NO_2C_6H_4NH_2$	C, 100	80.8	2,4-$Cl_2C_6H_3NH_2$	B, 120	90.5
3-$NO_2C_6H_4NH_2$	B, 40	79.5	2,4,6-$Cl_3C_6H_2NH_2$	B, 130	86.3
4-$NO_2C_6H_4NH_2$	B, 40	91.5			

Note. A = aqueous alkaline medium; B = nitrobenzene as solvent; C = toluene as solvent.

The diarylureas, in their turn, are also able to react further with the carbonyl chloride. They do not react at ordinary temperatures, but a rise in temperature leads to the formation of the arylcarbamoyl chlorides[63,64]:

$$RNHCONHR+COCl_2 \longrightarrow 2RNHCOCl\ .$$

The arylcarbamoyl chloride on being heated decomposes with elimination of hydrogen chloride and formation of the aryl isocyanate[65]:

$$RNHCOCl \longrightarrow RNCO+HCl.$$

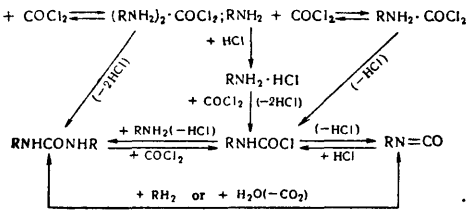
When an arylcarbamoyl chloride is heated in ethyl acetate with a large amount of hydrogen chloride, the latter reacts with the carbamoyl chloride, the resulting aniline and carbonyl chloride interacting to give the diarylurea[46]:

$$RNHCOCl+HCl \longrightarrow RNH_2+COCl_2,$$

$$2RNH_2+COCl_2 \longrightarrow RNHCONHR+2HCl.$$

The formation of a bistrichlorophenylurea is associated with the presence of a large amount of hydrogen chloride in the reaction mixture. At elevated temperatures the hydrogen chloride reacts with the carbamoyl chloride to form trichloroaniline and carbonyl chloride, which interact to yield the bistrichlorophenylurea. The possibility of the latter reactions occurring is confirmed by the decomposition of pure trichlorophenylcarbamoyl chloride to the isocyanate when it is heated in ethyl acetate in the presence of hydrogen chloride, bistrichlorophenylurea and trichloroaniline being isolated.

Thus it can be concluded from the above that the phosgenation of aromatic amines begins with the formation of addition compounds of the amines and carbonyl chloride, after which extremely complicated changes, depending on the conditions, take place. These reactions can be represented by the following scheme[20]:



It can be seen that the formation of addition compounds containing either one or two molecules of the aromatic amine combined with the carbonyl chloride molecule can take place simultaneously.

IV. SYNTHESIS OF DIARYLUREAS AND ARYLALKYLUREAS BY THE REACTION OF AMINES WITH ARYL ISOCYANATES

Aryl isocyanates are extremely reactive, their properties and preparation having been widely described in the literature[66]. They are formed by the reaction of aromatic amines with carbonyl chloride[67]:

$$RNH_2+COCl_2 \longrightarrow RNCO+2HCl.$$

The patent literature[68] gives methods for obtaining isocyanates by vapour-phase phosgenation of amines. Organic polyisocyanates are also formed from primary polyamines by the action of an excess of carbonyl chloride at 60°.[69]

An American patent[70] describes a continuous process for preparing aromatic isocyanates by the addition of carbonyl chloride to a solution of a primary diamine in a chlorinated aromatic solvent (boiling at 130°–300°).

A noteworthy process for obtaining aromatic isocyanates is the vapour-phase reaction of symmetrical diphenylurea with hydrogen chloride at 350°–370°.[71] Aniline hydrochloride is formed as well as phenyl isocyanate.

4,4'-Biphenylylene diisocyanate is obtained by the reaction of benzidine hydrochloride and carbonyl chloride in the presence of an inert organic liquid at 120°–140°.[72]

The preparation of some new polyhalogenated phenyl isocyanates is of great interest. Thus, for example, a process has been described for obtaining chlorophenyl isocyanates[73] by treating with carbonyl chloride a solution of 2,5-dichloroaniline hydrochloride in chlorobenzene, and then gradually heating the reaction mixture to boiling. 2,5-Dichlorophenyl isocyanate, 2,4,6-trichlorophenyl isocyanate, and also a mixture of various ring-chlorinated diarylureas are formed as a result of the reaction.

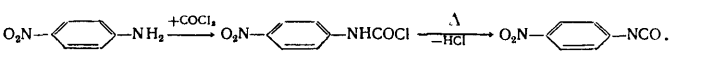
A process has been worked out for synthesising the isomeric 2,4,5-, 3,4,5-, and 2,4,6-trichlorophenyl isocyanates by heating in dichloroethane or in ethyl acetate the corresponding trichlorophenylcarbamoyl chlorides, which in turn are obtained from the corresponding anilines and carbonyl chloride[46].

In the preparation of trichlorophenyl isocyanates in ethyl acetate, the main reaction, resulting in formation of the isocyanate, is accompanied by the formation of up to 50% of the bistrichlorophenylurea. If, however, the solvent (ethyl acetate) is distilled from the reaction mixture in a vacuum at 30°, the yield of trichlorophenyl isocyanate reaches 75%, while the amount of bistrichlorophenylurea is considerably diminished.

Processes for obtaining organic di- and poly-isocyanates have been described in the patent literature[74-76]. There is an interesting method for the formation of chlorosulphonylaryl isocyanates — by the reaction of unsubstituted aromatic sulphonic acids or their salts with carbonyl chloride in an inert solvent at 150°, among the products obtained being *o*- and *p*-chlorosulphonylphenyl isocyanates, 4-chlorosulphonyl-1,3-phenylene diisocyanate, 4-chlorosulphonylnaphth-1-yl isocyanate, 3-chlorosulphonyl-6-methylphenyl isocyanate, etc.

Recently methods have been described in the literature for obtaining other aryl isocyanates. Most of them are based on the interaction of arylamines with carbonyl chloride, and differ little from those described above.

The arylcarbamoyl chlorides, obtained, like the aryl isocyanates, by the interaction of aromatic amines with carbonyl chloride[46,77], are also of definite value for the synthesis of diarylureas. Under the action of heat or of a dehydrochlorinating agent, however, they are converted into aryl isocyanates. For example, *p*-nitrophenyl isocyanate is readily formed by the reaction of *p*-nitroaniline with one equivalent of carbonyl chloride in an organic solvent, or when the resulting *p*-nitrophenylcarbamoyl chloride is distilled until hydrogen chloride is completely removed:



Thus published data indicate the relative ease with which aryl isocyanates can be synthesised, and their high reactivity, which enables them to be used extensively for the preparation of diarylureas.

The action of water on a solution of *p*-nitrophenyl isocyanate in acetone yields bis-4-nitrophenylurea[78].

Diarylureas are readily formed by the reaction of aryl isocyanates and arylcarbamoyl chlorides with aromatic amines, which makes it possible to synthesise both symmetrical and unsymmetrical diarylureas[79-81]:

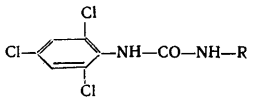
$$RNCO+RNH_2 \longrightarrow RNHCONHR,$$
$$RNCO+R'NH_2 \longrightarrow RNHCONHR'.$$

In most cases the reaction between aryl isocyanates and aromatic amines is carried out in an inert organic solvent, when practically all the amine undergoes reaction, and the yield of diarylureas are close to theoretical. Thus the reaction of phenyl isocyanate with *p*-toluidine gives 4-methyldiphenylurea:

$$C_6H_5NCO+CH_3C_6H_4NH_2 \longrightarrow CH_3C_6H_4NHCONHC_6H_5.$$

Methods have been described for obtaining nitro-derivatives of diarylureas from phenyl isocyanates and nitroanilines[82].

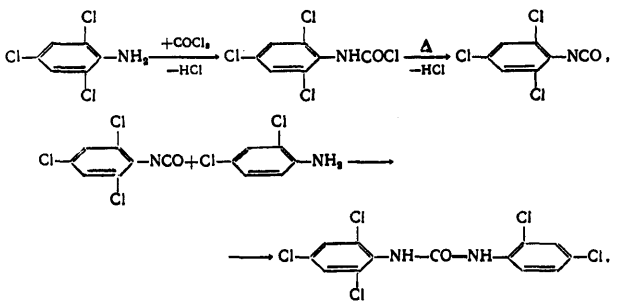
Unsymmetrical chlorinated diarylureas can be obtained[83] by the reaction of trichlorophenyl isocyanates with various halogenated anilines in inert organic solvents, the reaction products having the general formula



Among the compounds synthesised were 2,4,6,2′,6′- and 2,4,6,2′,5′-pentachloro- and 2,4,6,4′-tetrachloro-diphenylurea, etc. All these compounds were obtained by the reaction of 2,4,6-trichlorophenyl isocyanate with the appropriate chlorinated anilines in dry dichloroethane at 20°. Formation and separation of the final compounds takes place at different rates. The position and the number of chlorine atoms in the amine molecules will obviously have a considerable influence on the rate of their reaction with 2,4,6-trichlorophenyl isocyanate. The most reactive amine proved to be *p*-chloroaniline.

All the unsymmetrical substituted ureas obtained were colourless, odourless, amorphous powders, insoluble in water and sparingly soluble in organic solvents, melting in a sealed capillary quite sharply and without decomposition.

2,4,6,2′,4′-Pentachlorodiphenylurea was obtained according to the equations[83]



(I)

(II)

The following unsymmetrically chlorinated symmetrical diphenylureas have been obtained in a similar way: 2,4,6-, 2,4,6,4′-, 2,4,6,2′,4′-, 2,4,6,2′,5′-, 2,4,6,2′,4′,5′-, and 2,4,6,2′,3′,5′,6′-.

During synthesis of the trichlorophenyl isocyanates it was found[46] that, when 2,4,5-trichlorophenylcarbamoyl chloride is heated in ethyl acetate solution in the absence of hydrogen chloride, ethyl trichlorophenylcarbamate is formed.

$$RNHCOCl+C_2H_5O_2CCH_3 \longrightarrow RNHCO_2C_2H_5+CH_3COCl,$$

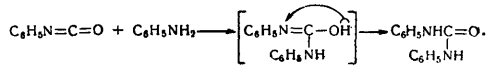
where R = $C_6H_2Cl_3$.

It was mentioned above that diarylureas are readily obtained by the reaction of arylcarbamoyl chlorides with aromatic amines, which makes it possible to synthesise also symmetrical and unsymmetrical diarylureas. In order to obtain high yields of diarylureas, the reaction is carried out in an excess of the base, which is an acceptor for hydrogen chloride. Several different unsymmetrical aryl-, arylalkyl-, and diaryl-ureas have been described[84,85]. These are formed by the reaction of aromatic amines with dialkylcarbamoyl chlorides, and also by the reaction of aryl isocyanates or arylcarbamoyl chlorides with aromatic and aliphatic amines.

Phenyl isocyanate reacts with ammonia forming phenylurea, and with aniline to yield diphenylurea:

$$C_6H_5NCO+NH_3 \longrightarrow C_6H_5NHCONH_2,$$
$$C_6H_5NCO+C_6H_5NH_2 \longrightarrow C_6H_5NHCONHC_6H_5.$$

In the latter case the aniline probably adds on at the carbonyl group with subsequent formation of the diphenylurea:



Phenyldimethylurea is obtained by the reaction of aniline with dimethylcarbamoyl chloride in an organic solvent (benzene or ether)[86].

Reaction between *p*-chloroaniline and dimethylcarbamoyl chloride in the presence of pyridine in dioxane at room temperature yields *N*-4-chlorophenyl-*N′N′*-dimethylurea[87]. This compound is also obtained by the reaction of *p*-chlorophenyl isocyanate with dimethylamine:

$$C_6H_4ClNCO+NH(CH_3)_2 \longrightarrow C_6H_4ClNHCON(CH_3)_2.$$

With diethylamine in dioxane at 20°–30°, *p*-chlorophenyl isocyanate yields *N*-4-chlorophenyl-*N′N′*-diethylurea[88]:

$$C_6H_4ClNCO+NH(C_2H_5)_2 \longrightarrow C_6H_4ClNHCON(C_2H_5)_2.$$

Methods have recently been described[89] for preparing aryldialkylureas without using the toxic carbonyl chloride as starting material. For example, heating an alcoholic solution of *p*-chlorophenyl isothiocyanate with dimethylamine yields *N*-4-chlorophenyl-*N′N′*-dimethylthiourea, which on oxidation with alkaline hydrogen peroxide is converted into 4-chlorophenyldimethylurea:

$$C_6H_4ClNCS+NH(CH_3)_2 \longrightarrow C_6H_4ClNHCSN(CH_3)_2,$$
$$C_6H_4ClNHCSN(CH_3)_2 \xrightarrow[-(H_2O+S)]{+H_2O_2} C_6H_4ClNHCON(CH_3)_2.$$

Syntheses have been described[90] for urea derivatives by the condensation of aminophenols with halogenophenyl isocyanates or of halogenophenols with isocyanates, azides, and esters of carbamic acid, *N*-3,4-dichlorophenyl-*N'*-4'--chloro-2'-hydroxyphenylthiourea, *N*-4-chlorophenyl-*N'*--3',4'-dichloro-6'-hydroxyphenylurea, as well as other urea derivatives being obtained. These compounds possess good bactericidal properties, and are used in the preparation of bactericidal soaps.

Condensation of ethylenedicarbamoyl chlorides $ClCONRCH_2CH_2NRCOCl$ with amines yields the biologically active urea derivatives $R'CONRCH_2CH_2NRCOR'$, where R = = C_6H_5, $C_6H_5CH_2$, etc., and R' = morpholino, piperidino, etc.[91]

The above methods have been used to obtain various aryldimethyl- and aryldiethyl-ureas containing fluorine, chlorine, bromine, or iodine in the aromatic ring, and also aryldialkylureas containing both halogeno and methyl or methoxy-groups in the ring[84].

Aryldialkylureas containing different alkyl radicals have been prepared[84].

Aryldialkylureas are of great value for the synthesis of various preparations. Several of them have found practical application as weed-killers, among them being *N*-phenyl--*N'N'*-dimethylurea (Phenuron), *N*-4-chlorophenyl-*N'N'*--dimethylurea (Monouron), *N*-3,4-dichlorophenyl-*N'N'*-dimethylurea (Diuron), and a new preparation of this group, *N*-3,4-dichlorophenyl-*N'*-n-butyl-*N'*-methylurea (Neburon)[85].

Aryldialkylureas in which the aryl is a naphthyl or a biphenylyl radical[85], for example *N*-2-naphthyl-*N'N'*-dimethylurea, have been prepared and recommended as weed-killers. However, compounds of this type are considerably inferior in such activity to the corresponding phenyl derivatives of urea[92].

Much attention has been paid to the synthesis of arylureas containing alkenyl instead of alkyl groups attached to nitrogen, for example *N*-3,4-dichlorophenyl-*N'*-allyl-*N'*--methylurea and other compounds. Preparations of this group possess high herbicidal activity[93].

Various urea derivatives containing a heterocyclic substituent have been synthesised, such as the *N*-methyl-, *N*-butyl-, *NN*-dimethyl-, *N,N,N'*-trimethyl-, and *N*-isopropyl-*N*-methyl-*N'*-benzothiazol-2-ylureas and other compounds of similar structure, obtained by the reaction of 2-aminobenzothiazole with alkyl isocyanates or *NN*-dialkylcarbamoyl chlorides[94].

Derivatives of urea, such as for example *N*-acylarylalkylureas, are formed by the reaction of amides and isocyanates or of anilides and carbamoyl chlorides. In the former case the reaction is carried out by heating in an organic solvent, toluene or dioxane. In the second case a toluene solution of the sodium salt of the anilide is first prepared from the latter and sodium methoxide, and is then made to react with the carbamoyl chloride[95,96].

A process has been described[97] for obtaining an unsymmetrical chlorinated phenylalkylurea containing a hydroxy--group, $3,4\text{-}Cl_2C_6H_3NHCONH[CH_2]_3OH$. This compound was prepared by the reaction of the corresponding dichlorophenyl isocyanate with 3-aminopropan-1-ol in ethyl ether. The compound $3,4\text{-}Cl_2C_6H_3NHCONHCH_2CH(OH)CH_3$ is obtained in a similar manner. Compounds of this type are effective antiseptics at contents of up to 5% in soaps.

Arylalkylurea derivatives containing other groups have also been obtained. Thus, for example, *N*-4-acetamidobenzenesulphonyl-*N'*-butylurea is formed by heating *N*-butylcarbamoyl chloride with *N*-acetylsulphanilamide in anhydrous pyridine at 120°–125° and then treating the mixture with aqueous sodium carbonate solution[98]. The synthesis has been described[99] of diarylureas of general formula $ArNRCONR'[CH_2]_nNR''R'''$ from the diamines $R'NH[CH_2]_n$. .$NR''R'''$ and carbamoyl chlorides ArNRCOCl or the isocyanates ArNCO. In this case Ar is an aryl, and R an alkyl, group. The resulting compounds of this type possess therapeutic properties.

Several arylurea derivatives have a sweet taste, among them being *NN'*-dimethyldiphenylurea and *p*-ethoxyphenylurea $p\text{-}C_2H_5OC_6H_4NHCONH_2$. The latter compound is sometimes used as a sugar substitute under the name "Dulcin".

V. SYNTHESIS OF DIALKYLUREAS AND DIARYLUREAS BY THE REACTION OF AMINES WITH UREA

Symmetrical dimethylurea was first obtained by Wurtz[100] by the action of water on methyl isocyanate:

$$2CH_3NCO+H_2O \longrightarrow CH_3NHCONHCH_3+CO_2.$$

He gives a method[101] for obtaining monoalkylureas by evaporating a solution of an amine hydrosulphate to dryness with potassium cyanate:

$$RNH_2\cdot H_2SO_4+KCNO \longrightarrow RNHCONH_2+KHSO_4.$$

Methylurea can be obtained by a process based on the Hofmann rearrangement of halogenoamides, by the action of bromine and caustic soda on acetamide and subsequent treatment with nitric acid[102]:

$$CH_3CONH_2 \xrightarrow[-(HBr+H_2O)]{+NaOH+Br_2} CH_3{-}\underset{\underset{Br-N}{\|}}{C}{-}ONa \xrightarrow[-(NaNO_2+HBr)]{+HNO_2} CH_3NCO \rightarrow$$

$$\xrightarrow{+CH_3CONH_2} CH_3NHCONHCOCH_3 \xrightarrow[-CH_3COOH]{+H_2O} CH_3NHCONH_2.$$

Symmetrical dialkylureas, like the diarylureas, are readily obtained by the phosgenation of aliphatic amines. Marckwald[103] prepared symmetrical dimethylurea by treating an aqueous solution of methylamine with carbonyl chloride in benzene solution in the presence of alkali. Dimethyl-, diethyl-, and difuryl-urea were obtained by this method. According to this worker, the yield is quantitative:

$$2RNH_2+COCl_2+2NaOH \longrightarrow RNHCONHR+2NaCl+H_2O\ .$$

Degner and von Pechmann[104] prepared mono- and di--methylurea *via* methyl isocyanate, the latter being formed from equimolar quantities of nitrourea and diazomethane. Methyl isocyanate in ethereal solution is converted by dry ammonia or alkali-metal carbonates into mono- and di--methylurea:

$$O{=}C\begin{matrix}NH_2\\NHNO_2\end{matrix} \longrightarrow O{=}C{=}NH+NH_2NO_2, \qquad (a)$$

$$HNCO+CH_2N_2 \longrightarrow CH_3NCO+N_2, \qquad (b)$$

$$CH_3NCO+NH_3 \longrightarrow CH_3NHCONH_2, \qquad (c)$$

$$2CH_3NCO+H_2O \longrightarrow CH_3NHCONHCH_3+CO_2. \qquad (d)$$

Boehmer [105] confirmed Wurtz's results, and obtained symmetrical dialkylureas by the action of water on aliphatic isocyanates:

$$2RNCO+H_2O \longrightarrow RNHCONHR.$$

Perret [106] gives a method for obtaining alkylated and arylated ureas from dicyanodiamidine (carbamidinourea) by the action of alkylamines and arylamines:

$$NH_2-C(=NH)-NH-C(=O)-NH_2+2RNH_2 \longrightarrow RNHCONHR+H_2NC(=NH)NH_2+NH_3.$$

This method gives a quantitative yield of benzylurea, but only a 10% yield of methylurea.

Davis *et al.* [107,108] obtained symmetrical dimethylurea by heating equimolar quantities of urea and the amine hydrochloride to 160°–170°. Minute amounts of methylurea are also formed:

$$2NH_2CONH_2+3CH_3NH_2\cdot HCl \longrightarrow CH_3NHCONHCH_3+CH_3NHCONH_2+3NH_4Cl.$$

Similarly, mono- and di-phenylurea are formed when a solution of aniline hydrochloride is boiled with urea:

$$2NH_2CONH_2+3C_6H_5NH_2\cdot HCl \longrightarrow C_6H_5NHCONHC_6H_5+C_6H_5NHCONH_2+3NH_4Cl.$$

Heating diethylurea with aniline to 170° yields symmetrical diphenylurea and ethylamine:

$$C_2H_5NHCONHC_2H_5+2C_6H_5NH_2 \longrightarrow C_6H_5NHCONHC_6H_5+2C_2H_5NH_2.$$

Methyl-, ethyl-, butyl-, and other alkyl-ureas are obtained [109] by the reaction of equimolar quantities of the primary amines and nitrourea in aqueous medium. This is a general method and is used for the synthesis of alkylureas.

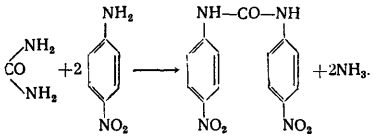
Davis and his coworkers showed that when urea reacts with amine hydrochlorides, either on fusion of the dry reactants or in boiling aqueous solution, whether a monosubstituted or a disubstituted urea is formed depends primarily on the concentration of the amine or its salt and also on the reaction conditions. In several cases only one of these two urea derivatives is formed. Thus when benzylamine is heated with urea in water (under reflux), only the monobenzylurea is formed (95.8%), even with a large excess of benzylamine. Attempts to bring urea into reaction with methylaniline (in water) or with dibutylamine hydrochloride (by melting together), however, were unsuccessful.

According to the patent literature [110], arylalkylureas are obtained by heating urea with an aromatic amine to 100°–200° in an alcohol of high boiling point, for example, cyclohexanol or phenol, ammonia being evolved. A dialkylamine is added to the hot mixture, and the solvent is distilled off, the aryldialkylurea being obtained in the residue. This reaction obviously takes place according to the following mechanism:

$$H_2NCONH_2+ClC_6H_4NH_2 \longrightarrow ClC_6H_4NCO+2NH_3,$$
$$ClC_6H_4NCO+NH(CH_3)_2 \longrightarrow ClC_6H_4NHCON(CH_3)_2.$$

Higher yields are obtained if the process is carried out in two stages. The arylamine (in excess) is then heated with urea with stirring at 140°–180° for 1½ h, after which the mixture is cooled and washed with acetic acid. In the second stage a mixture of the resulting symmetrical diarylurea and the dialkylamine (in excess) is passed through a tube heated to 400°, when the aryldialkylurea is obtained [111].

Great interest attaches to methods for obtaining substituted diarylureas by the reaction of urea with aromatic amines. Thus, for example, when urea is fused with *p*-nitroaniline at 190°, bis-4-nitrophenylurea is formed [112]:



This reaction takes place also in boiling isopentyl alcohol [113].

A series of substituted diarylureas have been obtained by the reaction of the corresponding arylamines with urea in various organic solvents. For example, bis-4-hydroxyphenylurea has been obtained by heating urea in isopentyl alcohol with *p*-aminophenol (molecular proportions 2 : 1) at 132° for 8 h. [3]

A very interesting method has been described in the patent literature [114–116] for obtaining bis-2,4,6-trichlorophenylurea from 2,4,6-trichloroaniline or its hydrochloride and urea in glacial acetic acid in the presence of sulphuric acid or hydrogen chloride.

The reaction is carried out by boiling with a (2–8)-fold excess of urea at 125°–132°. The bistrichlorophenylurea can be obtained continuously by first heating the reaction mixture of trichloroaniline (or its hydrochloride), urea, and acetic acid to 125°–132°, and then feeding it continuously into the reaction vessel at a rate of 25 ml min^{-1}. At the same time sulphuric acid is introduced in amount sufficient to give a pH of 1.5–1.8. With these concentrations and velocities of the reactants, which are optimum, the time of reaction is 2–3 h. The final product is obtained in yields up to 84.5%. The use of trichloroaniline hydrochloride halves the consumption of sulphuric acid compared with the use of trichloroaniline.

The preparation of substituted dibenzylureas has been described [117]. When a mixture of urea and 4-ethoxy-3-methoxybenzylamine is boiled in water for 4 h, *NN'*-bis-4-ethoxy-3-methoxybenzylurea is formed. *NN'*-Bis-3,4-dimethoxybenzylurea is obtained similarly. Corresponding symmetrical dialkyldiarylureas have also been synthesised, examples being *NN'*-diethyl-bis-4-ethoxy-3-methoxybenzylurea and *NN'*-diethyl-bis-3,4-dimethoxybenzylurea.

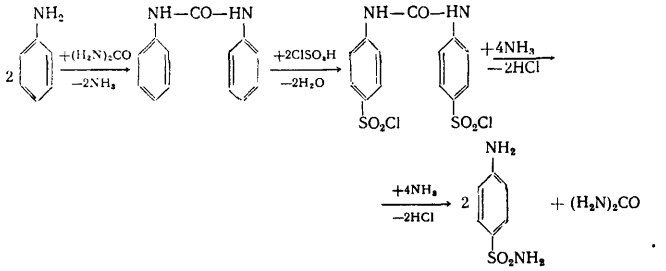
Heating urea with *N*-acetyl-*p*-phenylenediamine at 150° yields bis-4-aminophenylurea [118]. Urea reacts with *p*-phenylenediamine and its substituted derivatives in inert diluents at high temperatures [119,120], bis-4-aminophenylurea and bis-4-amino-3-methylphenylurea being obtained in this way. Diaminodimethyldiphenylurea is formed in a similar manner.

Bis-4-aminophenylurea is also obtained by heating urea and *p*-phenylenediamine in water to 103° and then distilling the reaction mixture [121,122].

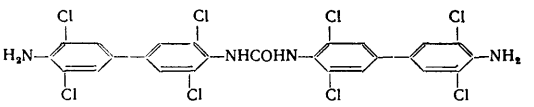
When urea is heated with an aqueous solution of the hydrochloride of 1-aminonaphth-2-ol at 200°, *NN'*-bis-2-hydroxynaphth-1-ylurea is formed. The product reacts with dimethyl sulphate to yield *NN'*-bis-2-methoxynaphth-1-ylurea [123].

In the synthesis of sulphanilamide from aniline, urea is used as an acylating agent [124,125]. Thus when diphenylurea

4,4′-disulphonyl chloride is heated with ammonia, sulphanilamide and urea are formed [126]:



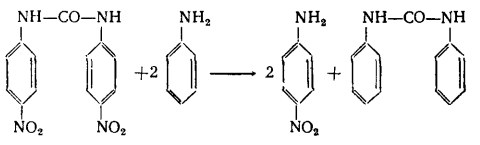
The reaction of urea with tetrachlorobenzidine has been studied [3], a mixture of the reactants being heated in isopentyl alcohol for 5 h. At 340° the product charred without melting. The structure of the resulting compound can be represented as a cyclic diamide [26,27] or as a bistetrachlorobenzidinourea of diamine type [127]:



The reaction of diphenylurea and its derivatives with aromatic amines has been extensively investigated during recent years. When, for example, *N*-phenyl-*N*′-*p*-tolylurea is heated with *p*-toluidine, bis-*p*-tolylurea and aniline are formed.

Bis-4-sulphamoylphenylurea reacts with aniline to form sulphanilamide and diphenylurea [129].

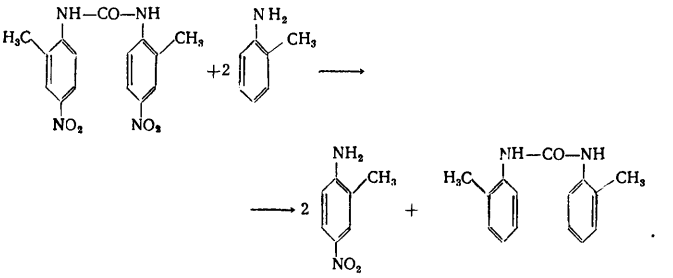
The present author has made a detailed investigation [130] of the reaction of bis-4-nitrophenylurea with aniline;



With optimum proportions of 3.2 moles of aniline per mole of the diphenylurea and heating at 180° for 15 min, the yield of *p*-nitroaniline approaches theoretical (99.4%). In ethylene glycol, at temperatures up to 190°–195°, the yield of *p*-nitroaniline reaches 99.8%. In the absence of ethylene glycol at the same temperature, the yield is considerably lower, and appreciable charring occurs.

The author has also studied the reaction of other nitrodiphenylureas with aniline [30,130]. For example, reaction of bis-3-nitrophenylurea with aniline at 180° for 15 min results in the formation of *m*-nitroaniline and diphenylurea.

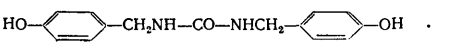
When bis-2-methyl-4-nitrophenylurea is heated with aniline at 180° for 1 h, 2-methyl-4-nitroaniline and diphenylurea are obtained. Similar reactions take place when bis-2-methoxy-4-nitrophenylurea and bis-2-chloro-4-nitrophenylurea are treated with aniline. Aniline can be replaced by other aromatic amines in the above reactions. Thus heating bis-2-methyl-4-nitrophenylurea with *o*-toluidine to 200° yields 2-methyl-4-nitroaniline and bis-*o*-tolylurea [130]:



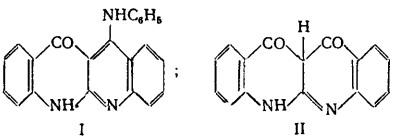
A paper by Gerchuk *et al.* [131] describes the reaction of *p*-dipropylaminoaniline with diphenylurea, the products being bis-4-dipropylaminophenylurea and aniline. When 2-aminopyridine is heated with diphenylurea, *NN*′-dipyrid-2-ylurea and aniline are obtained [131].

A process has been patented [132] for obtaining diarylureas by treating primary arylamines with carbonyl sulphide in the presence of an alkaline catalyst in an enclosed reaction vessel at 120° under pressure for 4 h. For example, $C_6H_5NH_2$, $N(C_2H_5)_3$, and COS yield bis-2-ethylphenylurea. Similarly, the corresponding aryl- and alkyl-amines and carbonyl sulphide give bis-2-methyl-, bis-4-chloro-, bis-4-methoxy-, bis-4-hydroxy-phenylurea, etc.

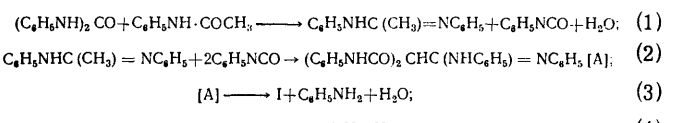
Interesting reactions of urea and its derivatives with other compounds have been described. Thus condensation of phenol and urea with formaldehyde yields the symmetrical bis-4-hydroxybenzylurea [133]:



When diphenylurea is heated with acetanilide at 250°–280° for 3 h, the mixture then treated with warm ethanol (to dissolve 2,4-dianilinoquinoline), and the residue extracted with benzene, the following substances are obtained [134]:



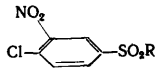
Compound I melts at 323°, and crystallises from 50% acetic acid. The other compound (II) is produced from the former by heating with KOH and ethyl alcohol at 200° under pressure. This compound melts at 400°, and forms solid acetates in concentrated acetic acid. The reaction mechanism proposed by the discoverers is:



Urea is sometimes used in chemical processes because it readily gives off ammonia. When it is heated with 2,4-dinitrophenol, for example, 2,4-dinitroaniline is formed, and with dinitronaphth-1-ol the product is dinitronaphth-1-ylamine [135].

Substituted aromatic compounds have been prepared [136] by the reaction of urea with halogenopolynitrobenzenes.

Aromatic compounds containing one halogen atom and one or two nitro-groups *ortho* or *para* to the halogen in the benzene nucleus were shown to react with urea forming amino-compounds. When compounds of the type



(where R can be CH_3, $NHCH_3$, C_6H_5, or $CH_2C_6H_5$) are fused with urea, amines are formed in lower yield (69% instead of 83%) than in the reaction of urea with 2-chloro-*N*-methyl--5-nitrobenzenesulphonamide.

The base-catalysed reaction of *S*-phenyl thiocarbamate $NH_2COSC_6H_5$ or of an *N*-monosubstituted derivative with ammonia or a primary or secondary amine, amide, or hydrazine results in the formation of substituted ureas such as *N*-phenyl-*N'*-pyrid-1-yl-, *N*-phenyl-*N'N'*-dimethyl-, and *N*-phenyl-*N'*-n-butyl-urea, symmetrical diphenylurea, etc.[137]

A review[138] has described the reactions of compounds, formed at 100°–300°, containing isocyanate, urea, and urethane groups. These reactions are very valuable for the preparation of polyureas and polyurethanes having improved thermal stability, and also for studying the changes in properties undergone by these substances at elevated temperatures. All these problems require special consideration.

VI. CONDITIONS FOR AND MECHANISM OF THE REACTION OF DIARYLUREAS WITH AROMATIC AMINES

The interaction of urea and its derivatives with aromatic amines has been frequently studied. Reactions of this type were first investigated in the case of urea and aniline. Thus Baeyer[139] obtained diphenylurea by heating 1 part of urea with 3 parts of aniline to 150°–170°. Fleischer[140] obtained monophenylurea on heating urea with one mole of aniline. Claus[141] demonstrated the reversibility of this process:

$$C_6H_5NHCONHC_6H_5+2NH_3 \rightleftarrows H_2NCONH_2+2C_6H_5NH_2.$$

When diphenylurea is fused with alkalis, aniline is split off, and triphenylguanidine is formed[142].

In the presence of glacial acetic acid as catalyst, reaction between urea and aniline results in the formation of diphenylurea[143].

Davis and his collaborators have published a series of papers[107-109,144,145] on the reaction of amines with urea and its derivatives, in which they showed that urea on being heated undergoes an intramolecular rearrangement leading to the formation of ammonium cyanate:

$$NH_2—\underset{\underset{O}{\|}}{C}—NH_2 \rightleftarrows HNCO+NH_3 \rightleftarrows NH_4NCO\ .$$

Similar changes were observed by Werner[146], who obtained ammonia and isocyanic acid on heating dry urea.

The above rearrangement of urea explains the formation of alkyl- and aryl-urea:

$$RNH_2+HNCO \rightleftarrows RNHCONH_2 \rightleftarrows RNCO+NH_3\ ,$$

$$RNH_2+RNCO \rightleftarrows RNHCONHR\ .$$

On the basis of the existence of a reversible equilibrium between urea, ammonia, and isocyanic acid, Davis and his coworkers consider that, on being heated with aniline (or other primary amine) at 160°, urea dissociates into ammonia and isocyanic acid, the former escaping from the reaction zone, while the acid combines with the aniline to form phenylurea, which at 160° can undergo the following rearrangement

$$HNCO+C_6H_5NH_2 \rightleftarrows C_6H_5NHCONH_2 \rightleftarrows C_6H_5NCO+NH_3\ .$$

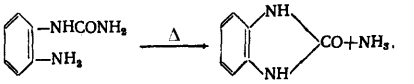
The phenyl isocyanate which is formed reacts with the aniline, resulting in the production of diphenylurea:

$$C_6H_5NCO+C_6H_5NH_2 \rightleftarrows C_6H_5NHCONHC_6H_5\ .$$

This process can be represented by the following general scheme:

$$H_2NCONH_2+C_6H_5NH_2 \xrightarrow[-NH_3]{} H_2NCONHC_6H_5 \xrightarrow[-NH_3]{} C_6H_5NCO \xrightarrow{+C_6H_5NH_2} C_6H_5NHCONHC_6H_5.$$

Interesting changes are observed when arylureas are heated above their melting points. Thus unsymmetrical arylureas containing an amino-group *ortho* to a urea nitrogen are converted, on being heated, into the corresponding *NN'-o*-phenyleneureas. For example, prolonged heating at 150°–180° converts 2-aminophenylurea into *NN'-o*--phenyleneurea[147]:



Substituted ureas in which different substituents are attached to the nitrogen atoms undergo a series of changes at high temperatures, associated with the formation of new compounds and decomposition products[148,149]. When 4-nitrophenylurea is heated above its melting point, bis-4-nitrophenylurea is obtained.

Heating *N*-ethyl-*N'*-naphthylurea above its melting point results in formation of the symmetrical *NN'*-dinaphthyl- and *NN'*-diethyl-ureas[150,151].

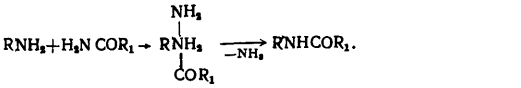
Bognar *et al.*[152] also mention that monoarylureas are converted at their melting points into diarylureas. The rate and the extent of conversion depend mainly on the reaction conditions and also on the position and nature of the ring substituents.

When ethoxy-derivatives of diarylureas (p-$C_2H_5OC_6H_4$·$NHCONHC_6H_4OC_2H_5$-p) are heated[153] with urea dissolved in an aliphatic alcohol, dissociation occurs into the aryl isocyanate (p-$C_2H_5OC_6H_4NCO$) and the aromatic amine (p-$C_2H_5OC_6H_4NH_2$).

In confirmation of this, the same workers[153] obtained an unsymmetrical substituted diarylurea (p-$C_2H_5OC_6H_4NH$··$CONHC_6H_5$) by the reaction of bis-4-ethoxyphenylurea and phenyl isocyanate. These results showed that, in the reaction between aromatic amines and diarylureas, the process begins with dissociation of the latter into aromatic amines and aryl isocyanates.

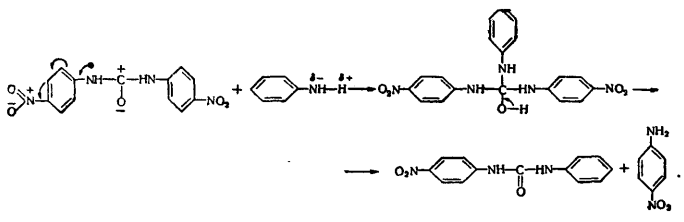
Until recently there was no generally accepted view concerning the mechanism of the reaction between diarylureas and aromatic amines. Porai-Koshits[154,155] proposed a mechanism for this reaction after having investigated the analogous reaction between phthalamic acids and aromatic

amines. According to him, the process involves the intermediate addition of the amide to the aniline:

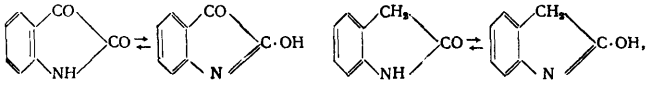


Formation of an intermediate product involving addition of an amino-group to the amino-nitrogen and the formation of a hydrazine group is not very probable. A nitrogen atom could hardly be linked by five covalent bonds with other atoms, when it would be surrounded by ten electrons instead of an octet.

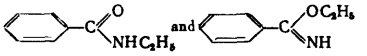
At relatively low temperatures, when dissociation of the substituted diarylurea into aromatic amine and aryl isocyanate has not yet occurred, another reaction mechanism seems more probable, in which aniline is added to a tautomeric form of bis-4-nitrophenylurea or, more precisely, to the polarised molecules [3,130]:



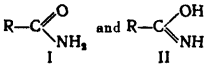
The most significant feature of such changes is the addition of an amino-group not to nitrogen but at the double bond in the tautomeric form of the carbamide. The existence of such tautomeric forms in carboxyamides is a general property of acid amides. We may point to the tautomerism of isatin and oxindole [150,156]:



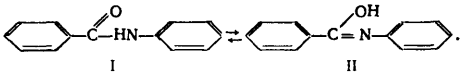
and that of acid amides, for example benzamide, with which the existence of *O*- and *N*-ethyl derivatives of the two tautomeric forms has been demonstrated [157,158]:



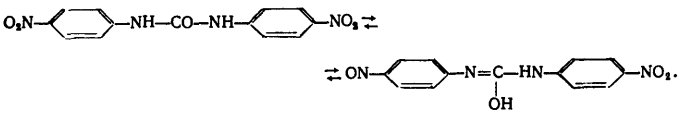
Hantzsch [159] found, in an investigation of the tautomerism of carboxyamides, that the actual amide form (I) should be assigned to amides in the solid state, whereas in alkaline solution they react in the tautomeric imidic acid form (II):



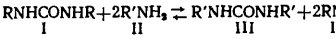
Like acid amides, anilides also react in two forms, as the anilide (I) and the *N*-phenylimidic acid (II):



As Orlov [160] showed, the anilide and the toluidide of formic acid exist in two forms, one of which is readily soluble, while the other is insoluble, in aqueous caustic potash. It is therefore quite likely that bis-4-nitrophenylurea will react with aniline in the tautomeric imidic form, as was established for similar compounds by Gershzon [161]:

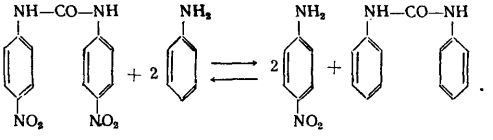


Gerchuk *et al.* [162] established that the reactions between diarylureas and primary aromatic amines are fundamentally reversible, and lead to the formation of symmetrical diarylureas:



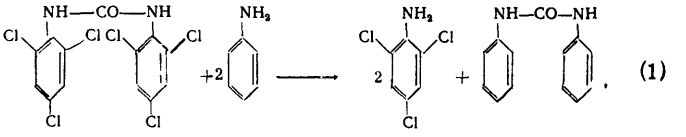
These workers conclude that the more marked the basic properties of the amine II, the higher is the yield of the substituted urea III. Hence in the reaction of primary amines with the substituted urea I, the equilibrium is shifted towards the formation of the amine IV having the feebler basic properties. Since *p*-nitroaniline is a weaker base than aniline, they conclude that practically no reaction takes place between the former and diphenylurea. However, this last statement requires correction, as will be shown below.

It was mentioned above [130] that the reaction between bis-4-nitrophenylurea and aniline is almost complete at 180°, with the formation of *p*-nitroaniline and diphenylurea. The possibility of the occurrence of the reverse reaction was investigated. For this purpose, diphenylurea was fused with an excess [(10–15)-fold compared with the theoretical amount] of *p*-nitroaniline. The reaction was carried out both in nitrobenzene and in the absence of solvent at 190°–195° for 2–3 h. It proved possible to isolate bis-4-nitrophenylurea from the reaction mass. Thus investigation of this reaction showed that it is reversible and takes place as follows:

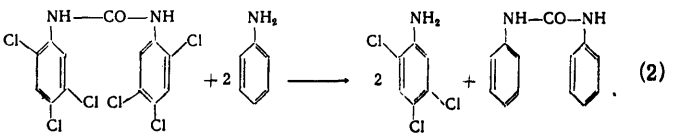


The reverse process occurs with considerably greater difficulty than the forward reaction, and requires a large excess of *p*-nitroaniline.

The present author and Potashnik [163] investigated the reaction of two isomeric bistrichlorophenylureas with aniline:



(1)



(2)

Several intermediate compounds were isolated, such as trichloroaniline and the unsymmetrical 2,4,6-trichlorodiphenyl urea. On the basis of published information and the experimental results, the mechanism of the reaction between bistrichlorophenylureas and aniline at high temperatures can be represented by the scheme[163]:

$$C_6H_2Cl_3NH\cdot CO\cdot NHC_6H_2Cl_3 \rightleftharpoons C_6H_2Cl_3NH_2 + C_6H_2Cl_3NCO, \quad (I)$$

$$C_6H_2Cl_3NCO + C_6H_5NH_2 \longrightarrow C_6H_2Cl_3NH\cdot CO\cdot NHC_6H_5, \quad (II)$$

$$C_6H_2Cl_3NH\cdot CO\cdot NHC_6H_5 \longrightarrow C_6H_2Cl_3NH_2 + C_6H_5NCO, \quad (III)$$

$$C_6H_5NCO + C_6H_5NH_2 \longrightarrow C_6H_5NH\cdot CO\cdot NHC_6H_5. \quad (IV)$$

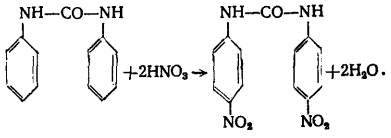
It has been shown experimentally that trichlorophenyl isocyanate is formed when bistrichlorophenylureas is heated[163]. The latter was heated in decalin, and the 2,4,6-trichlorophenyl isocyanate formed under these conditions gave with 2,4-dichloroaniline the 2,4,6,2',4'-pentachlorodiphenylurea, which was isolated in pure form.

Investigation of the reaction of urea and its derivatives with aromatic amines has shown that all derivatives of urea undergo this reaction. The reaction of diarylureas with aromatic amines at high temperatures is a complicated process, involving thermal decomposition of the diarylureas in addition to transamidation, accompanied by oxidation, resinification, and degradation of the breakdown products.

VII. SYNTHESIS OF SUBSTITUTED DIARYLUREAS BY NITRATION, CHLORINATION, AND SULPHONATION OF DIPHENYLUREA

Apart from the methods described above, other pathways exist for the synthesis of substituted diarylureas, namely nitration, chlorination, or sulphonation of diphenylurea. For a long time there was no accepted view as to the orientation or the number of nitro-groups entering the diphenylurea.

Comparatively recently a detailed study has been made[3,164] of the nitration of diphenylurea with nitric acid:

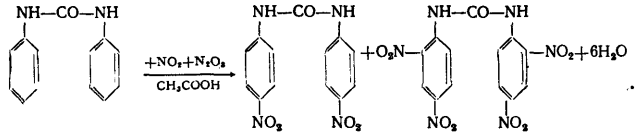


Nitration of diphenylurea was carried out in concentrated sulphuric acid, glacial acetic acid, various organic solvents, in aqueous medium, and also in aqueous medium containing various antioxidants and dispersing agents. It was established that, in most cases of nitration with nitric acid, the nitro-group enters the *para*-position with respect to the acylated amino-group, and only to an insignificant extent the *ortho*-position. In no case was the formation of bis-3-nitrophenylurea observed.

At about the same time more reliable information appeared in the literature[165,166] to the effect that bis-4-nitrophenylurea is formed when diphenylurea is nitrated with nitric acid in glacial acetic acid. These papers, too, indicate that the nitro-group enters the *para*-position with respect to the acylated amino-group.

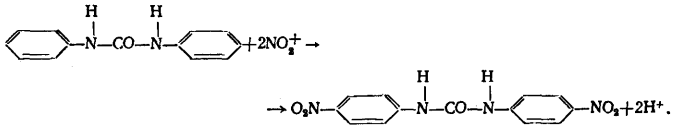
Curtius's view[167] that bis-3-nitrophenylurea is formed in the nitration of diphenylurea with nitric acid was not confirmed. Nitration with concentrated nitric acid, containing oxides of nitrogen, also yielded bis-4-nitrophenylurea, but more highly nitrated products, 2,4,2',4'-tetranitro- and 2,4,6,2',4',6'-hexanitro-diphenylurea, were formed as well.

The action of oxides of nitrogen on diphenylurea in acetic acid solution results in the formation of dinitro- and tetranitro-diphenylurea derivatives[112]:



Nitration of diphenylurea in aqueous suspension with dilute nitric acid at high temperatures (90°–100°) yields almost exclusively bis-4-nitrophenylurea[168]. Under these conditions, too, the group which directs the nitro-groups to the *para*-positions of the aromatic rings in diphenylurea is the carbamido-group. Thus in the nitration of diphenylurea with nitric acid, the nitro-group enters mainly the *para*-position with respect to the acylated amino-group, and only to a slight extent the *ortho*-position, as in the numerous other cases of the nitration of acylated derivatives of aniline (formanilide, acetanilide, oxanilide, etc.).

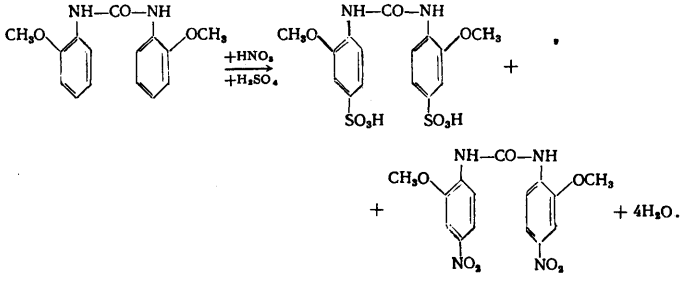
The nitrating agent is known to be the nitronium cation[169-172]:



Conditions were determined[3,164] for the nitration of diphenylurea with nitric acid, on the basis[173] that too acid a medium has a detrimental effect on nitration and proton transfer to the acceptor, while too low an acidity diminishes the concentration of NO_2^+ and thereby affects the process adversely. The optimum concentration of nitric acid was found to be 20–30%. With lower concentrations the yield of nitro-compounds was always reduced, since the NO_2^+ concentration is then diminished. With higher concentrations of nitric acid, the concentration of proton-acceptors (bases) is decreased, which hinders proton transfer to the acceptor, so that the yield of nitro-compounds is lower than under the optimum conditions.

The effect of temperature on the yield of the final products of the nitration of diphenylurea with 20% and 30% nitric acid for 5 h was also investigated. The optimum temperature for nitration under these conditions was 90°.

When bis-2-methoxyphenylurea is treated with nitric acid in concentrated sulphuric acid, sulphonation takes place, and only minute amounts of nitro-derivatives are formed[174,175]:



When bis-2-methoxyphenylurea is nitrated in acetic acid, bis-2-methoxy-4-nitrophenylurea is formed, together with other nitro-derivatives [176].

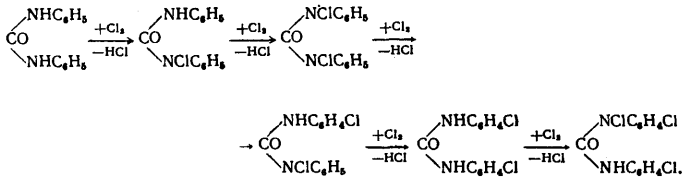
It was shown later [177] that bis-2-methoxy-4-nitrophenylurea is readily formed by the nitration of bis-2-methoxyphenylurea with weak nitric acid in aqueous medium at high temperatures. The bis-2-methoxy-4-nitrophenylurea is prepared by nitrating the initial diarylurea in aqueous suspension with 15% nitric acid at 80° for 3 h, the yield of the final product reaching 93%. The isomeric bis-2-methoxy--6-nitrophenylurea is formed only in extremely minute amounts, while the corresponding 5-nitro-isomer is not formed at all under these conditions.

Bis-2-methyl-4-nitrophenylurea was synthesised in a similar manner [3]. Nitration of the initial bis-2-methoxyphenylurea and bis-*o*-tolylurea in organic solvents (chlorobenzene, etc.) does not improve the results, the yield of the final products in no case exceeding 80%.

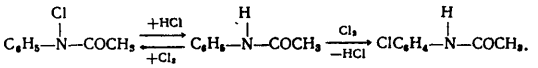
Nitrosation of the initial diarylureas yields various nitroso-derivatives. Thus Lastovskii [178], for example, synthesised *N*-nitrosodiarylureas, and studied the conditions for the nitrosation of monoarylureas and symmetrical diarylureas. He demonstrated the influence of substituents in the aromatic ring on the formation of the mono-*N*-nitrosodiphenylurea.

At the beginning of this century it was shown by the work of Chattaway and his collaborators [179-184] that chlorinated mono- and di-phenylureas can be obtained by treating the initial compounds with elementary chlorine, for example with the urea derivatives dissolved in glacial acetic acid in the presence of sodium acetate.

This method was used to synthesise the unsymmetrical 4-chloro-, 2,4-dichloro-, and 2,4,6-trichloro-phenylureas, and also the symmetrical bis-4-chlorophenyl-, bis-2,4--dichlorophenyl-, and bis-2,4,6-trichlorophenyl-ureas. The symmetrical bis-2,4,6-trichlorophenyl-*NN'*-dichlorourea was prepared by chlorination of diphenylurea. The above workers started from diphenylurea (without ring substituents), which they chlorinated with elementary chlorine in dilute acetic acid in the presence of sodium acetate. The resulting *N*-chloro-derivatives were then heated in glacial acetic acid, when the chlorine atoms migrated into the aromatic rings:



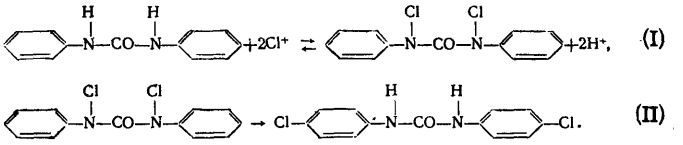
Such reactions are characteristic also of *N*-chloroacetanilides, in which the chloramide rearrangement takes place under the influence of hydrochloric acid [185,186]:



This arrangement makes it possible to obtain successively compounds containing one, two, or three chlorine atoms in the ring. The quantitative conversion of *N*-chloroacetanilide into a mixture of *o*- and *p*-chloroacetanilides is due to the irreversibility of the ring chlorination. The method described above for obtaining octachlorodiphenylurea is only of theoretical interest, and is of no practical value, since the yield of the final product is negligible.

Recently the present author and his coworkers [187] have developed methods for preparing chlorinated diphenylureas, and in particular bis-2,4,6-trichlorophenylurea, based on the chlorination of diphenylurea with elementary chlorine both in aqueous medium and in various organic solvents. In all cases a reasonable yield of the final product is obtained. In isolated cases the reaction does not go to completion, the hexachlorodiphenylurea sometimes containing up to 20–22% of the tetrachloro-derivative.

The reaction itself was also investigated [187]. The chlorine cation, formed in acid medium by the dissociation of hypochlorous acid, is known to be the chlorinating agent. The highly electrophilic Cl^+ cations attack the benzene rings of the diarylurea, first replacing the hydrogen atoms attached to nitrogen, and then migrating from the nitrogen into the ring in conformity with the rules of orientation:



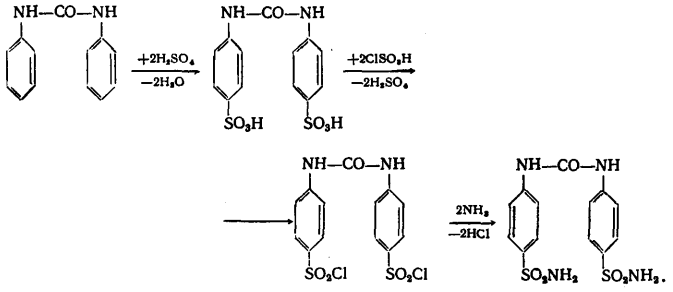
The *para*-hydrogen atoms are replaced first, and only then the hydrogen atoms in the *ortho*-positions of the phenyl radicals in diphenylurea. Introduction of the last two chlorine atoms into the *ortho*-positions of bis-2,4-dichlorophenylurea or of one chlorine atom into the *ortho*-position of 2,4,6,2',4'-pentachlorodiphenylurea is therefore difficult. In order to obtain reasonable yields of the final product, bis-2,4,6-trichlorophenylurea, chlorination must be carried out at a high temperature for a long time. These difficulties can probably be explained by steric factors and the inductive effect, due to the presence of the electronegative chlorine atoms in the aromatic rings of the diphenylurea.

Chlorination of diphenylurea in acetic acid leads to the formation [187] not only of impurities of a low degree of chlorination but also of heptachlorocyclohexenone (up to 10%), while in aqueous medium tetrachloro-*p*-benzoquinone (chloranil) is formed. These results must obviously be due to the simultaneous occurrence of a more extensive chlorination of the diphenylurea with subsequent breakdown of the diarylurea molecule and further reactions of the decomposition products.

The formation of brominated diarylureas has been described [188,189]. Di-, tetra-, and hexa-brominated diphenylureas have been prepared by dissolving diphenylurea in hot glacial acetic acid containing sodium acetate, and then saturating the solution for a prolonged period with bromine.

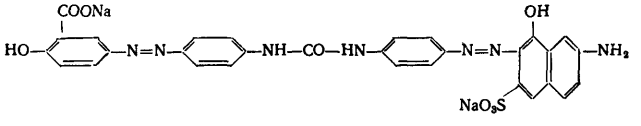
Published information on the sulphonation of diarylureas is extremely limited. In a study of the hydrolysis of diphenylurea in sulphuric acid, it has been established [3,190] that cleavage of the molecule is accompanied by the formation of diphenylurea-4,4'-disulphonic acid.

Later a report appeared[166] stating that heating diphenylurea with fuming sulphuric acid at 140° yields the 4,4′-disulphonic acid, which can be subsequently converted into various diarylurea derivatives:



The 4,4′-disulphonyl chloride can be prepared[191] by treating diphenylurea with an excess of chlorosulphonic acid at 50°–70°, removing the sulphonated mass from the apparatus, and cooling it to 20°–25°. A later investigation[192] showed that the diphenylurea first undergoes sulphonation, and the resulting disulphonic acid is converted into the corresponding disulphonyl chloride.

Many other substituted diarylureas of various types have been described. Those obtained by reduction of the corresponding nitro-derivatives are noteworthy, particularly bis-4-aminophenylurea, obtained[193] by reducing bis-4-nitrophenylurea with iron in acid medium. This compound is very valuable for the synthesis of azo-dyes. Thus, for example, it has been diazotised and coupled with *m*-phenylenediamine, *p*-nitroaniline, salicylic and sulphanilic acids, 4-amino-5-hydroxynaphthalene-2,7-disulphonic acid, phenol, and 6(and 7)-amino-4-hydroxynaphthalene-2-sulphonic acids to yield brownish dyes. The direct brown dye obtained by coupling bis-4-aminophenylurea with 6-amino-4-hydroxynaphthalene-2-sulphonic acid and salicylic acid showed good results on being tested.

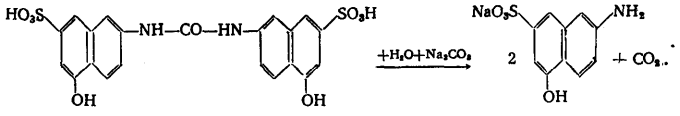


The new dye showed better fastness than the direct brown formed by coupling benzidine with gamma-acid and salicylic acid[193] [2-hydroxynaphthalene-6,8-disulphonic acid (Ed. of Translation)].

VIII. HYDROLYSIS AND OTHER REACTIONS OF DIARYLUREAS

Diarylureas are hydrolysed only under relatively severe conditions. For example, diphenylurea is split into aniline and carbon dioxide on being heated with concentrated hydrochloric acid in a sealed tube[194,196]. Breakdown products of diphenylurea are formed also on prolonged boiling with acetic anhydride in the presence of sodium acetate[196]. Cleavage of diphenylurea is quite complete in glacial acetic acid or in boiling aqueous pyridine[197]. Claus[141] obtained aniline and urea on heating diphenylurea in alcoholic ammonia in a sealed tube to 140°–150°. According to the patent literature[198], hydrolysis of diphenylurea and its nitro-derivatives also occurs when they are heated in aqueous ammonia under pressure.

Heating diphenylurea in 80–90% sulphuric acid at 170°–180° leads to the formation of aniline and sulphanilic acid[199]. In this case ring sulphonation takes place at the same time as hydrolysis of the diphenylurea. The hydrolysis products of diphenylurea are stable in alkaline medium. For example, 5,5′-dihydroxydinaphth-2-ylurea-7,7′-disulphonic acid is hydrolysed on being heated in sodium carbonate solution, and is converted into a salt of J-acid, the degree of hydrolysis depending on the temperature and the duration of heating[200]:



Bis-*o*-tolylurea, which is little affected by treatment with acid or alkali at normal pressures, is almost completely hydrolysed in acid medium under high pressures[195]. Also, bisnitrotolylurea and bischloronitrophenylurea are readily hydrolysed in concentrated acetic acid or in aqueous pyridine on heating[197].

A detailed investigation[3,190,201] of the hydrolysis of diphenylurea and bis-4-nitrophenylurea showed that the hydrolysis of these diarylureas is greatly affected by the medium, the temperature, and the duration of heating.

Hydrolysis of diphenylurea in hydrochloric acid is observed only when the mixture is heated in a sealed glass tube above 100°. The degree of hydrolysis increases with rise in temperature, and also in the concentration of hydrochloric acid. Whereas at 105° the yield of aniline is 55.9% after 2 h, at 150° it reaches 99%.

A similar situation is found in the hydrolysis of diphenylurea and bis-4-nitrophenylurea in sulphuric acid. The yield of aromatic amines increases as the concentration of sulphuric acid is increased. The optimum acid concentration is 75%, further increase leading to a diminution in the yield of amines.

In alkaline medium the hydrolysis of diphenylurea takes place as in acid media, but at temperatures above 100°. When the compound is heated with 10% caustic soda solution to 150°, the yield of aniline is 98.8%. Increasing the caustic soda concentration to 20% diminishes the yield of aniline, and a tarry black product appears.

Heating diphenylurea in 4.5% aqueous ammonia in a sealed glass tube at 150° for 4 h gives an almost theoretical (99.25%) yield of aniline. The peculiar ease of hydrolysis of diphenylurea in the presence of ammonia is probably due to the ammonia reacting directly with the diphenylurea to form aniline and urea, the latter being decomposed by water to yield ammonia and carbon dioxide:

$$C_6H_5NHCONHC_6H_5+2NH_3 \rightarrow 2C_6H_5NH_2+H_2NCONH_2,$$

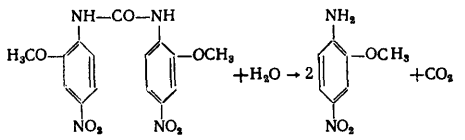
$$H_2NCONH_2+H_2O \rightarrow 2NH_3+CO_2.$$

The resulting ammonia then reacts afresh with the diphenylurea, and so on. With bis-4-nitrophenylurea, the best hydrolysing agent is aqueous ammonia, which even in minute concentrations effects almost quantitative hydrolysis of the starting material.

Alkaline hydrolysis takes place more readily than does acid hydrolysis. Complete hydrolysis of diphenylurea requires the use of concentrated hydrochloric acid (36.37%),

whereas the same degree of hydrolysis requires only 10% alkali.

An investigation has been reported[177] of the hydrolysis of bis-2-methoxy-4-nitrophenylurea with aqueous ammonia:



Hydrolysis was carried out at 150° under pressure. In 1% aqueous ammonia it went smoothly, giving a yield of 2-methoxy-4-nitroaniline exceeding 90% of theoretical. It was also found that bis-2-methoxy-4-nitrophenylurea is comparatively readily hydrolysed under pressure at high temperatures in aqueous medium even without the addition of ammonia. However, when the diarylurea is heated in aqueous medium (without ammonia) to 150° and above under pressure, resinification of the product occurs, indicating that the main reaction (hydrolysis) is accompanied by side-reactions involving oxidation.

Hydrolysis in aqueous ammonia under pressure at 150° has been studied also[3] in the case of bis-3-nitrophenylurea, bis-*o*-tolylurea, bis-2-methyl-4-nitrophenylurea, and bis-4-aminophenylurea. In all cases high yields of the final products were obtained.

Under identical conditions, bis-4-nitrophenylurea is somewhat more difficult to hydrolyse than is diphenylurea itself. The presence of two electrophilic nitro-groups in the molecule increases the stability of the molecule as a whole, so that more severe conditions are required for reaction.

The present author made a detailed study[202] of the hydrolysis of bis-2,4,6- and bis-2,4,5-trichlorophenylureas. These compounds are more stable to hydrolysis and undergo cleavage only under severe conditions. This hydrolytic stability is considerably influenced by the medium (acid or alkaline), elevated temperatures, and the duration of the process. These compounds undergo hydrolysis relatively easily in aqueous ammonia. A comparative estimate of the rate of hydrolysis of bis-4-nitrophenylurea and bis-2,4,6-trichlorophenylurea (containing considerable amounts of tetra- and penta-chloro-derivatives) showed the chlorinated diarylureas to be more resistant to hydrolysis. The results are illustrated by the curves in Fig. 1.

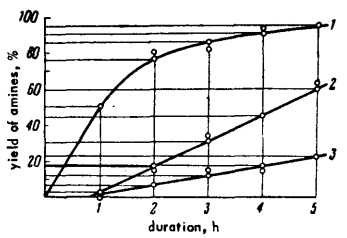
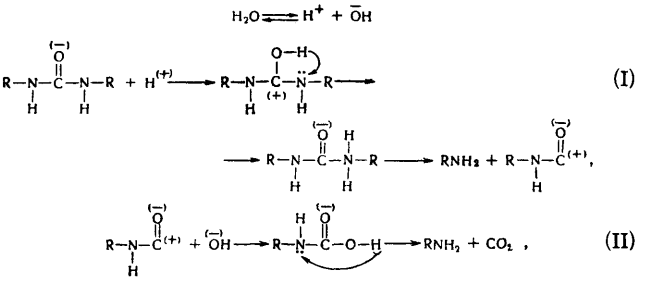


Fig. 1. Yield of amines in the hydrolysis of substituted ureas: 1) *p*-nitroaniline; 2) 2,4,6-trichloroaniline; 3) 2,4-dichloroaniline.

It was found that, of the two bistrichlorophenylureas, the 2,4,5-isomer is more difficult to hydrolyse in sulphuric acid than is the 2,4,6-compound. In 90% sulphuric acid at room temperature, the former remains unchanged for 24 h, whereas under the same conditions the bis-2,4,6-trichlorophenylurea slowly breaks down into trichloroaniline and carbon dioxide. This difference in behaviour between the two isomers can obviously be explained by the presence in each ring of the 2,4,6-isomer of two *ortho*-chlorine atoms, which strengthen the inductive effect, and tend to weaken the amide bond.

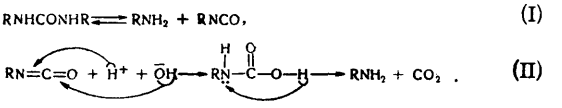
Hydrolysis of diarylureas takes place by an ionic mechanism[202]:



(I)

(II)

where R = C_6H_5, $C_6H_2Cl_3$, $C_6H_3Cl_2$, $C_6H_4NO_2$, etc. At higher temperatures under pressure, however, it is likely that hydrolysis can take place also by a different mechanism[202]:



(I)

(II)

According to this mechanism, the diarylurea, under the influence of temperature and pressure, dissociates into an aromatic amine and an aryl isocyanate, and the latter, being extremely reactive, reacts rapidly with a dissociated water molecule, forming a transition compound, which owing to its instability is decarboxylated with formation of a second molecule of the aromatic amine.

In spite of the great stability of the diarylureas to hydrolysis, they are able to undergo several chemical reactions, which have also been investigated recently. However, the differences in chemical properties among individual diarylureas are not substantial, and are exhibited only under severe conditions. An attempt was made to examine the reasons for the differences in chemical properties between several diarylureas as a function of their structure[203].

In order to study the influence of the number and nature of the substituents in the benzene rings on the stretching vibration of the carbonyl group, the infra-red spectra of a series of diarylureas were determined. The results in Table 2 show that the frequencies of the stretching vibrations of the carbonyl groups are fundamentally the same in all the diarylureas examined. They are practically unaffected by introducing different numbers and different types of substituents into the aromatic rings. In this case the inductive effect, for example of chlorine atoms present in the aromatic rings of a diarylurea, is unable to affect the vibration frequency of the carbonyl group.

This phenomenon is probably due to the ability of the carbonyl group to form a hydrogen bond of the type >C=O...H–N<.[204,205] It must be assumed that the hydrogen

TABLE 2.

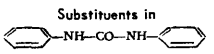
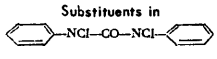
Substituents in 	ν_{max}, cm^{-1}
Unsubstituted diphenylurea	1640
2,4,2′,4′-Tetrachloro-	1640
2,4,6,2′,4′,6′-Hexachloro-	1640
2,3,5,6,2′,3′,5′,6′-Octachloro-	1640
2,4,6,2′,4′-Pentachloro-	1643
2,4,6,4′-Tetrachloro-	1645
2,4,5,2′,4′,5′-Hexafluoro-	1646 and 1683

TABLE 3.

Substituents in 	ν_{max}, cm^{-1}
2,4,2′,4′-Tetrachloro-	1709
2,6,2′,6′-Tetrachloro-	1714
2,4,6,2′,4′,6′-Hexachloro-	1721
2,4,5,2′,4′,5′-Hexachloro-	1723
2,3,5,6,2′,3′,5′,6′-Octachloro-	1735
2,4,5,2′,4′,5′-Hexafluoro-	1727
2,4,6,2′,4′-Pentachloro-	1730

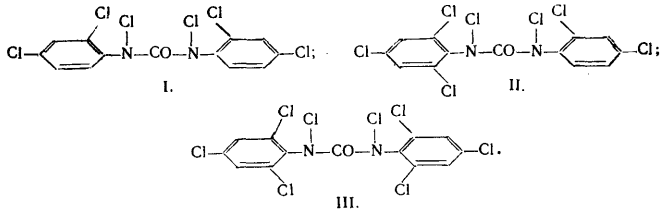
bond exerts a stronger influence than does the inductive effect transmitted through the aromatic ring. This results in the effect of the hydrogen bond on the C=O frequency predominating over that due to the substituents. On the basis of these ideas it is possible to explain the constancy of the C=O frequencies in the case of ring-chlorinated diarylureas and unsubstituted diphenylurea.

In this way the peculiarities in the chemical properties of diarylureas can obviously be explained by the presence of hydrogen bonds between the carbonyl oxygen and the hydrogen atoms attached to the nitrogen atoms. This explains the slight diminution in the basic properties of the diarylureas — the suppression of the reactivity of the carbonyl double bond and thereby an increase in chemical stability.

Replacement by chlorine of the hydrogen atoms attached to nitrogen in a diarylurea produces a marked change in the physical state of the compounds. The infra-red absorption spectra of various *N*-chlorinated diarylureas were therefore examined[203], and the frequencies of the carbonyl stretching vibrations in these compounds determined.

It is evident from the results (Table 3) that in this case the situation is completely different. Whereas the carbonyl stretching frequencies in the original diarylureas were fundamentally constant at 1640 cm^{-1}, in the *N*-chlorinated derivatives the frequencies varied, their minimum value being 1709 cm^{-1}. Furthermore, the C=O stretching frequencies increase with increase in the number of halogen atoms in the aryl radicals of the *N*-chlorinated diarylureas. Obviously, this fact also indicates the presence of hydrogen bonds in the original diarylureas. The observed vibrational frequencies of the carbonyl group in the *N*-chlorinated diarylureas are consistent with modern views on the inductive effect of substituents on such frequencies[205,206].

The increase in the frequency of the stretching vibration of the carbonyl group in *N*-chlorinated diarylureas with increasing number of substituents in their benzene rings, is consistent with the variation in the dipole moments. The latter were determined for several *N*-chlorodiarylureas, the values obtained being 3.29 D for *NN′*, 2,4,2′,4′-hexachlorodiphenylurea (I), 3.45 D for *NN′*, 2,4,6,2′,4′-heptachlorodiphenylurea (II), and 3.88 D for *NN′*, 2,4,6,2′,4′,6′-octachlorodiphenylurea (III).[203]



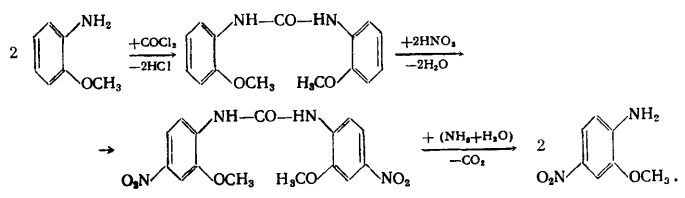
I. II.

III.

The results indicate that the dipole moments of *N*-chlorinated diarylureas increase with increasing number of chlorine atoms in the aromatic radicals.

IX. SYNTHESIS OF AROMATIC AMINES *VIA* DIARYLUREAS AND BY OTHER NEW METHODS

The results obtained for the nitration, chlorination, and hydrolysis of the diarylureas, and also the work on their interaction with aniline and other reactions, have been of definite practical value. They have formed the basis of new processes for preparing *p*-nitro-*o*-anisidine, *p*-nitroaniline, trichloroanilines, and other aromatic amines, as well as some benzene derivatives. Thus, for example, a new method[177] has been developed for obtaining *p*-nitro-*o*-anisidine (Azoamin Pink O, C.I. Azoic Diazo Component 5) *via* the diarylurea and its dinitro-derivative:



In this process carbonyl chloride is used as an acylating agent, which with *o*-anisidine readily yields bis-2-methoxyphenylurea. Nitration of this product with nitric acid forms bis-2-methoxy-4-nitrophenylurea, hydrolysis of which under appropriate conditions gives up to 93% yields of *p*-nitro-*o*-anisidine. Azoamin Pink O is an important intermediate in the production of azo-dyes.

It has been suggested[3,164] that *p*-nitroaniline could be produced in a similar manner *via* bis-4-nitrophenylurea.

Nitration of diphenylurea is effected with dilute nitric acid, when bis-4-nitrophenylurea is formed almost exclusively[168]. Hydrolysis of the latter with aqueous ammonia under pressure yields *p*-nitroaniline[201].

A noteworthy new process[130] for obtaining *p*-nitroaniline from aniline and nitric acid without an acylating agent involves a closed cycle based on displacement of one amine by another (transamidation), which can be represented diagrammatically as in Fig. 2. In this process the diphenylurea also undergoes nitration with dilute nitric acid[168]. The final products, *p*-nitroaniline and diphenylurea, are formed by the reaction of the resulting bis-4-nitrophenylurea with

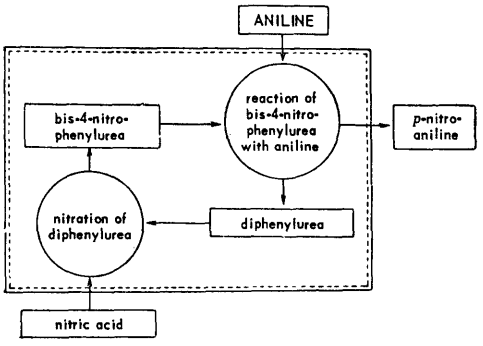
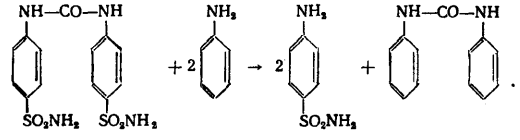


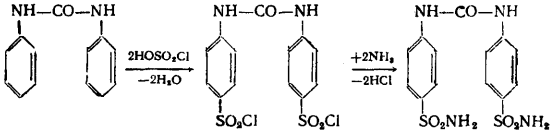
Fig. 2.

the aniline. After separation of the *p*-nitroaniline, the diphenylurea again undergoes nitration, and so on.

Gerchuk and Livshits [207,208] suggested a method based on transamidation for producing sulphanilamide (Prontosil Album) from diphenylurea 4,4'-disulphonamide. When the latter is heated with aniline, reaction takes place with the formation of sulphanilamide and diphenylurea:

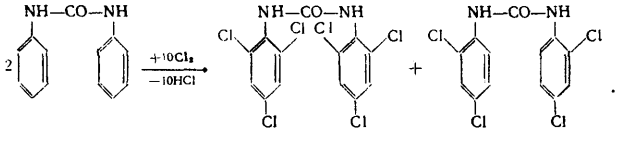


After separation of the sulphanilamide, the resulting diphenylurea is successively chlorosulphonated with an excess of chlorosulphonic acid and amidated with ammonia:



The resulting diphenylurea 4,4'-disulphonamide again reacts with aniline, and so on.

In the course of research on the chlorination and the hydrolysis of diarylureas, the present author and his collaborators [187,202] developed a process for the simultaneous production of 2,4,6-trichloroaniline and 2,4-dichloroaniline *via* chlorinated diarylureas. For this purpose, diphenylurea is chlorinated with elementary chlorine in aqueous medium at 70° for 40 h:



The resulting mixture of bis-2,4,6-trichlorophenylurea and bis-2,4-dichlorophenylurea is hydrolysed.

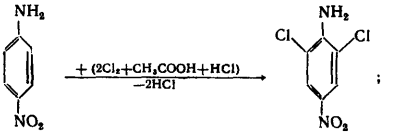
This process is very simple and practicable, in contrast to those described in the literature for preparing chlorinated anilines [209].

A very interesting new method for preparing 2,4,6-trichloroaniline from aniline and chlorine [163] can be applied as a closed cycle (see Fig. 3). Diphenylurea is chlorinated with elementary chlorine in acetic acid. The resulting bis-2,4,6-trichlorophenylurea is heated with aniline, and displacement of one amine by the other results in the formation of 2,4,6-trichloroaniline and diphenylurea. The latter, after separation of the trichloroaniline, is again subjected to chlorination, and so on.

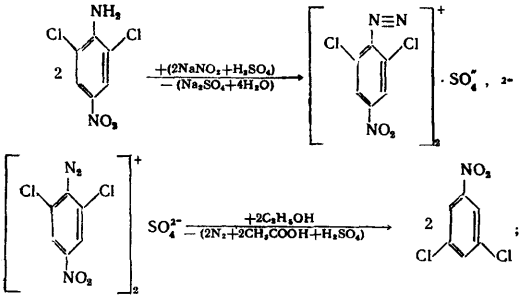
Since small amounts of bis-2,4-dichlorophenylurea are formed in the chlorination of diphenylurea, 2,4-dichloroaniline will, of course, be formed in the transamidation. The latter is readily removed by treating the mixture of chloroanilines with 5% hydrochloric acid [202]. Better results are obtained by separating the chloroanilines by partition chromatography [210].

The present author and Rozanova [13] have also developed a process for preparing chemically pure 2,4,6-trichloroaniline by introducing chlorine into a specified position in the aromatic ring:

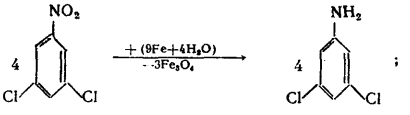
1. Preparation of 2,6-dichloro-4-nitroaniline



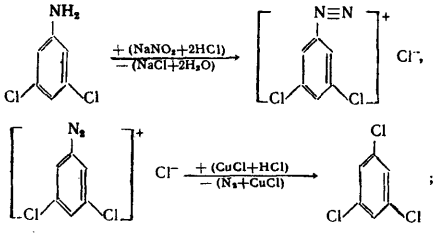
2. Preparation of 3,5-dichloronitrobenzene



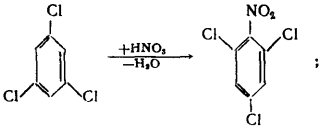
3. Preparation of 3,5-dichloroaniline



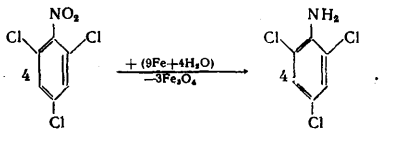
4. Preparation of 1,3,5-trichlorobenzene



5. Preparation of 2,4,6-trichloronitrobenzene



6. Preparation of 2,4,6-trichloroaniline



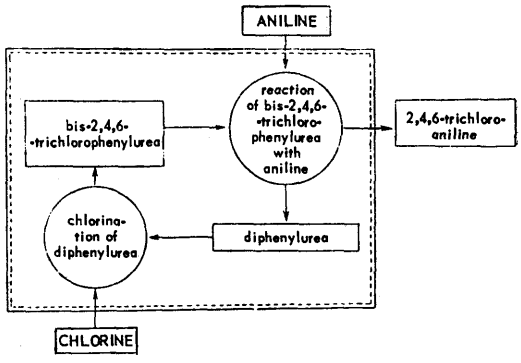
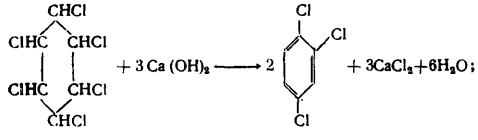


Fig. 3.

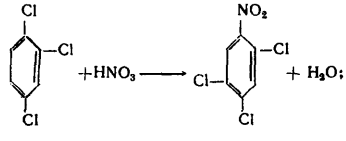
The preparation of the 3,5-dichloronitrobenzene involves diazotisation of the 2,6-dichloro-4-nitroaniline followed by reaction of the diazonium salt with alcohol[211]. Conversion of the 3,5-dichloroaniline into 1,3,5-trichlorobenzene is effected by replacement of the amino-group in the former with chlorine by Sandmeyer's method[212].

Chemically pure 2,4,6-trichloroaniline was used in the synthesis of bis-2,4,6-trichlorophenylurea of a high degree of purity for physicochemical investigations and for other purposes.

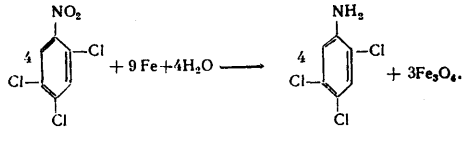
The results obtained in work on the starting materials for the synthesis of diarylureas enabled a method to be developed for preparing 2,4,5-trichloroaniline from non-toxic hexachlorocyclohexane isomers[213]:



Preparation of 2,4,5-trichloronitrobenzene

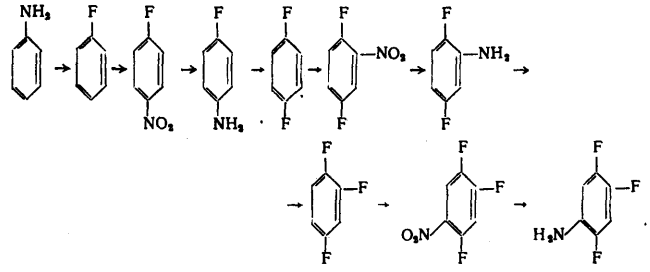


Preparation of 2,4,5-trichloroaniline



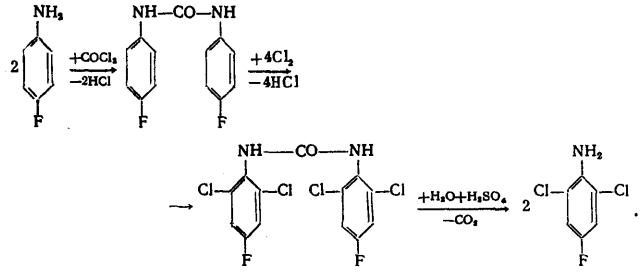
2,4,5-Trichloroaniline is of practical value for the synthesis of bis-2,4,5-trichlorophenylurea and for other preparations.

In the course of the synthesis of diarylureas, methods were worked out[17] for obtaining fluorinated nitrobenzenes and anilines:



Fluorobenzene is prepared from aniline by Schiemann's method[18], which is also used to introduce subsequent fluorine atoms into the ring. Nitration of the fluorinated benzenes is carried out with either fuming nitric acid or with a nitrating mixture. The nitro-compounds are reduced to the corresponding fluorinated anilines by means of iron filings in the presence of acetic acid and emulsifier OP-7.

The present author and his collaborators[13,15,16] have elaborated methods for obtaining various chlorinated, brominated, and iodinated nitrobenzenes and anilines. For example, 2,6-dichloro-4-fluoroaniline is obtained as follows[15]:



Similarly, 2,4-dichloro-6-fluoroaniline has been obtained starting from *o*-fluoroaniline. 4-Bromo-2,6-dichloroaniline is readily obtained in good yield by bromination of 2,6-dichloroaniline in acetic acid. Iodination of 2,6-dichloroaniline with iodine monochloride in acetic acid yields 2,6-dichloro-4-iodoaniline.

All these compounds are of great value for the production of lightfast dyes, and for various technological materials, including polymers.

---oOo---

Thus we see that considerable progress has been made during recent years in synthesis and reactions of diarylureas. A large number of previously undescribed substituted diarylureas have been synthesised as a result of the research that has been done. These comprise primarily ring-halogenated derivatives containing fluorine, chlorine, and the other halogens. In several cases other ring substituents are also present.

Chlorinated and fluorinated diarylureas are widely used in the synthesis of various medicinal preparations, while

their *N*-chloro-derivatives serve as degasifying, disinfecting, and disinfesting agents. *N*-Substituted dialkyldiphenylureas are employed as stabilisers for smokeless powders, etc.

Investigations of the diarylurea series have involved the synthesis of several new starting materials, in particular fluorinated and chlorinated benzenes, aromatic amines, aryl isocyanates, and other compounds, which are of great practical interest and may serve as intermediates for the production of stable, lightfast organic dyes, for weed-killers, insecticides, and fungicides, and also for the preparation of various new polymeric materials possessing superior physical and mechanical properties.

Several theoretical studies have been undertaken. The influence of substituents, of their nature and number, on the properties of diarylureas, in particular on the reactivity, has been elucidated. For the first time a detailed study has been made of the mechanism of the reaction between aromatic amines and carbonyl chloride, the possible steps involved have been given, and some intermediate compounds have been isolated. The reactivity of aromatic amines towards carbonyl chloride has been studied, and its fundamental causes have been established. All these results are of practical value for the development of industrial methods for the preparation substituted diarylureas.

The reactions studied are of great interest. During the course of these investigations various new chlorinated aryl isocyanates have been synthesised, enabling processes to be worked out for obtaining unsymmetrical diarylureas, which had not previously been described in the literature, and are also of practical interest.

Theoretical studies have been made of the transamidation of diarylurea derivatives. This reaction was investigated in detail in the case of the interaction of bisnitro- and trichloro-phenylureas with aromatic amines. The reversibility of the reaction between bis-4-nitrophenylureas and aniline has been demonstrated. New methods have been worked out, based on the reaction between aromatic amines and urea, for obtaining substituted diarylureas, bistrichlorophenylurea, and others, without using carbonyl chloride.

Noteworthy work has been done on the preparation of substituted diarylureas by direct nitration or chlorination of the original diphenylurea. These researches have led to a detailed study of the nitration and chlorination processes. On the basis of these reactions, a new method has been worked out for obtaining bis-4-nitrophenylurea by nitrating diphenylurea with nitric acid. Processes have also been developed for preparing bistrichlorophenylurea by chlorinating diphenylurea with elementary chlorine. All these methods are of great practical value.

The hydrolytic properties of diarylureas and their substituted derivatives have been studied. It has been found that these compounds possess great stability to hydrolysis, undergoing cleavage only under severe conditions. A mechanism has been proposed for the hydrolysis of diarylureas. Several of their other chemical properties have been studied.

The studies on the nitration, chlorination, and hydrolysis of diphenylurea and its derivatives, as well as research on the reaction of diarylureas with aniline, have led to new methods for preparing *p*-nitroaniline, trichloroaniline, and other aromatic amines.

The advances which have been made in synthesis and reactions of diarylureas are of undoubted theoretical interest and of great practical value.

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THE CHEMISTRY OF AQUEOUS SOLUTIONS OF ZIRCONIUM SALTS (DOES THE ZIRCONYL ION EXIST?)

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