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INVESTIGATION OF THE REACTION OF 1-METHYL-2,5-DICHLORO-3,4-DIFORMYLPYRROLE WITH AMINES

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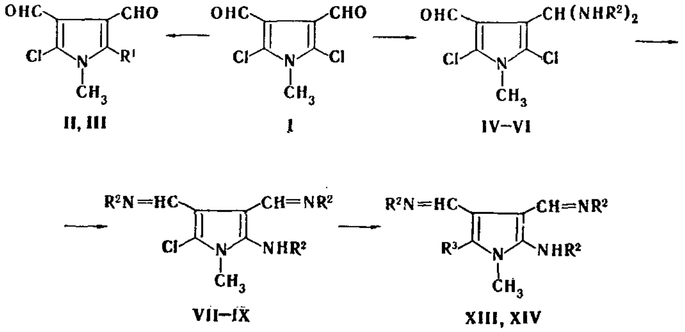
UDC 547.743.4

The reaction of 1-methyl-2,5-dichloro-3,4-diformylpyrrole with amines of the aliphatic series leads to products of replacement of one chlorine atom. With aromatic amines the reaction takes place at one of the formyl groups to give aminals. The latter in the presence of excess amine readily give bisazomethines of 1-methyl-2-chloro-5-arylamino-3,4-diformylpyrrole, which can also be obtained directly by the reaction of dichlorodiformylpyrrole with arylamines. It is shown that in this case one of the formyl groups and the adjacent chlorine atom react initially, after which the second formyl group reacts. The chlorine atom in bisazomethines of 1-methyl-2-chloro-5-arylamino-3,4-diformylpyrrole has high nucleophilic lability and is easily replaced by a hydroxy group or a piperidine residue.

During a study of the properties of 1-methyl-2,5-dichloro-3,4-diformylpyrrole (I) [1] it was observed that its reaction with amines proceeds in a rather complex manner and that the reaction pathway depends to a considerable extent on the nature of the amine. Thus the reaction does not occur with methylamine, cyclohexylamine, and piperidine under mild conditions (60% aqueous alcohol, 20°C), whereas primarily products of replacement of one chlorine atom by an amine residue, viz., II and III, are formed under severe conditions.

In contrast to alkylamines, the dichlorodiformylpyrrole reacts with aromatic amines even under mild conditions (aqueous alcohol, 20°C) to give aminals IV-VI.



II R^1 = piperidino III R^1 = cyclohexylamino IV, VII R^2=C_6H_5; V, VIII R^2=p-$CH_3OC_6H_4$; VI, IX R^2=p-BrC_6H_4; XIV R^2=C_6H_5, R^3= piperidino XIII R^2=C_6H_5, R^3=OH

Aminals of aromatic and heterocyclic aldehydes are usually obtained in the reaction with strongly basic amines [2-5]. For example, brief heating of benzaldehyde in an aqueous solu-

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Lensovet Leningrad Technological Institute, Leningrad 198013. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1489-1493, November, 1981. Original article submitted December 2, 1980.

TABLE 1. Yields, Results of Elementary Analysis, and Physicochemical Constants of VII-XIV

Compound	mp, °C	IR spectrum, ν, cm^{-1} (KBr)	UV spectrum, λ_{max} (log ε), nm (ethanol)	Found, %		Empirical formula	Calc., %		Yield, %
				Cl	N		Cl	N	
VII	244—245[a]	1665, 1610	280 (4,33), 430 (4,11)	9,1	13,5	$C_{25}H_{21}ClN_4$	8,6	13,6	59
VIII	211—213[b]	1670, 1610	275 (4,27), 355 (4,09), 450 (4,21)	6,8	11,0	$C_{28}H_{27}ClN_4O_3$	7,0	11,1	60
IX	245—247[c]	1668, 1610	280 sh (4,47), 350 (4,14), 450 (4,29)	5,6	8,3	$C_{25}H_{18}Br_3ClN_4$	5,5	8,6	69
X	178—180	1662, 1638, 1600	270 (4,37), 350 (4,53)	6,9	8,4	$C_{19}H_{14}Br_2ClN_3O$	7,2	8,5	36
XI	221—224[c]	1668, 1610	278 (4,41), 350 (4,1), 450 (4,25)	6,2	9,6	$C_{25}H_{19}Br_2ClN_4$	6,2	9,8	60
XII	217—218[a]	1675, 1615	260 (4,39), 350 (4,12), 455 (4,3)	7,9	12,5	$C_{28}H_{23}ClN_4O$	8,0	12,7	65
XIII	88—90[d]	1650, 1598	245 (3,74), 300 (3,95)		14,1	$C_{25}H_{22}N_4O$[e]		14,2	80
XIV	198—199	1650, 1630, 1598	255 (4,32), 330 (4,11)		15,2	$C_{13}H_{31}N_5$[g]		15,2	74

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[a] From methanol. [b] From methanol ether. [c] From chloroform. [d] From aqueous ethanol. [e] Found: C 76.5%. Calculated: C 76.3%. [f] From n-octane. [g] Found: C 78.5%. Calculated: C 78.1%.

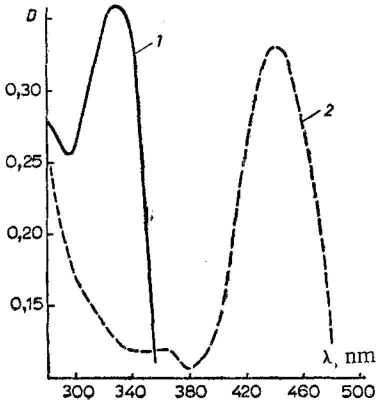
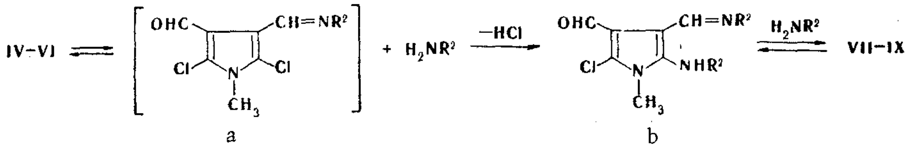


Fig. 1. Absorption spectra of 1-methyl-2,5-dichloro-3-formyl-4-dianilinomethylpyrrole (IV): 1) freshly prepared solution; 2) the same solution after 48 h.

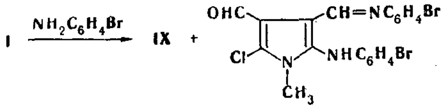
tion of dimethylamine or piperidine leads to the corresponding aminal [2, 3]. The tendency to form aminals in the heterocyclic α-aldehyde series depends both on the electrophilicity of the carbon atom of the carbonyl group and on the basicity of the amine [4]. Thus 2-formylindole, 2-formylindazole, and 2-formylbenzothiazole do not react with piperidine or dimethylamine, whereas 2-formylquinoline, 2-formylpyridine, and 2-formylimidazole react readily with the same amines to give aminals and hemiaminals [5].

Aminals IV-VI are crystalline, weakly colored, unstable substances (Table 1). The electronic spectra of these compounds are similar to one another; the long-wave maximum is shifted bathochromically 25-45 nm as compared with the starting dialdehyde, and its position depends on the nature of the substituent in the aromatic ring. Of the investigated compounds, the aminal with a donor substituent (R = OCH_3) is the most deeply colored. In the IR spectra of the aminals the position of the principal characteristic bands (νCO of the formyl group 1670-1675 and δNH 1625-1628 cm^{-1}) is virtually independent of the substituent in the amine.

Upon prolonged storage in the solid state or upon heating in organic solvents the aminals undergo decomposition to give deeply colored compounds with the evolution of hydrogen chloride. A new maximum at 430 nm, the intensity of which increases with time, appears in the electronic spectrum of 1-methyl-2,5-dichloro-3-formyl-4-dianilinomethylpyrrole recorded in benzene, whereas the maximum at 330 nm gradually disappears (Fig. 1). The observed changes evidently correspond to conversion of the aminal to an anilinoformylpyrrole azomethine, which proceeds through a number of steps, viz., splitting out of an amine to give a monoazomethine, and nucleophilic replacement of the chlorine atom. If the calculated amount of amine is added to the solution of the aminal, one observes the formation of a compound, to which bisazomethine structures VII-IX were assigned on the basis of the results of elementary analysis and the spectral properties:

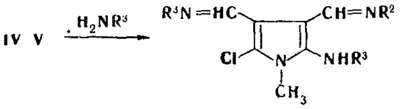


In the case of the reaction with p-bromoaniline the last step, viz., the formation of the bisazomethine, proceeds with difficulty, and the final compound is a mixture of bis- and monoazomethines IX and X.



X

The formation of unsymmetrical bisazomethines is observed when another aromatic amine is added to one or another aminal; in this case the amine reagent, even if it is weakly basic, replaces a chlorine atom and



XI, XII

XI $R^2 = C_6H_5$, $R^3 = p\text{-}BrC_6H_4$, XII $R^2 = p\text{-}CH_3OC_6H_4$, $R^3 = C_6H_5$

gives a bisazomethine. These data, as well as the fact that in the presence of other bases (piperidine and sodium acetate) aminals are stable and do not undergo the transformations described above, make it possible to assume that nucleophilic replacement of the chlorine atom proceeds through the formation of a monoazomethine (a). The latter then reacts with primary aromatic amines to give arylaminopyrrole azomethines (b). This step is virtually independent of the basicity of the amine, and the formation of a compound that is stabilized by an intramolecular hydrogen bond and the evolution of hydrogen chloride favor it. However, complex mixtures of substances that consist primarily of mono- and bisazomethines of 1-methyl-2-chloro-3,4-diformyl-5-arylaminopyrrole are formed in all cases.

This sort of reaction pathway has not been noted among the previously described [6, 7] reactions of o-chloro aldehydes of the benzene and heterocyclic series, including those that contain additional acceptor substituents. Such unusual replacement of the chlorine atom by relatively weak bases such as arylamines is evidently associated with the high nucleophilic lability of the chlorine atom in I, which is due to the effect of acceptor substituents, as well as the favorable geometry of the molecule.

As we noted above, bisazomethines VII-XII are formed in the reaction of aminals with amines. Bisazomethines VII-XII can be obtained in one step by refluxing I in benzene or ethanol with excess aromatic amine. This method was used to obtain bisazomethines VII-IX, the IR spectra of which contain bands of vibrations of a C=N bond (1670-1680 cm^{-1}) and deformation and stretching vibrations of NH groups (1610, 1625, 3470 cm^{-1}). The position and intensity of these bands are virtually independent of the substituent in the phenyl ring. Their electronic spectra are also similar and contain three absorption maxima. The long-wave maximum is shifted bathochromically on passing from R = C_6H_5 to R = $p\text{-}CH_3OC_6H_4$. Its intensity decreases with time, which is probably associated with hydrolysis of the azomethine group that is not stabilized by a hydrogen bond or hydrolysis of the chlorine atom. A study of the nucleophilic lability of the chlorine atom showed that, in contrast to monoazomethines of the X type with an aldehyde group in the 3 position, the chlorine atom in bisazomethines is readily replaced by a piperidine residue or a hydroxy group. The ease of replacement of the chlorine atom in these compounds is evidently associated with the difference in the spatial orientation of the azomethine and aldehyde groups.

Thus the reaction of 1-methyl-2,5-dichloro-3,4-diformylpyrrole with aromatic primary amines proceeds extremely readily and leads to bisazomethines of arylaminodiformylpyrrole, one of the formyl groups and the chlorine atom adjacent to it react initially, after which the second formyl group reacts.

EXPERIMENTAL

1-Methyl-2-chloro-3,4-diformyl-5-piperidinopyrrole (II). A mixture of 0.63 g (0.003 mole) of dialdehyde I and 5 g (0.06 mole) of piperidine was heated at 80-90°C for 2 h, after which it was cooled and diluted with water, and the resulting precipitate was washed with water and dried to give 0.48 g (63%) of a product with mp 84-86°C (from hexane). IR spectrum (in CCl_4): 1697, 1685 (CO); 1520, 1490 cm^{-1} (ring). UV spectrum (in ethanol), λ_{max} (log ε): 245 (4.22) and 317 nm (4.07). Found: C 56.6; N 10.9%. $C_{12}H_{15}ClN_2O_2$. Calculated C 56.6) N 11.0%.

1-Methyl-2-chloro-3,4-diformyl-5-cyclohexylaminopyrrole (III). A solution of 0.2 g (0.001 mole) of dialdehyde I and 0.36 g (0.003 mole) of cyclohexylamine in 20 ml of ethanol was refluxed for 2 h, after which the solvent was removed by distillation, and the residue was chromatographed with a column (on L 100/160 μ silica gel, elution with chloroform; R_f 0.3 for dialdehyde I, and R_f 0.2 for III) to give a product with mp 86-89°C (from pentane) in 56% yield. IR spectrum (in KBr): 1665, 1680 (CO); 2875, 2960 (CH); 3320 cm^{-1} (NH). UV spectrum (in ethanol), λ_{max} (log ε): 240 (4.41) and 300 nm (4.16). Found: N 10.0%. $C_{13}H_{17}ClN_2O_2$. Calculated: N 10.4%.

1-Methyl-2,5-dichloro-3-formyl-4-dianilinomethylpyrrole (IV). A 0.5-g (0.005 mole) sample of aniline was added to a solution of 0.41 g (0.002 mole) of dialdehyde I in 100 ml of 60% aqueous ethanol, and the mixture was maintained at 20°C for 1 h. The resulting precipitate was removed by filtration, washed with water, and dried to give a product with mp 126-128°C (from n-octane) in 70% yield. IR spectrum ($CHCl_3$): 1670 (CO) and 1625 cm^{-1} (C=C). UV spectrum (ethanol), λ_{max} (log ε): 235 (4.44) and 320 nm (4.09). Found: Cl 19.0; N 11.9%. $C_{19}H_{17}Cl_2N_3O$. Calculated: Cl 19.0; N 11.8%.

Aminals V and VI were similarly obtained.

1-Methyl-2,5-dichloro-3-formyl-4-dianisidinomethylpyrrole (V). This compound, with mp 147-148°C (from octane), was obtained in 72% yield. IR spectrum ($CHCl_3$): 1675 (CO) and 1625 cm^{-1} (C=C). UV spectrum (in ethanol), λ_{max} (log ε): 230 (4.40), 270 (4.14), and 340 nm (4.24). Found: Cl. 16.9; N 10.1%. $C_{21}H_{21}Cl_2N_3O_3$. Calculated: Cl 16.4; N 9.7%.

1-Methyl-2,5-dichloro-3,4-bis(p-bromoanilino)methylpyrrole (VI). This compound, with mp 142-143°C (from octane), was obtained in 80% yield. IR spectrum ($CHCl_3$): 1675 (CO) and 1628 cm^{-1} (C=C). UV spectrum (in ethanol), λ_{max} (log ε): 230 sh (4.10) and 330 nm (4.23). Found: Cl. 13.2; N 7.6%. $C_{19}H_{15}Br_2Cl_2N_3O$. Calculated: Cl 13.4; N 7.9%.

1-Methyl-2-chloro-3,4-diformyl-5-arylaminopyrrole Bisazomethines (VII-IX). An alcohol solution of 2.06 g (0.01 mole) of dialdehyde I and 3 g (0.03 mole) of the corresponding aromatic amine was refluxed for 2 h, after which it was cooled, and the resulting precipitate was removed by filtration, washed with acetone, and dried. 1-Methyl-2-chloro-3,4-diformyl-5-(p-bromoanilino)pyrrole monoazomethine (X), which was formed along with the corresponding bisazomethine, was separated from the latter by crystallization from octane. Data on VII-X are presented in Table 1.

1-Methyl-2-piperidino-3,4-diformyl-5-anilinopyrrole Bisazomethine (XIV). A twofold excess of piperidine was added to 0.82 g (0.002 mole) of VII suspended in 50 ml of ethanol, and the mixture was maintained at 20°C for 30 min. The yellow precipitate was removed by filtration, washed, and dried.

1-Methyl-2-hydroxy-3,4-diformyl-5-anilinopyrrole Bisazomethine (XIII). This compound was obtained by the reaction of 0.41 g (0.001 mole) of azomethine VII in 80% aqueous methanol with a tenfold excess of potassium hydroxide. The reaction mixture was maintained at 20°C for 30 min, after which it was diluted with water, and the precipitate was removed by filtration, washed with water, and dried. Mixed bisazomethines XI and XII were obtained by refluxing aminals IV and V and a threefold excess of the corresponding aromatic amine in ethanol for 2 h. Data on XI-XIV are presented in Table 1.

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PECULIARITIES OF NUCLEOPHILIC SUBSTITUTION IN INDOLYLIODONIUM SALTS

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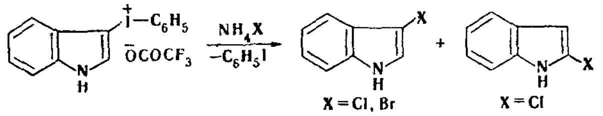
3-Indolylphenyliodonium trifluoroacetate reacts with ammonium bromide and lithium chloride and bromide to give 3-haloindoles. The reaction with ammonium chloride and tetrabutylammonium chloride leads to a mixture of 2- and 3-chloroindoles. The same mixture of chloroindoles is also formed by the action of lithium chloride but in the presence of 15-crown-5 ether. The course of the reaction is explained by ambident reaction of the cation of the iodonium salt.

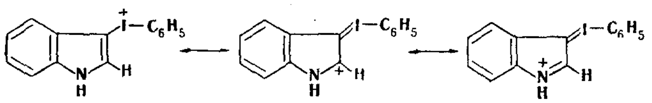
We have previously shown [1] that the phenyliodonium grouping is replaced in the reaction of alkali metal halides with 3-indolylphenyliodonium tosylate to give 3-haloindoles; it was also established that substitution occurs only in the indole ring.

Continuing our research, we studied the nucleophilic substitution by halide ions in 3-indolylphenyliodonium trifluoroacetate. We found that lithium chloride and bromide react with the trifluoroacetate in precisely the same way as with the tosylate, i.e., exclusively 3-haloindoles and iodobenzene are formed. However, the reaction pathway changes somewhat when the alkali metal salt is replaced by an ammonium salt. Whereas the iodonium salt reacts with ammonium bromide exclusively to give 3-bromoindole, a mixture of 3- and 2-chloroindoles, with preponderance of the former, is formed in the case of ammonium chloride.



It is known [2, 3] that 2- and 3-isomeric indoles undergo interconversion under the influence of acids. We demonstrated by special experiments that 2- and 3-chloroindoles do not undergo isomerization to one another under the reaction conditions [dimethyl sulfoxide (DMSO), 2 h, 100°C]. In addition, we found that replacement of ammonium chloride, which is capable of undergoing decomposition to hydrogen chloride and ammonia when it is heated, by tetrabutylammonium chloride does not change the reaction pathway, and the chloroindoles are formed in approximately the same ratio. The difference in the reactions is explained by the fact that lithium halides are dissociated to a lesser extent in solution than the corresponding ammonium halides [4]. In fact, a mixture of chloroindoles is also formed in the reaction of 3-indolylphenyliodonium trifluoroacetate with lithium chloride in the presence of 15-crown-5 ether, which complexes lithium ions.

The iodonium salt is an ambident electrophile that permits nucleophilic attack at the iodine atom and at the α-carbon atom of the indole ring.



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