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CYCLIZATION OF 2,4-DICHLORO-1,5-PENTANEDIONES WITH NUCLEOPHILIC REAGENTS

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The mechanism of reaction of 2,4-dichloro-1,5-pentanediones with ammonia has been studied. Intramolecular cyclization of the intermediate resulting from nucleophilic attack at the carbonyl group can occur in two ways, depending on the reaction conditions, either at the α-chloromethylene fragment or at the second carbonyl group, leading to the formation of 2-aroylpyrroles or 3-chloropyridines, respectively. In reactions with thio- and phenylthiourea both chlorophenacyl fragments are involved, resulting in the formation of di(2-amino-4-arylthiazolyl-5)methanes.

We have previously demonstrated that in reactions of 2,4-dichloro-1,5-pentanediones with ammonia 2-aroylpyrroles [1] are formed, in addition to the expected chloropyridine products; the formation of 2-aroylpyrroles represents a novel heterocyclization pathway for 1,5-dicarbonyl compounds, and can be attributed to the presence of a chloromethylene fragment in the structure.

In the present paper we have attempted to elucidate the mechanism of aroylpyrrole formation, and have also examined the cyclization characteristics of 2,4-dichloro-1,5-pentanediones I with other nucleophiles, such as thio- and phenylthiourea.

The presence of several reactive sites in the molecular structure of compounds I opens up the possibility of the existence of different cyclization pathways. Based on literature reports [2] concerning the synthesis of pyrroles from β, γ-dichloroalkylketones, we postulated that aroylpyrrole formation from dichloropentanediones I could occur via dehydrochlorination resulting in the formation of 4-chloro-2-pentene-1,5-dione (II) as an intermediate. It was found, however, that reaction of 1,3,5-triphenyl-2,4-dichloro-1,5-pentanedione (Ie) with triethylamine, acting as a dehydrochlorinating agent, concluded unexpectedly with the formation of 2-benzoyl-4-chloro-3,5-diphenyl-2,3-dihydrofuran (IIIe).

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TABLE 1. Reaction Conditions for the Reaction of 2,4-Dichloropentanediones Ia, c-f with Ammonia and Ammonium Acetate, and Their Product Yields

Compound	Reagent	Solvent	t_r, h*	Reaction products	Yield, %
Ia	NH_3	Dioxane	14	IVa	80
	CH_3COONH_4	Dioxane	22	IVa	34
				Va	58
	CH_3COONH_4	CH_3COOH	3	Va	80
Ic	NH_3	Dioxane	6	IVc	59
	CH_3COONH_4	Dioxane	50	IVc	11
				Vc	68
	CH_3COONH_4	CH_3COOH	45	IVc	8
				Vc	79
Id	NH_3	Dioxane	12	IVd	67
				Vd	16
	CH_3COONH_4	Dioxane	18	IVd	37
				Vd	50
	CH_3COONH_4	CH_3COOH	3	Vd	80
Ie	NH_3	Dioxane	5	IVe	53
	CH_3COONH_4	Dioxane	12	IVe	21
				Ve	67
	CH_3COONH_4	CH_3COOH	3	Ve	92
If	NH_3	Dioxane	6	IVf	47
				Vf	9

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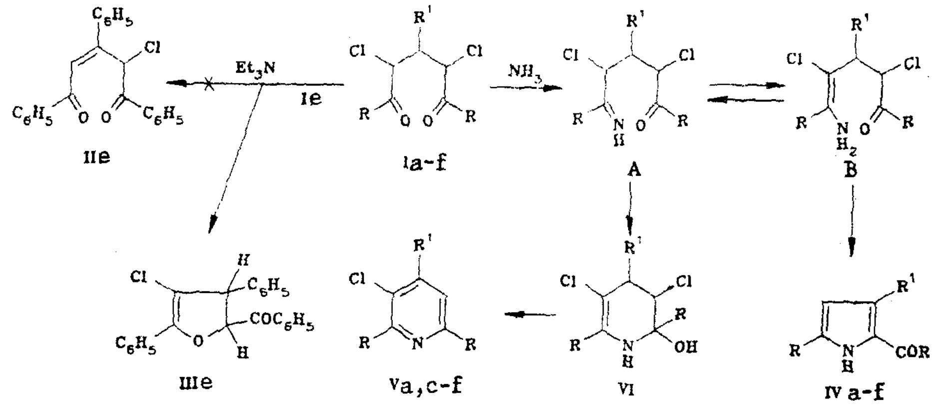
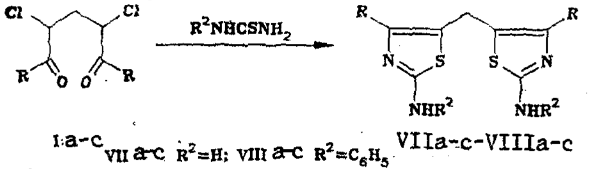
*Reaction temperature, 60°C; t_r, reaction time.



I—V a $R=C_6H_5$, $R^1=H$; b $R=C_6H_4OCH_3$, $R^1=H$; c $R=C_6H_4Cl$, $R^1=H$; d $R=C_6H_5$, $R^1=CH_3$; e $R=R^1=C_6H_5$; f $R=C_6H_5$, $R^1=C_6H_4Cl$

It was also found that recyclization of compound IIIe to the corresponding 2-aroylpyrrole IVe did not occur upon reaction with ammonia. It follows, therefore, that compound IIIe cannot be an intermediate in the formation of aroylpyrroles IV. It is therefore improbable that aroylpyrroles IV can be formed via preliminary or initial dehydrochlorination of chlorodiketone starting materials I.



We propose, therefore, that both aroylpyrrole IV and 3-chloropyridine V formation accompanying reaction of pentanediones I with ammonia occur via a single common intermediate, involving initial addition of the nucleophile to a ketone group. This hypothesis is consistent with our other results, showing that the nature of the reaction products obtained from I and ammonia depends on the reaction conditions (cf. Table 1). Thus, upon reaction of diketones Ia, c-f with ammonia in dioxane, for instance, 2-aroylpyrroles IVa, c-f are formed predominantly, in yields as high as 80%. Upon treatment of dichloropentanediones Ia, d, e with ammonium acetate in dioxane at 60°C, on the other hand, the yields of 2-aroylpyrroles IVa, d, e are significantly reduced, and predominant formation of

3-chloropyridines Va, d, e is observed, in 60-70% yields. Heating dichloropentanediones Ia-d with ammonium acetate in acetic acid at 60-80°C results in the exclusive formation 3-chloropyridines Va-d. We conclude, based on these results, that formation of five- and six-membered rings can be attributed to the existence of tautomeric equilibrium involving forms A and B, which are formed via addition of ammonia to a carbonyl group in diketone I. In acidic media (such as upon reaction with ammonium acetate in acetic acid), the equilibrium is shifted in favor of imine A, which then undergoes cyclization to give chloropyridines V [apparently via an intermediate stage involving the formation of 2-hydroxy-3,5-dichloro-1,2,3,4-tetrahydropyridines (VI)]. Indeed, independent experiments revealed that reaction of dichlorodiketone Ie with ammonia in benzene solution at 15°C generated compound VIe, which could then be converted upon subsequent treatment with ammonia to the corresponding 3-chloropyridine derivative Ve. Also, in agreement with literature data [3], in the absence of acid the enamine tautomeric form B is more stable, such that upon reaction with ammonia in dioxane solution transformation to enamine B results in five-membered ring formation to give the corresponding aroylpyrroles IV.

The presence of several reactive sites in the structure of pentanediones I means that, depending on the reaction conditions, cyclization with ammonia can proceed via two alternative competing pathways, involving either the CO groups and the chloromethylene fragment, or only the two carbonyl groups, leading to the formation of 2-aroylpyrroles IV or 3-chloropyridines V, respectively.

Yet another cyclization reaction pathway exists for the reaction of dichloropentanediones I with 1,3-dinucleophiles. Thus, upon heating compound I in alcohol with thio- and phenylthiourea di(2-amino-4-arylthiazolyl-5)methanes VII and VIII are obtained. Formation of these products appears to be the consequence of cyclization of pentanediones I involving both α-chlorophenacyl fragments.

We should note, however, that these reactions take place readily only in the case of 1,5-disubstituted dichloropentanediones Ia-c, which do not contain substituents in the 3-position. Reaction of 3-substituted diketones Id-f with thioureas proceeds very slowly and is accompanied by more profound and unidentified structural transformations. Apparently, chlorine substitution is more difficult or complex in reactions involving sterically hindered diketones Id-f. According to other literature data [4], hydrocarbon skeleton branching in the α-position in haloketones inhibits their reaction with thioamides.

The structures of compounds III-VIII were established based on the results of IR, PMR, and ^{13}C-NMR spectroscopic analysis (Tables 2 and 3).

The IR spectrum of compound IIIe exhibits absorption in the 1703-1693 cm^{-1} region, suggesting the retention of one CO group. The PMR spectrum of compound IIIe contains, in addition to the aromatic proton signals, doublets for the $H_{(2)}$ and $H_{(3)}$ protons at 5.65 and 4.67 ppm. ^{13}C nuclear signal assignments were made based on corresponding data for 2-benzoyl-3,5-diphenyl-4-chlorofuran [5]. The characteristic signals in this regard are the chemical shift values for the carbonyl group C atom (193.7 ppm) and the C atoms in the dihydrofuran ring: 148.4 [$C_{(2)}$]; 139.9 [$C_{(3)}$]; 55.9 [$C_{(4)}$]; and 86.6 ppm [$C_{(5)}$].

The IR spectra of compounds VIIa-c exhibit absorption due to both (free N—H bonds, as well as broad absorption bands due to amino groups involved in intermolecular hydrogen bonding. The bands due to the latter type of amino groups appear in the same region in the spectra of aminothiazoles VIIIa-c, which contain secondary amino groups (Table 3).

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer (in Vaseline oil or hexachlorobutadiene). PMR spectra were obtained on a Varian FT-80A (80 MHz) spectrometer, ^{13}C-NMR spectra on a Varian FT-80A (at 20 MHz). HMDS was used as internal standard.

The course of these reactions and the composition of the reaction mixtures was followed by TLC on Silufol UV-254 plates using hexane—ether—chloroform (3:1:1) as the solvent system.

The results of elemental analysis agreed with calculations.

The 2,4-dichloro-1,5-pentanedione starting materials Ia-f were synthesized according to a literature procedure [6].

2-Benzoyl-3,5-diphenyl-4-chloro-2,3-dihydrofuran (IIIe, $C_{23}H_{17}ClO_2$). A solution of 1 g (2.5 mmoles) pentanedione Ie and 0.5 ml (3.6 mmoles) triethylamine in 6 ml dioxane was heated for 6 h at 60°C, and another 0.5 ml (3.6 mmoles) triethylamine was added and the mixture heated an additional 5 h. The reaction mixture was diluted with 30 ml of a 2:1 mixture of hexane and benzene, washed with water, and dried over Na_2SO_4. Compound IIIe was isolated by column chromatography on silica gel with a mixture of hexane—benzene (2:1) eluent; yield 0.38 g (41%), mp 96-97°C. IR spectrum: 1803, 1693 cm^{-1} (C=O). PMR spectrum (in $CDCl_3$): 5.65 [1H, d, $H_{(2)}$]; 4.7 ppm [1H, d, $J_{2,3}$ = 6.0 Hz, $H_{(3)}$]. ^{13}C-NMR spectrum (in $CDCl_3$): 86.6 [$C_{(2)}$], 55.9 [$C_{(3)}$], 139.9 [$C_{(4)}$], 148.4 [$C_{(5)}$], 193.7 ppm (C=O).

TABLE 2. Properties of 2-Aroylpyrroles IVb, c, e, f and 3-Chloropyridines Vc, f

Compound	Molecular formula	mp, °C	IR spectrum, cm^{-1}		PMR spectrum, δ, ppm					
					δ, ppm				J, Hz	
			N—H	C=O	$H_{(1)}$ br.s	$H_{(3)}$ dd	$H_{(4)}$	$H_{(5)}$ s	3,4	1,4
IVb	$C_{19}H_{17}NO_3$	206...208	3250	1600	10,0	6,89	6,50 d		3,8	2,7
IVc	$C_{17}H_{11}Cl_2NO$	209...211	3310	1615	9,8	6,86	6,60 d		4,1	2,7
IVe	$C_{23}H_{17}NO$	158...160	3300	1610	10,1		6,67 d			3,0
IVf	$C_{23}H_{16}ClNO$	211...214	3240	1600	10,2		6,64 d			2,9
Vc	$C_{17}H_{10}Cl_3N$	156...158	1570*				—**	—**		
Vf	$C_{23}H_{15}Cl_2N$	138...140	1577*					7,62		

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*The frequency values for the C=C bond in the heterocycle are given here.

**The H(4) and H(5) signals fall within the aromatic proton region.

TABLE 3. Properties of Di(2-amino-4-arylthiazolyl-5)methanes VIIa-c, VIIIa-c

Compound	Molecular formula	mp, °C	IR spectrum, cm^{-1}			PMR spectrum, δ, ppm		Yield, %
			N—H free	N—H assoc.	CH(CH$_2$)	CH$_2$, s	CH$_3$, s	
VII a	$C_{19}H_{16}N_4S_2$	210...212	3481, 3382	3382, 3088	2935, 2870	4,14*		99
VII b	$C_{21}H_{20}N_4O_2S_2$	189...192	3415, 3020	2938	2965	3,73	3,49	25
VII c	$C_{19}H_{14}Cl_2N_4S_2$	237...240	3470, 3282	3230, 2990	2930, 2722	3,86		99
VIII a	$C_{31}H_{24}N_4S_2$	217...221		3270, 3115	2936, 2868	3,76		96
VIII b	$C_{33}H_{22}N_4O_2S_2$	193...197		3280, 3114	2920	3,77	3,50	35
VIII.c	$C_{31}H_{22}Cl_2N_4S_2$	240...245		3290, 3122	2940, 2865	3,73		92

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*The spectrum was recorded in DMSO-D_6.

Reaction of 2-Benzoyl-3,5-diphenyl-4-chloro-2,3-dihydrofuran (IIIe) with Ammonia. A solution of 0.2 g (0.6 mmoles) compound IIIe in 3 ml dioxane was saturated with ammonia at 60°C and heated for 6 h. TLC analysis revealed the absence of any changes in the starting material.

Reaction of Dichloropentanediones Ia, c-f with Ammonia in Dioxane (General Procedure). A solution of 2 g (6 mmoles) dichlorodiketone Ia, c-f in 12 ml dioxane was saturated with ammonia at 60°C until complete conversion of the starting material was observed. Pure compounds IVa, c-f were isolated by column chromatography on Al_2O_3 with a 2:1 mixture of hexane—benzene eluent.

Reaction of Dichloropentanediones Ia, c-e with Ammonium Acetate in Dioxane (General Procedure). A mixture of 2 g (6 mmoles) dichlorodiketone Ia, c-f, 1.5 g (20 mmoles) ammonium acetate, and 12 ml dioxane was heated at 60°C until complete conversion of the starting material was observed by TLC analysis. The reaction mixture was diluted with 30 ml benzene and washed with water. Compounds IV and V were isolated by column chromatography on Al_2O_3 with a 2:1 hexane—benzene solvent mixture.

Reaction of Dichlorodiketones Ia, c-f with Ammonium Acetate in Acetic Acid (General Procedure). A mixture of 2 g (6 mmoles) dichlorodiketone, 1.5 g (20 mmoles) ammonium acetate, and 20 ml acetic acid was heated at 80°C until complete starting material conversion was observed by TLC. The mixture was then diluted with 30 ml ether and washed with water. Chloropyridines V were recrystallized from alcohol.

2-Hydroxy-2,4,6-triphenyl-3,5-dichloro-1,2,3,4-tetrahydropyridine (VIe, $C_{23}H_{19}ClNO$). A solution of 1 g (2.5 mmoles) compound Ie in 15 ml benzene was saturated with ammonia and allowed to stand 14 days at 15°C. The resulting precipitate was removed by filtration, washed with water and benzene, and reprecipitated from acetone with water; yield 0.41 g (41%) of compound VIe, mp 88-89°C. IR spectrum: 3600-3100 (O—H, N—H), 1633 cm^{-1} (C=C). PMR spectrum (in $CDCl_3$): 5.09 [1H, d, $H_{(3)}$]; 4.18 ppm [1H, d, $J_{3,4}$ = 1.2 Hz, $H_{(4)}$]. TLC of the mother liquor revealed the presence of diketone Ie, benzoylpyrrole IVe, and 3-chloropyridine Ve.

Reaction of 2-Hydroxy-2,4,6-triphenyl-1,5-dichloro-1,1,2,3,4-tetrahydropyridine (VIe) with Ammonia. A solution of 1.1 g (0.25 mmoles) compound VIe in 2 ml dioxane was saturated with ammonia at 60°C and heated for 15 min, then diluted with 10 ml benzene, washed with water; the solvent was evaporated to give 0.05 g (75%) of 2,4,6-triphenyl-3-chloropyridine (Ve), mp 154-156°C, which was identical to the sample prepared according to the above procedure.

2-(2-Methoxybenzoyl)-5-(4-methoxyphenyl)pyrrole (IVb). A solution of 1.91 g (5 mmoles) dichlorodiketone Ib in 15 ml benzene was treated with 60 ml alcohol which was saturated with ammonia, and the mixture was allowed to stand at room temperature for 5 h. The resulting precipitate was separated, and washed with boiling alcohol, to give 0.21 g (13%) of compound IVb.

Reaction of Dichloropentanediones Ia-c with Thioureas (General Method). A mixture of 1 g (2.5-3.1 mmoles) dichlorodiketone Ia-c, 1 g (13 mmoles) thiourea or 2 g (13 mmoles) phenylthiourea in 10 ml alcohol was heated at 80°C for 2-4 h (until complete disappearance of the diketone starting material was detected by TLC), and was then worked up with 100 ml of dilute sodium hydroxide solution. The resulting precipitate of di(aminothiazolyl)methane VIIa-c (or VIIIa-c) was separated and washed with water.

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