CHLOROFORMYLATION OF N-SUCCINIMIDE AND SYNTHESIS OF ENAMINES – PYRROLONE DERIVATIVES

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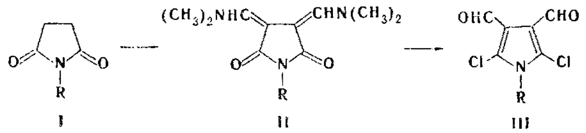
UDC 547.743.1.2'745.07:542.944.1

Treatment of N-substituted succinimides with dimethylformamide in the presence of phosphorus oxychloride leads to aromatization of the ring and the formation of N-substituted dichlorodiformylpyrroles. The latter have quite high reactivities. Replacement of one chlorine atom in 1-methyl-3,4-diformyl-2,5-dichloropyrrole by a hydroxyl group gives an aldehyde of pyrrolone, which forms the corresponding enamines with various amines. It was shown by spectral methods that they exist primarily in the enamine form.

The introduction of a β-chloroformyl group under the conditions of the Vilsmeier reaction has been practiced quite widely in recent years, but the available data pertain to compounds that contain one carbonyl group [1-5]. It seemed of interest to introduce into this reaction compounds that contain two methylene groups activated by carbonyl groups. We selected N-substituted imides of succinic acid (I) for this purpose. As a result of the reaction of the latter with dimethylformamide in the presence of phosphorus oxychloride, one might have expected the formation of the corresponding dimethylaminomethylene derivatives (II), which are usually obtained under these conditions [6].



However, as we established in [7], the reaction in this case proceeds further with aromatization of I and the formation of dichlorodiformylpyrroles III-VI (Table I). Since N-substituted succinimides do not react with phosphorus oxychloride under the conditions used, it might be assumed that chloroformylation proceeds in analogy with [2] to form compounds of the II type, which we were unable to isolate. Their formation is apparently the limiting step that determines the rate of the overall reaction.

Substituent R has an appreciable effect on the course of the reaction. Replacement of the phenyl group by an ethyl or isopropyl group leads to the formation, although in low yield, of considerably purer substances, probably because of an increase in the electron density on the oxygen atoms, which promotes the chlorination.

All of the dichlorodiformylpyrroles have quite reactive aldehyde groups, which form the corresponding oximes and thiosemicarbazones and are readily oxidized to dicarboxylic acids. All of the reactions, which were studied primarily in the case of III, are presented in the scheme (see scheme on following page).

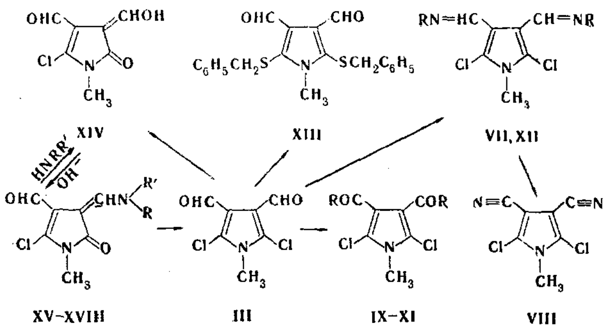
Dinitrile VIII was obtained from the oxime of 1-methyl-2,5-dichloro-3,4-diformylpyrrole on treatment with acetic anhydride. The corresponding acid chloride (X) and amide (XI) were synthesized from dicarboxylic acid IX. It should be noted that the preparation of the dinitrile can be carried out in steps. The nitrile of 3-acetoxyimino-2,5-dichloropyrrole-4-carboxylic acid ($\nu_{C\equiv N}$ 2234 cm^{-1}, $\nu_{C=N}$ 1616 cm^{-1}, $\nu_{C=O}$ 1770 cm^{-1}) is formed initially, and repeated treatment of it with acetic anhydride gives VIII.

Lensovet Leningrad Technological Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 507-510, April, 1973. Original article submitted April 7, 1972.

TABLE 1. Dichlorodialdehydes of the Pyrrole Series (III)-(VI)

Compound	R	mp, °C	λ_{max}, nm (log ε) (in ethanol)	ν_{CO}, cm^{-1} (in $CHCl_3$)	Empirical formula	Found, %		Calc., %		Yield, %
						Cl	N	Cl	N	
III	CH_3	138–140^a	245(4,3), 295(4,0)	1673	$C_7H_5Cl_2NO_2$	34,3	6,8	34,4	6,8	72
IV	C_2H_5	85–88^b	245(4,2), 297(4,0)	1675	$C_8H_7Cl_2NO_2$	32,4	6,5	32,3	6,4	40
V	i-C_3H_7	144–146^c	245(3,8), 303(3,7)	1689	$C_9H_9Cl_2NO_2$	30.2	5,9	30,8	6,0	41
VI	C_6H_5	214–216^d	220(4,2), 300(3,8)	1675	$C_{12}H_7Cl_2NO_2$	26,5	5,2	26,5	5,2	74

a) From water; b) from petroleum ether; c) from cyclohexane; d) from octane.



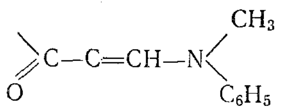
VII R=OH; XII R=NHSCNH$_2$; IX R=OH; X R=Cl; XI R=NH$_2$

The chlorine atoms in III are quite labile and are readily substituted on reaction with the benzylmercaptide ion to give the corresponding dibenzyl derivative. During alkaline hydrolysis, only one chlorine atom is replaced to give 1-methyl-2-chloro-3,4-diformyl-5-pyrrolone (XIV). The latter has acidic properties (pK_a in 50% ethanol at 25° is 3.6), dissolves readily in solutions of sodium carbonate and alkali, and reacts with amines under very mild conditions to give high yields of enamines XV-XVIII (Table 2), which are converted to starting XIV on treatment with alkalis and subsequent acidification.

The reaction of 4-dimethylaminomethylene derivative XVI with phosphorus oxychloride gave dichlorodialdehyde III; this is evidence for the retention of the pyrrole ring under the conditions of the chemical reactions.

The structures of XIV and its nitrogen derivatives (XV-XVIII), which are capable of existing in several tautomeric forms, were studied by means of the IR and UV spectra (Table 2).

Two bands at 1669 and 1636 cm^{-1} are observed in the IR spectrum of a chloroform solution of XIV in the region of the absorption of a carbonyl group, while the absorption band of the formyl groups in 1-methyl-2,5-dichloro-3,4-diformylpyrrole is found at 1673 cm^{-1}. A broad band of low intensity at 3050-3300 cm^{-1}, the position of which, as shown by special experiments, depends only slightly on the concentration, is observed in the region of OH-group absorption; from this it can be assumed that XIV is stabilized by intramolecular hydrogen bonding. The presence of two absorption bands of a carbonyl group which are observed in the spectra of XVI and XVII (Table 2), which are compounds with a fixed enamine structure, makes it possible to conclude that XIV exists in the hydroxymethylene structure, stabilized by an intramolecular hydrogen bond. The shift of one of the ν_{CO} bands by ~ 40 cm^{-1} (as compared with ν_{CO} of III) for XIV, XV, and XVII is associated with polarization of the carbonyl group, conjugation with the hydroxy or amino group, and the formation of an intramolecular hydrogen bond.

The IR spectra of monosubstituted enamines XV and XVIII (Table 2) are close to the spectra of the disubstituted compounds; this attests to their enamine structure. On comparison of the data from the electronic spectra of III and XIV (Tables 1 and 2), it is seen that replacement of the chlorine led to a bathochromic shift in λ_{max} in alcohol and cyclohexane by 20 and 100 nm, respectively. Such a significant effect of a solvent on the position of λ_{max} is evidently associated with ionization of XIV in alcohol; this was confirmed by the identical character of the curve of the absorption spectrum of its anion. Replacement of the methyl group by a phenyl group led to a bathochromic shift of 30 nm, probably due to inclusion of the π electrons of the benzene ring in conjugation. One should note the unexpectedly strong effect of the nature of the solvent on the position of λ_{max} of methylphenyl derivative XVII. In cyclohexane, the position of the absorption maxima is close to their position in the spectrum of aniline derivative XVIII, but in alcohol one observes a hypsochromic shift of 48 nm as compared with XVIII and of 15 nm as compared with XVI. Polarization of the  $\gt C(=O)-C{=}CH-N(CH_3)C_6H_5$ system in XVII is probably weakened because of interaction with the alcohol; this leads to the hypsochromic shift. Weakening of the polarization of the carbonyl group in XVI also affected the position of the ν_{CO} band of the pyrrolone ring, which is shifted by 10 cm^{-1} as compared with ν_{CO} of XVI and by 6 cm^{-1} for XVIII.

EXPERIMENTAL

1-Methyl-2,5-dichloro-3,4-diformylpyrrole (III). A. A 235-g (1.5 mole) sample of phosphorus oxychloride was added at 25° to a solution of 35 g (0.3 mole) of methylsuccinimide in 110 g (1.5 mole) of dimethylformamide (DMF). After 30 min, the reaction mixture was heated to 80° and held at this temperature for 10 h. It was then poured into ice water, and the aqueous mixture was neutralized to pH 7. Workup gave 44.5 g (72%) of III. Dioxime VII had mp 208-210° (from aqueous methanol). Found: N 17.6%. $C_7H_7Cl_2N_3O_2$. Calculated: N 17.8%. Dithiosemicarbazone XII did not melt up to 360° (from aqueous DMF). Found: N 27.7; S 18.3%. $C_9H_{11}Cl_2N_7S_2$. Calculated: N 27.8; S 18.2%.

Compounds IV-VI were similarly obtained (Table 1).

B. A mixture of 0.1 g (0.5 mmole) of XVI and 1 ml (10 mmole) of phosphorus oxychloride was heated at 60° for 15 h, after which it was poured into water. The aqueous mixture was then neutralized and worked up to give 0.08 g (78%) of III with mp 127-129°. The product was identified by a mixed-melting-point determination.

1-Methyl-2,5-dichloro-3,4-dicyanopyrrole (VIII). Compound VII was refluxed for 2 h in acetic anhydride, after which the excess acetic anhydride was removed by distillation, and the residue was diluted with water. The precipitate was removed by filtration and dried to give 85% of VIII with mp 136-138° (from octane). Found: Cl 34.6; N 21.2%. $C_7H_3Cl_2N_3$. Calculated: Cl 35.5; N 21.0%.

1-Methyl-2,5-dichloropyrrole-3,4-dicarboxylic Acid (IX). A 63-g (0.4 mole) sample of potassium permanganate was added slowly to a heated (at the boiling point) solution of 16 g (0.078 mole) of dialdehyde III in 200 ml of 80% dioxane, after which the mixture was held at this temperature for 5 h and filtered hot. The filtrate was evaporated and neutralized to give 6.5 g (35%) of acid IX with mp 265-266° (from aqueous methanol). Found: Cl 30.2; N 5.8%. $C_7H_5Cl_2NO_4$. Calculated: Cl 29.8; N 5.9%. Acid chloride X was obtained by treatment of the acid with thionyl chloride. The oily liquid was crystallized from petroleum ether. Amide XI was obtained from the acid chloride by treatment with alcoholic ammonia solution. The product had mp 254-255° (from water). Found: Cl 28.4; N 16.7%. $C_7H_9Cl_2N_3O_3$. Calculated: Cl 28.0; N 16.5%.

1-Methyl-2,5-dibenzylthio-3,4-diformylpyrrole (XIII). A mixture of 1.26 g (0.006 mole) of III, 2.45 g (0.02 mole) of benzylmercaptan, and 1.3 g (0.023 mole) of potassium hydroxide in 50 ml of 80% methanol was refluxed for 3 h. After two-thirds of the methanol had been removed by evaporation, the residue was neutralized with 10% hydrochloric acid. The precipitate was removed by filtration, washed with ether, and dried to give 0.86 g (38%) of a product with mp 92-94° (from petroleum ether). Found: N 3.5%. $C_{21}H_9NO_2S_2$. Calculated: N 3.7%.

TABLE 2. 2-Pyrrolone Derivatives

Compound	R	mp, °C	Empirical formula	Found, %		Calc., %		ν_{CO}, cm^{-1} (in $CHCl_3$)	λ_{max}, nm (lg ε)		Yield, %
				Cl	N	Cl	N		in ethanol	in cyclohexane	
XIV	OH	192—193 a	$C_7H_6ClNO_3$	18,9	8,1	18,9	7,9	1636, 1669	227(4,1), 278(4,1), 385(4,4)	250(3,6), 280(3,5), 315(3,5)	40
XV	$NHCH_3$	216—217b	$C_8H_9ClN_2O_2$	17,5	13,5	17,7	13,9	1631, 1679	230(3,7), 293(4,2), 400(4,2)	300(4,2), 410(4,0)	93
XVI	$N(CH_3)_2$	162—164c	$C_9H_{11}ClN_2O_2$	16,0	13,0	16,6	12,5	1629, 1678	232(3,9), 294(4,4), 400(4,3)	300(4,1), 410(3,9)	94
XVII	$N(CH_3)C_6H_5$	148—150b	$C_{14}H_{13}ClN_2O_2$	12,8	10,9	12,8	10,3	1640, 1678	230(4,2), 278(4,1), 385(4,3)	315(4,0), 430(3,9)	96
XVIII	NHC_6H_5	160—162d	$C_{13}H_{11}ClN_2O_2$	14,3	10,9	13,5	10,7	1634, 1679	250(3,8), 330(3,9), 430(4,2)	335(4,3), 430(4,4)	76

a) From octane; b) from heptane; c) from cyclohexane; d) from aqueous methanol.

1-Methyl-2-chloro-3,4-diformyl-5-pyrrolone (XIV). A mixture of 6.3 g (0.03 mole) of III and 11.2 g (0.2 mole) of potassium hydroxide in 150 g of methanol was refluxed for 3 h, after which it was cooled, and the precipitate was removed by filtration and dissolved in the minimum amount of water. The solution was then acidified to give 2.2 g (40%) of XIV with mp 190-192° (from octane). Found: Cl 18.9; N 8.1%. $C_7H_6ClNO_3$. Calculated: Cl 18.9; N 7.9%.

1-Methyl-2-chloro-3-formyl-4-methylaminomethylene-5-pyrrolone (XVI). This compound was obtained from XIV and excess methylamine by heating them in benzene solution for 1.5 h. The resulting precipitate was removed by filtration and crystallized from heptane. Compounds XVI-XVIII (Table 2) were similarly obtained.

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