REACTIONS OF N-CHLOROSUCCINIMIDE WITH 4-PHENYL-1,4-DIHYDRO-PYRIDINES

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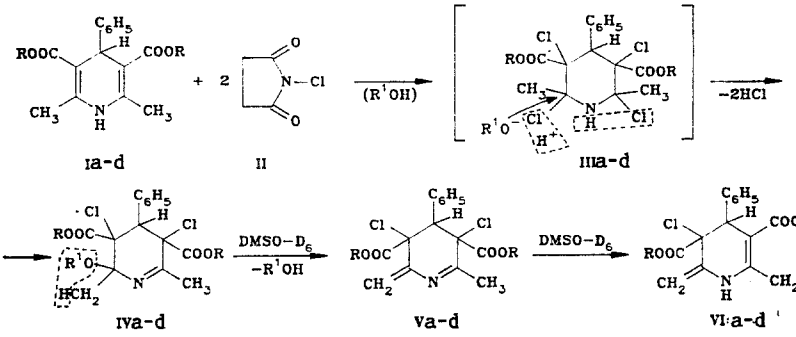
The action was studied of N-chlorosuccinimide on 2,6-dimethyl-3,5-dialkoxycarbonyl-4-phenyl-1,4-dihydropyridines. 3,4,5,6-Tetrahydropyridines having various degrees of chlorination were obtained according to the ratio between the reagents.

The reaction of N-chlorosuccinimide with 1,4-dihydropyridines is not known to occur. The action of N-bromosuccinimide on 1,4-dihydropyridines has recently been described [1, 2]. However, in these reactions, rather than the bromo derivatives of 1,4-dihydropyridines, their cyclization products – furo-1,4-dihydropyridines – were isolated.

We studied the reaction of N-chlorosuccinimide (II) with 2,6-dimethyl-3,5-dialkoxycarbonyl-4-phenyl-1,4-dihydropyridines (Ia, b) in methanol at room temperature. The cation of a double excess of II on Ia gave 2,6-dimethyl-3,5-dimethoxycarbonyl-3,5-dichloro-4-phenyl-6-methoxy-3,4,5,6-tetrahydropyridine (IVa), which was isolated from the reaction mixture in a good yield. It can be assumed that the addition of chlorine to the double bonds of the 1,4-dihydropyridine ring first takes place, and an unstable intermediate compound IIIa is formed.



I—IV a $R=R^1=CH_3$; d $R=R^1=C_2H_5$; c $R=CH_3$, $R^1=C_2H_5$; d $R=C_2H_5$, $R^1=CH_3$

Compound IIIa splits off hydrogen chloride and simultaneously adds a methoxy group (from the solvent), resulting in the formation of compound IVa. If the reaction is carried out in ethanol, the ethoxy group of the solvent is added, and compound IVc is obtained.

We observed a similar addition reaction of chlorine to the double bonds of the 1,4-dihydropyridine ring with subsequent splitting off of hydrogen halide during chlorination of 1,4-dihydropyridines with gaseous chlorine [3]. A similar addition was also observed during the halogenation of pyrimidines [4, 5].

In the reaction of compounds Ia, b with a fourfold amount of succinimide II, besides the addition of chlorine to the double bonds of the dihydropyridine ring, the methyl group in the 6-position is chlorinated, and compounds VIIa,b are formed. It can be assumed that in this case the reaction proceeds via the stage of formation of intermediate products IIIa, b (scheme 1). When the amount of II is increased sixfold, the methyl group in the 2-position is also chlorinated and 3,4,5,6-tetrahydropyridine (IXa) is formed.

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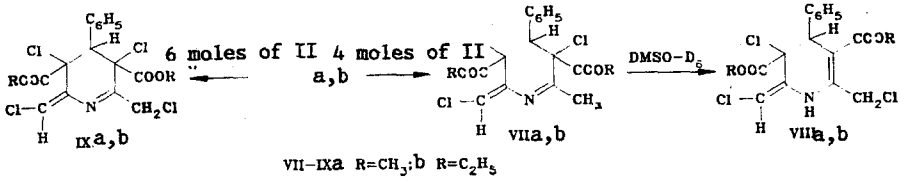
TABLE 1. 3,4,5,6-Tetrahydropyridines

Compound	Empirical formula	mp, °C	R_f	UV spectrum, λ_{max} (log ε)	IR spectrum, cm^{-1}	Yield, %
IVa	$C_{18}H_{21}Cl_2NO_5$	83...85 (dec.)	0,32	208 (4,0)	1662, 1744	50
IVc	$C_{19}H_{23}Cl_2NO_5$	80...82	0,60	207 (4,05)	1666, 1747	31
VIIa	$C_{17}H_{16}Cl_3NO_4$	112...115 (dec.)	0,88	207 (4,2); 247 (4,0); 297 (3,5)	1622, 1752	68
VIIb	$C_{19}H_{20}Cl_3NO_4$	100...103	0,80	205 (4,1); 246 (4,0); 295 (3,4)	1630, 1738, 1751	23
IXa	$C_{17}H_{15}Cl_4NO_4$	170...174	0,70	205 (4,2); 251 (3,6); 306 (3,0)	1632, 1725	35



VII–IXa R=CH_3; b R=C_2H_5

The compounds formed during the chlorination of compounds Ia,b do not have a long-wave absorption maximum in the UV spectra, such as is characteristic for 1,4-dihydropyridines; hence they are 3,4,5,6-tetrahydropyridines.

In the IR spectra of compounds IV, VII, and IX, the absorption band of the NH group is absent, while the absorption of the ester groups is observed in the 1744-1752 cm^{-1} region, which is much higher than in the initial 1,4-dihydropyridine (Table 1).

The structure of the reaction products was established by means of ^1H and ^{13}C NMR spectra (Tables 2 and 3). In assigning the signals in the ^{13}C spectra, the long-range ^{13}C-H SSCC were used. In the ^1H and ^{13}C NMR spectra of compounds IV and VII signals of only one 2-CH_3 group attached to the double bond were observed. The chemical shifts of the ^1H and ^{13}C nuclei for the $C_{(6)}$ and $C_{(6R)}$ atoms of these compounds indicate (Tables 2, 3) the formation of an exocyclic double bond. The absence of an NH proton signal in the ^1H NMR spectrum indicates the presence of a $C = C_{(6)} - N_{(1)} = C_{(2)} - CH_3$ fragment in the molecules of compounds VIIa,b. The $C_{(3)}$ and $C_{(5)}$ atoms absorb in the 65...60 ppm region in the ^{13}C spectra, which indicates the addition of two chlorine atoms in these positions of the heterocycle.

The sharp difference between the chemical shifts of the 3- and 5-$OOCH_3$ groups in the ^1H NMR spectra (Table 2) of compounds VIIa and also of the 3,5-$COOC_2H_5$ of compound VIIb, is clearly due to the anisotropic phenyl group in the 4-position. Hence the COOR groups are oriented asymmetrically with respect to the 4-phenyl substituent. This suggests a trans-addition of the chlorine atoms at 3 and 5 positions of the dihydropyridine ring.

The chlorine atom at the exocyclic double bond in compounds VIIa,b has a cis-orientation relative to the $N_{(1)}$ atom, which shows that the value of the long range SSCC is $^3J(^{13}C_{(5)}\text{-}C_{(6)} = C - {}^1H) \approx 2$ Hz

It should be noted that compounds IVa, b are very unstable in DMSO-D_6. They spontaneously split off a molecule of methanol (ethanol) and convert into compounds Va,b, which in turn rearrange into VI. Compounds VII also rearrange relatively readily in $CDCl_3$ into compound VIII, as seen from the ^1H and ^{13}C NMR spectra. The presence of a chlorine atom at the 6-position in compounds VIIa,b decreases the rate of the rearrangement. Thus, compound Va rearranges completely after only 1-2 h, while compound VIIa requires several days to accomplish this, and the reaction does not proceed quantitatively.

EXPERIMENTAL

The UV spectra were recorded on a Hitachi 557 spectrophotometer in ethanol (c $5 \cdot 10^{-5}$ mole/liter). The IR spectra were run on a Perkin-Elmer 580 B spectrophotometer in the form of a suspension in Nujol. The NMR spectra were taken on WH-90/DS and WH-360 spectrometers in $CDCl_3$ or DMSO-D_6 at frequencies of 90 and 360 MHz (^1H); 22.63 and 90.5 MHz (^{13}C), using TMS as internal standard. The course of the reaction and the purity of the compounds were monitored by TLC on Silufol-254 plates in a 1:1:1 hexane – chloroform – ethyl acetate system.

TABLE 2. Parameters of ^1H NMR Spectra of Compounds IV-IX

Compound	Solvent	Chemical shift, δ, ppm (J, Hz)				
		2-R	COOR	4-H	6-R	C_6H_5
IVa	DMSO	2,22	3,74; 3,41	4,72	1,59 (CH_3); 3,32 (OCH_3)	7,4...7,0
	$CDCl_3$	2,28	3,80; 3,42	4,85	1,68 (CH_3); 3,31 (OCH_3)	7,4...7,0
IVc	$CDCl_3$	2,24	3,78; 3,32	4,91	1,59 (CH_3); 1,24 (т, CH_2CH_3); 3,68 (м, CH_2CH_3)	7,4...7,0
Va	DMSO	2,33	3,74; 3,49	4,32	6,07 ($^2J_{HH}=0$); 5,78	7,3...6,9
VIa*	DMSO	4,82	3,57; 3,51	4,42	5,05 ($^2J_{HH}=0$); 4,87	7,2...6,9
VIIa	$CDCl_3$	2,50	3,51; 3,15	4,40	7,30	7,3...6,8
VIIb	$CDCl_3$	2,50	3,96, 3,55 (OCH_2); 1,16, 0,91 (CH_3)	4,41	7,34	7,3...6,8
VIIIb**	DMSO	4,99 ($^2J=10,0$); 5,14	3,61; 3,54	4,47	6,47	7,4...6,8
IXa	$CDCl_3$	4,54	3,52; 3,18	4,48	7,41	7,3...6,8

*δ_{NH} = 9.61 ppm.
**δ_{NH} = 8.86 ppm.

TABLE 3. Parameters of ^{13}C NMR Spectra of Compounds IVa, Va, VIa, VIIa,b VIIIa

Compound	Chemical shift, δ, ppm (in DMSO-D_6)								
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	2-R	3,5-R	6R	C_6H_5
IVa	163,79	69,77	58,09	77,48	86,24	22,91	166,96 and 165,58 (COO); 53,30 (OCH_3)	20,13 (CH_3); 50,30 (OCH_3)	132,94 (C_α); 128,22 (C_o); 130,37 (C_m); 128,51 (C_p)
Va	158,73	64,59	57,84	61,47	144,13	23,49	166,27 and 166,07 (COO); 52,97 (OCH_3)	120,75	132,96 (C_α); 128,17 (C_o); 130,17 (C_m); 129,58 (C_p)
VIa	137,63	97,90	52,64	64,78	145,49	40,11	166,40 and 165,75 (COO); 50,76 and 50,44 (OCH_3)	97,87	139,26 (C_α); 128,28 (C_o and C_m); 127,50 (C_p)
VIIa	161,40	64,72	57,90	61,86	137,63	23,88	165,75 (COO); 53,23; 53,03 (OCH_3)	124,25	132,50 (C_α); 128,09 (C_o); 129,91 (C_m); 129,13 (C_p)
VIIb	161,53	64,59	57,58	61,67	137,63	24,01	165,36 (COO); 62,77 (OCH_2); 13,17 and 12,91 (CH_3)	124,45	132,57 (C_α); 128,15 (C_o); 130,23 (C_m); 129,26 (C_p)
VIIIa	137,37	100,49	53,16	64,79	145,23	30,60	165,94; 165,42 (COO); 51,15 and 50,63 (OCH_3)	102,83	138,35 (C_α); 128,22 (C_o); 128,41 (C_m); 128,09 (C_p)

2,6-Dimethyl-3,5-dimethoxycarbonyl-3,5-dichloro-4-phenyl-6-methoxy-3,4,5,6-tetrahydropyridine (IVa). A mixture of 3.01 g (0.01 mole) of 1,4-dihydropyridine Ia and 2.67 g (0.02 mole) of compound II in 200 ml of methanol was stirred for 2 h. A 110 ml portion of water was added, and the precipitate that separated out was crystallized from aqueous methanol (1:1) to yield 2.0 g (50%) of IVa in the form of crystals (Table 1).

Compounds IVc (by carrying out the reaction in ethanol), VIIa,b (with 4 moles of chlorosuccinimide II) and IXa (with 6 moles of chlorosuccinimide II) were obtained in a similar way (Table 1).

The formation of compounds Va, VIa and VIIIa was observed at 20°C in a DMSO-D_6 solution from compounds IVa (Va and VIa) and VIIa (VIIIa). The structure of compounds V, VI and VII was confirmed by the ^1H and ^{13}C NMR spectroscopy.

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REACTION OF 9-DIAZO-4-AZAFLUORENE WITH UNSATURATED COMPOUNDS AND CYCLIC KETONES

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Spiro[4-azafluorene-9,1'cyclopropanes] were obtained by the reaction of 9-diazo-4-azafluorene with various alkenes in the form of a mixture of geometrical isomers differentiated according to the position of the substituents in the cyclopropane ring and also also according to position relative to the pyridine ring. In the reaction of 9-diazo-4-azafluorene with cyclopentanone, di(4-azafluorene-9 nyl) oxide is formed, while from its reaction with cyclohexanone, 2'-oxo-spiro-[4-azafluorene-9,1'-cycloheptane] is obtained.

The availability of a 9-diazo-4-azafluorene (I) [1] made it possible to start a systematic study of this compound, particularly for obtaining previously unknown spiro compounds.

Spiro[4-azafluorene-9,1'-cyclopropanes] II-VII substituted in the cyclopropane ring were obtained in the reaction of the diazo compound I with ethyl cinnamate, cinnamaldehyde, trimethylvinylsilane, 2-methyl-4-penten-2-ol, maleic anhydride, and tetracyanoethylene.

The diacid VIII was obtained by hydrolysis of anhydride VI. The presence of two signals from each of the 1-H and 8-H protons in the PMR spectra (Table 1) of compounds II-VI shows that they are mixtures of Z- and E-isomers differentiated according to the disposition of the substituents in the cyclopropane ring relative to the pyridine fragment of azafluorene. The difference in the chemical shifts is especially great in compounds II and III, where the effect of the phenyl radical causes a strong-field shift (by 1.33-1.62 ppm of the 1-H proton

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