STEREOCHEMISTRY OF NITROGEN HETEROCYCLES.

67.* TRANSFORMATIONS OF STEREOISOMERIC 1-CHLORO-2-METHYL-4-KETO-trans-DECAHYDROQUINOLINES IN AN ACIDIC MEDIUM

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It is shown that epimeric [with respect to the $C_{(2)}$ atom] 1-chloro-2-methyl-4-keto-trans-decahydroquinolines in an acidic medium undergo intermolecular monochlorination in the α position relatve to the carbonyl group with the formation of epimeric [with respect to the $C_{(2)}$ atom] 3e-chloro- and 10a-chloro-2-methyl-4-keto-trans-decahydroquinolines and 2-methyl-4-keto-10-chloro-cis-decahydroquinolines. The mechanism of the transformations is examined, and an assumption regarding the possibility of cis-trans isomerization of the intermediately formed π-chloronium complex is expressed.

We have previously shown that isomeric 1-chloro-4-keto-trans-decahydroquinolines are converted to 2-methyl-4-hydroxy- and 2-methyl-4-hydroxy-3-chlorotrans-5,6,7,8,9,10-hexahydroquinilines in an alkaline medium (triethylamine) [2].

In this paper we describe the transformations of epimeric [with respect to the $C_{(2)}$ atom] 1-chloro-2-methyl-4-keto-trans-decahydroquinolines in an acidic medium.

The conversion in an acidic medium to δ-chloroamines (and, to a lesser extent, ε-chloroamines), which undergo cyclization to azaheterocyclic compounds under the influence of alkali, is well known for haloamines with an open chain (the Hofmann–Löffler reaction) [3]. The reaction proceeds most smoothly with the use of a solution of H_2SO_4 in CH_3COOH, heating, and irradiation or the application of Fe^{2+} ions [4].

The literature does not contain data on the behavior of functionally substituted N-haloamines in acidic solutions. In this connection it seemed of interest to us to study the transformations in an acidic medium of the previously obtained (by us) 1-chloro-2-methyl-4-keto-trans-decahydroquinolines, which contain an oxo group in the γ position relative to the chloroamino group.

The investigation showed that only the hydrochlorides of the starting amino ketones are formed in the action of hydrochloric acid on these N-chloroamino ketones:

$$R_2NCl+2HCl\rightarrow R_2NH\cdot HCl+Cl_2.$$

The reaction proceeds similarly in acetic acid. The use of concentrated sulfuric and trifluoroacetic acids leads to the formation of α-chloro ketones; however, the yield of the amino ketone is still high, and, in addition, pronounced resinification of the reaction mixture occurs in sulfuric acid. The reaction proceeds smoothly in high yields in a solution of 4 moles/liter H_2SO_4 in acetic acid or in a solution of 1.5 M HCl in acetic acid at room temperature with the formation of mixtures of isomers of 2-methyl-3-chloro- and 2-methyl-10-chloro-4-ketodecahydroquinolines (V-X).

2a-Methyl-3e-chloro-4-keto-trans-decahydroquinoline (V) was isolated in the form of the base by fractional crystallization from hexane from the mixture of isomers obtained from 1-chloro-2a-methyl-4-keto-trans-decahydroquiniline (III) in a solution of 1.5 M HCl in acetic acid. 2a-Methyl-4-keto-10-chloro-trans-decahydroquinoline hydrochloride (VI·

*See [1] for Communication 66.

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HCl) and cis-2-methyl-4-keto-cis-10-chlor-r-9H-cis-decahydroquinoline hydrochloride (VII·HCl) were isolated by crystllization of the residual mixture of aminochloro ketones from acetone.

2e-Methyl-3e-chloro-4-keto-trans-decahydroquinoline (VIII), 2e-methyl-4-keto-10-chloro-trans-decahydroquinoline hydrochloride (IX·HCl), and trans-2-methyl-4-keto-cis-10-chloro-r-9H-cis-decahydroquinoline hydrochloride (X·HCl) were similarly obtained from 1-chloro-2e-methyl-4-keto-trans-decahydroquinoline (IV) (Scheme 1). The yields of these compounds were determined by analysis of the sum of the α-chloro ketones by GLC (Table 1).

The same compounds are formed when the reaction is carried out in a solution of 4 M sulfuric acid in acetic acid, but the yields of isomers V and VIII decrease somewhat, while the yields of isomers VI and IX increase.

Known correlations were used to establish the structures of the isolated compounds. Thus an equatorially oriented chlorine atom shifts the band of the n—π transition of the carbonyl group in the UV spectrum to the short-wave region by, on average, 5 nm without changing the extinction, while an axial chlorine atom shifts it 15 nm to the long-wave region with an increase in the extinction by a factor of two to three [5, 6]. In the IR spectrum an equatorial chlorine atom increases the frequency of the C=O vibrations by 18-31 cm^{-1}, while an axial chlorine atom increasesit by 2-10 cm^{-1} as compared with the C=O frequency in the spectrum of the starting amino ketone; the band of stretching vibrations for the $C-Cl_{(a)}$ bond lies at 550-730 cm^{-1}, as compared with 736-860 cm^{-1} for $C-Cl_{(e)}$ [6]. The multiplicities of the signals and the effects of substituents in the ^1H and ^{13}C NMR spectra are reliable criteria of the structures.

Let us demonstrate the use of these correlations for the determination of the configurations and conformations of the α-chloro ketones in the case of isomers of a single epimeric series.

A 1-nm shift of the absorption band of the carbonyl group to the short-wave region without an increase in the extinction is observed in the UV spectrum (Table 1) of the hydrochloride of isomer V; this constitutes evidence for an equatorial orientation of the chlorine atom relative to the carbonyl-containing ring. The 20 cm^{-1} shifts of the frequency of the stretching vibrations of the carbonyl group in the IR spectra (Table 1) for the hydrochloride and the base and the high frequencies of the stretching vibrations of the C—Cl bond confirm this orientation of the chlorine atom. At the same time the ^1H NMR spectrum (Table 2) reliably proves equatorial localization of the chlorine atom in the 3 position and trans fusion of the rings, which is attested to by the character of the splitting of the $3-H_a$ (d, J = 6.6 Hz) and $9-H_a$ (t, J = 9.5 Hz; d, J = 3.5 Hz) protons. The ^{13}C NMR spectrum also confirms the 2a-methyl-3e-chloro-4-keto-trans-decahydroquinoline (V) configuration (Table 3): the chemical shifts of only three carbon atoms undergo substantial changes as compared with the ketone: for $C_{(3)}$ one observes a marked increase in the chemical shift due to the α effect of chlorine and conversion of the triplet to a doublet, for $C_{(2)}$ one observes an increase of 8.0 ppm in the chemical shift (the β effect of the equatorial chlorine atom), and for $C_{(4)}$, instead of an increase in δ (the β effect of the chlorine atom), one observes a decrease, which is understandable if one takes into account the opposite directions of the inductive effects of the oxo group and the chlorine atom.

A 17-nm shift of the absorption band of the carbonyl group to the long-wave region with an increase in the extinction by a factor of 2.5 is observed in the UV spectrum of the hydrochloride of chloro ketone VI, and a 9-cm^{-1} shift of the band of C=O stretching vibrations is observed in its IR spectrum; this constitutes evidence for an axial orientation of the chlorine atom relative to the carbonyl-containing ring. In the ^1H NMR spectrum of base VI the signal of the $3-H_a$ proton (3.4 ppm, SSCC 13 and 7 Hz) proves the axial orientation of the $2-CH_3$ group, while the signal of the $9-H_a$ proton (2.85 ppm, dd, SSCC 8.0 and 6.2 Hz) constitutes evidence for trans fusion of the rings and attachment ofthe chlorine atom in the 10 position. The presence of the chlorine atomat the $C_{(10)}$ atom and the trans fusion of the rings are also confirmed by the ^{13}C NMR spectrum, in which the signal of the $C_{(10)}$ atom is shifted markedly to weak field (77.7 ppm) and remains a singlet in the spectrum with incomplete suppression of the proton resonance, whereas the chemical shifts of the $C_{(3)}$, $C_{(6)}$, and $C_{(8)}$ atoms are decreased as a consequence of the γ effect of the axial chlorine atom (Table 3). Thus the 2a-methyl-4-keto-10a-chloro-trans-decahydroquinoline (VI) configuration can be assigned to this amino chloro ketone.

TABLE 1. Yields and IR and UV Spectra of Stereoisomeric 3- and UV Spectra of Stereoisomeric 3- and 10-Chloro-2-methyl-4-ketodecahydroquinolines V-X and the Corresponding Amino Ketones I, II, and XI

Compound	Orientation of CH_3 relative to 9-H	Ring fusion	Position and orientation of Cl*	mp, °C	IR spectrum, cm^{-1}			UV spectrum, nm			Yield, %	
					$\nu_{C=O}$	$\Delta\nu_{C=O}$	ν_{C-Cl}	λ_{max}	$\Delta\lambda_{max}$	ε	A*2	B*3
V	cis	trans	3e	96	1721	21	790 (s)*4	—	—	—	19	12
V·HCl				192	1742	20	790 (s)	289	−1	17	—	—
VI	cis	trans	10a	Oil	1718	18	577 (s), 720 (w), 760 (w), 780 (s)	—	—	—	46	50
VI·HCl				173	1731	9	577 (m), 718 (m), 742 (m)	307	+17	44	—	—
VII	cis	cis	10a	Oil	1723	17	650 (w), 770 (v.s), 792 (v.s)	—	—	—	32	34
VII·HCl				160	1727	10	607 (s), 781 (s), 795 (m)	307	—	45	—	—
I	cis	trans	—	—	1700	—	—	—	—	—	6	3
I·HCl					1722	—	—	290	—	17	—	—
XI	cis	cis	—	—	1706	—	—	—	—	—	—	—
XI·HCl					1717	—	—	—	—	—	—	—
VIII	trans	trans	3e	146	1710	−1	775 (s), 790 (s), 806 (v.s)	—	—	—	25	20
VIII·HCl				196	1740	13	786 (s), 806 (m)	280	−8	17	—	—
IX	trans	trans	10a	Oil	1715	4	592 (m), 776 (s)	—	—	—	43	51
IX·HCl				186	1733	6	588 (s), 781 (m)	302	+14	32	—	—
X	trans	cis	10e	71	1725	—	585 (s), 796 (m)	—	—	—	9	8
X·HCl				183	1717	—	582 (v.s), 790 (w)	287	—	17	—	—
II	trans	trans	—	—	1711	—	—				8	5
II·HCl				—	1727	—	—	288	—	17	—	—

*The orientation of the chlorine atom relative to the carbonyl-containing ring.
*2Solution of 1.5 M HCl in glacial acetic acid.
*3Solution of 4 M H_2SO_4 in glacial acetic acid.
*4Abbreviations: s) strong, w) weak, m) medium, and vs) very strong.

TABLE 2. ^1H NMR Spectra of Stereoisomers of 3-Chloro- and 10-Chloro-2-methyl-4-ketodecahydroquinolines

Compound	Chemical shifts, δ, relative to TMS, ppm (multiplicity, J, Hz)				
	3-H_e	3-H_a	2-H	9-H	2-CH_3
V	—	4,72 (d 6,6)	3,81 (p 6,5)	2,75 (t 9,5, d 3,5)	1,13 (d 6,5)
VI	—	3,4 (d 13, d ~7)	3,6 m	2,85 (d 8,0, d 6,2)	1,12 (d 7,0)
VII	2,26 (d 14, d 4)	2,71 (d 14, d 11)	3,3 (m, 2H)		1,18 (d 6,0)
VIII	—	4,05 (d 10,0)	2,95 (d 10,4, q 6,2)	2,46 (t 10,0, d 4,0)	1,36 (d 6,2)
IX*	~2,2		2,5...3,0 (m 3H)		1,21 (d 6,0)
X	1,71 (d 18,5, d 1,5)	2,65 (d 18,5, d 8)	3,3 m	2,21 (d 4,0, d 1,3)	1,21 (d 6,6)

*The spectrum is difficult to interpret because of the closeness of the chemical shifts of the 2-H_a, 3-H_a, 3-H_e, and 9-H_a protons. Spectrum of IX·HCl in CD_3OD, ppm (SSCC, Hz): 2-H_a and 9-H_a 3.5-3.9, 3-H_a 3.21 (d 15.5, d 12.5), 3-H_e 2.59 (d 15.5, d 4.0), CH_3 1.45 (d 6.2).

TABLE 3. ^{13}C NMR Spectra of 3- and 10-Chloro-2-methyl-4-ketodecahydroquinolines V and X and the Corresponding Amino Ketones I, II, XI, and XII (δ relative to TMS, ppm)

Compound	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$	CH_3
I**	50,4	48,5	210,0	(24,9)***	(25,2)	(23,5)	34,4	(56,1)	(57,0)	20,0
II**	53,0	50,7	208,9	(25,2)	(24,9)	(23,6)	34,0	61,6	55,6	22,6
XI*	43,6	49,5	—	23,6	21,0	25,3	29,9	61,0	48,3	20,2
XII*	52,0	44,9	—	24,2	24,8	19,7	30,4	59,6	53,1	19,9
V*	61,4	81,5	—	24,9	25,0	23,5	34,4	54,1	57,0	14,0
V**	(58,4 d)	67,3 d	201,1 s	(25,0 t)	(24,1 t)	(24,8 t)	33,9 t	(57,7 d)	(56,7 d)	14,3q
VI*	49,4	42,5	—	31,9	19,2	22,5	28,4	63,1	90,0	20,0
VI**	49,6 d	43,4 t	201,9 s	31,3 t	20,7 t	24,9 t	27,6 t	57,3 d	77,7 s	19,8 q
VII*	42,6	43,5	—	34,6	21,0	23,3	29,9	68,0	81,3	20,3
VII**	47,5 d	45,8 t	200,4 s	35,6 t	(24,2 t)	(25,4 t)	29,6 t	64,2 d	73,4 s	22,6 q
VIII*	64,0	83,6	—	23,2	24,9	23,6	34,1	59,6	55,6	22,6
VIII**	(61,1 d)	70,0 d	201,0 s	(24,1 t)	(24,7 t)	(24,7 t)	33,6 t	60,9 d	56,8 d	20,9 q
IX*	52,0	49,6	—	32,2	18,9	22,6	28,1	68,6	88,6	22,6
IX**	53,3 d	45,8 t	203,5 s	31,4 t	(20,7 t)	(24,8 t)	27,7 t	62,9 d	76,0 s	22,5 q
X*	50,0	44,9	—	31,2	18,8	18,7	24,4	66,6	86,4	19,9
X**	52,1 d	47,9 t	203,5 s	31,9 t	22,4 t	21,5 t	27,9 t	61,3 d	77,5 s	19,6q

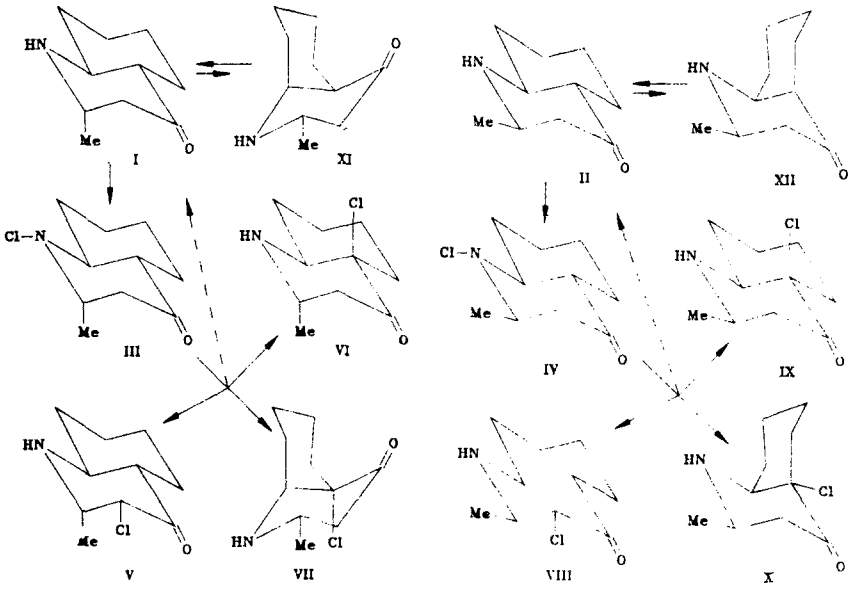
*These are the chemical shifts calculated using isomers of 2-methyldecahydroquinoline and 2-methyl-4-ketodecahydroquinoline as base models.
**These are the experimentally found chemical shifts.
***The chemical shifts presented in parentheses may change places.

A 2.5-fold increase in the extinction is observed in the UV spectrum of the hydrochloride of VII; this proves the axial orientation of the C–Cl bond with respect to the carbonyl-containing ring. The orientation of the chlorine atom attached to the $C_{(10)}$ atom is proved by the ^{13}C NMR spectrum: the signal of the $C_{(10)}$ atom (73.4 ppm) in the spectrum with incomplete suppression of the proton resonance remains a singlet. In the ^1H NMR spectrum of base VII the signals of the 3-H protons in the form of a doublet of doublets (3-H_a, 2.71 ppm, SSCC 14 and 11 Hz; 3-H_e, 2.26 ppm, SSCC 14 and 4 Hz) constitute evidence for the existence of an axial proton attached to the $C_{(2)}$ atom, i.e., for ring inversion, which is possible only in the case of cis fusion of the rings. The increase in the chemical shift of the CH_3 carbon atom in the ^{13}C NMR spectrum (22.6 ppm) also constitutes evidence in favor of this conformation. All of these data prove the configuration and conformation of chloro ketone VII as cis-2e-methyl-4-keto-cis-10a-chloro-r-9e-H-cis-decahydroquinoline [the a,e orientation of the substituents attached to the $C_{(9)}$ and $C_{(10)}$ atoms is indicated relative to the piperidine ring bearing the carbonyl group].

The configurations and conformations of the epimeric [with respect to the $C_{(2)}$ atom] amino chloro ketones VIII, IX, and X were similarly proved on the basis of the spectral data presented in Tables 1-3.

Thus, in contrast to the Hofmann–Löffler reaction, in whch the δ- and ε-carbon atoms of the amine are chlorinated, in the case of N-chloro amino ketones chlorination takes place in the α position relative to the keto group. The reason that determines the different direction of the reaction, is the development of a new more reactive center – the CH–C=O group. In contrast to the slow Hofmann–Löffler reaction, which proceeds via an ion-radical mechanism (the formation of radicals is stimulated by UV irradiation, heating, and the introduction of Fe^{2+} ions), rapid α chlorination of the ketones via a mechanism involving chlorination of the enol form occurs: a strongly acidic medium promotes the formation of the enol form, and the latter acts as a pseudobase with respect to the soft acid – the N-chloroammonium cation – as a result of which an α-chloro ketone is formed through the positively charged chloronium π complex. The reaction is thus intermolecular chlorination of the α atoms of the ketone by the N-chloroamino group.

Scheme 1

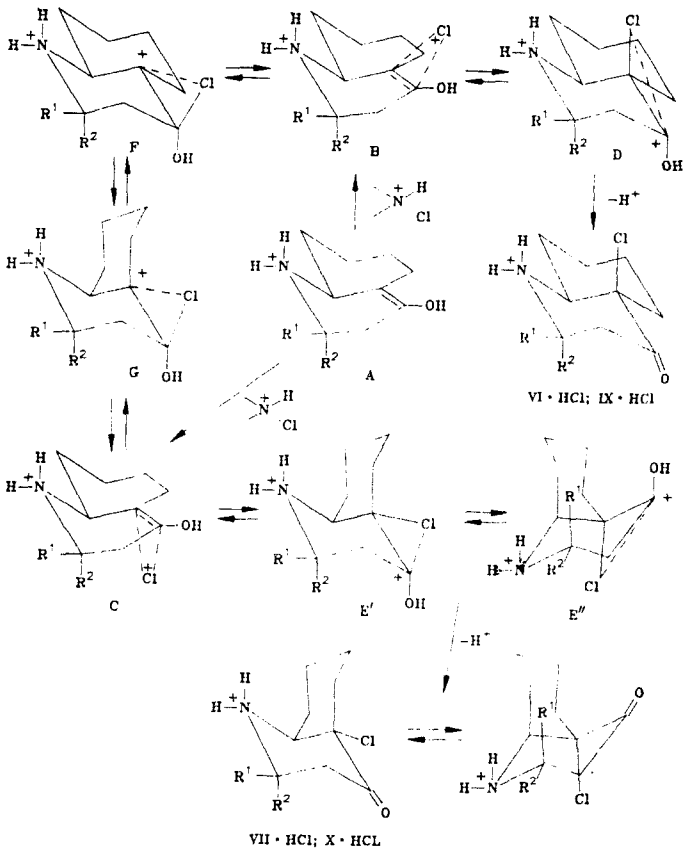


Since the first step (protonation of the oxygen atom of the carbonyl group) in the mechanism of the chlorination of ketones is fast, the second step (deprotonation with the formation of the enol form) is slow, and the third step (chlorination of the enol form) is very fast, the regiospecificity of enolization can be judged from the yields of α-chloro-substituted ketones.

It is apparent from the data in Table 1 that enolization on the part of the $C_{(10)}$ atom predominates significantly [80-87% $\Delta^{4(10)}$ and 13-20% $\Delta^{3(4)}$] in the case of N-chloroamino ketone III with an axial methyl group, whereas this predominance is expressed less markedly [68-75% $\Delta^{4(10)}$ and 25-32% $\Delta^{3(4)}$] in the case of N-chloroamino ketone IV with an equatorial methyl group. These results become understandable if one takes into account the fact that in an acidic medium, in conformity with the reaction mechanism, enolization on the part of the more substituted α-carbon atom [$C_{(10)}$ in our case] is preferable, which ensures greater hyperconjugation of the double bond with the C–H bonds that lie in the same plane as the π orbitals [7]. However, if one also takes into account the steric orientation of the substituents in the β position relative to the carbonyl group, the higher percentage of enolization on the part of $C_{(3)}$ in the case of ketone IV as compared with ketone III becomes understandable: the Δ^3 double bond of the enol form from ketone IV enters into conjugation with the $C_{(2)}$–H_a bond, whereas the enol form of ketone III does not have this possibility, since the methyl group is axially oriented.

In analogy with the α,α' equilibration of α-chloro ketones of the decalin series in an acidic medium [8] we attempted to equilibrate the α-chloro ketones of the decahydroquinoline series. However, analysis by GLC did not show the development of peaks of new α-chloro ketones when isomers V and VIII were allowed to stand for a month in a solution of 1.5 M HCl in acetic acid. Since the mechanism of this isomerization suggests ionization of the C–Cl bond with the formation of a Cl^- anion and the cation of the enol form of the ketone, it might

Scheme 2



For hydrochlorides VI, VII $R^1=H$, $R^2=CH_3$; IX, X $R^1=CH_3$, $R^2=H$

be assumed that the α-chloro ketones of the decahydroquinoline series become incapable of this sort of ionization because of conversion to the positively charged decahydroquinolinium cation in an acidic medium. It hence follows that isomers of 2-methyl-4-keto-10-chlorodecahydroquinoline with trans- and cis-fused rings should be formed only in the process of the synthesis of the α-chloro ketones themselves (they naturally cannot be formed from, respectively, the trans and cis isomers of the N-chloroamino ketones, since, according to the reaction mechanism, the process takes place through a common enol form). It is also apparent that the explanation of the formation of different isomers via the addition of the chloronium cation (or its carrier — the N-chloroammonium cation) on different sides of the double bond of the enol form is also excluded, since in the case of the sterically unhindered enol form of N-chloroamine IV one should observe the formation of either approximately equal amounts of the trans (IX) and cis (X) isomers or else, at the very least, the percentage of the cis isomer should be greater than in the case of ketone III, for which approach from the axial methyl side is hindered, which, in fact, is not observed.

Thus, only one explanation remains: the chloronium π complex, first of all, should have the possibility to undergo cis-trans isomerization and, second, should be sufficiently long-lived for this possibility to be realized. In this connection it may be assumed that the bond between the chlorine atom and the $C_{(10)}$ atom in one of the mesomeric forms is so weak (probably only an electrostatic bond) that cis-trans isomerization of the chloronium complex prior to its deprotonation is possible. The following scheme of the transformations of the chloronium π complex (Scheme 2) can be proposed.

The addition of the chloronium cation to enol form A is possible from different sides of the double bond; mesomeric forms B and C of the π-chloronium complex with a delocalized charge and different orientations of the chlorine atom relative to the ring can be formed. They exist in equilibrium with mesomeric forms D and E of this complex with the charge on the $C_{(4)}$ atom (these forms are possibly the preponderant forms) and forms F and G with the

charge on the $C_{(10)}$ atom; equilibration of trans and cis complexes D and E, the deprotonation of which leads to the α-chloro ketones, occurs through the F and G forms [the cation apparently becomes nonplanar because of interaction of the charge on the $C_{(10)}$ atom with the chlorine atom].

In the case of ketone VI the $D \rightleftharpoons B \rightleftharpoons F \rightleftharpoons G \rightleftharpoons C \rightleftharpoons E$ equilibrium is shifted markedly to favor trans isomer D, since the free energy of the cis isomer in both the E' conformation [axial $C_{(5)}$] and E" conformation [axial 2-CH_3 and $C_{(8)}$] considerably exceeds the free energy of trans isomer D (in addition, $\Delta G_{Cl_{ax}}^{Cl_{eq}}$ for the piperidinium salts is positive). In the case of ketone III trans isomer D and cis isomer E in the E" conformation have close free energies [the trans isomer has an axial 2-CH_3 group, while the cis isomer has an axial $C_{(8)}$ atom]. As a result of deprotonation of mesomeric forms D and E of the chloronium complex primarily α-chloro ketone IX with trans fusion of the rings is formed in the case of ketone IV (the ratio of isomers with trans and cis fusion of the rings in both methods of synthesis is ~85:15), whereas the ratios of the trans (VI) and cis (VII) isomers are close (~60:40) in the case of ketone III.

As we have already noted above, the combined effect on the $C_{(4)}$ atom of the oxo group and the chlorine atom in the α position relative to the carbonyl group leads, as a consequence of the opposite directions of polarization, to a decrease in the chemical shift of the carbon atom of the carbonyl group as compared with the unsubstituted ketone. The data that we obtained make it possible to determine this effect differentially for the α-equatorial and α-axial chlorine atoms: it is −8.4 ± 0.5 ppm for equatorial chlorine and −6.8 ± 1.4 ppm for axial chlorine (the minus sign corresponds to a shift to strong field). Similarly, as a consequence of the opposite polarization by the chlorine atom and the carbonyl group of the carbon atom in the α position relative to the chlorine atom [$C_{(3)}$ and $C_{(10)}$], their chemical shifts are also decreased as compared with the values calculated by an additive scheme: this difference is −13.9 ± 0.3 ppm in the case of equatorial chlorine, whereas it is −12.4 ± 0.2 ppm in the case of axial chlorine (the analogous data for α-chloro ketones of the cis series have the same order but are less reliable, since it is necessary to compare them with the calculated spectra of cis-ketones XI and XII). These corrections of the increments of the chlorine atom and the oxo group can be used in the calculation of the ^{13}C NMR spectra of α-chloro ketones.

EXPERIMENTAL

The IR spectra of the compounds obtained – KBr pellets of the bases and KCl pellets of the hydrochlorides – were recorded with a UR-20 spectrometer. The UV spectra of solutions ($1 \cdot 10^{-5}$ M) of the compounds in anhydrous ethanol were obtained with a Specord UV-vis spectrophotometer. The ^1H NMR spectra were recorded with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The ^{13}C NMR spectra were obtained with a Bruker WP-80 spectrometer (20.155 MHz) with $CHCl_3$ as the solvent and tetramethylsilane (TMS) or HMDS as the internal standard (the shift of the latter relative to TMS was 1.91 ppm).

Analysis by GLC was carried out with a Khrom-41 chromatograph with a flame-ionization detector and a glass column (ℓ = 1.2 m, d = 3 mm) packed with Chromaton N-Super with 5% SE-30 applied to it; the temperature was 120°C, and the carrier-gas (helium) flow rate was 40 ml/min. The retention times of the ketones and corresponding α-chloro ketones (in minutes) were as follows: I 3.3, II 3.2, V 11.4, VI 5.3, VII 4.0, VIII 9.6, IX 5.0, X 2.8, nonisolated substance formed from chloro amine IV 6.5, and nonisolated substance formed from chloro amine III 6.3. The sum of the amino chloro ketone bases after isolation from the reaction mixture was subjected to analysis.

Transformation of N-Chloroamine III in a Solution of 4 M H_2SO_4 in Acetic Acid. A 19.0-g (0.09 mole) sample of N-chloroamine III was added dropwise at room temperature to 200 ml of 4 M H_2SO_4 in glacial acetic acid in the course of 15 min, after which the reaction mixture was allowed to stand at room temperature for 1 h until it gave a negative reaction for active chlorine (the absence of coloration when a sample was treated with a 5% solution of NaI in 50% aqueous acetone). The mixture was then treated with 0.5 liter of CCl_4, and the addition of anhydrous sodium carbonate gave the base, which was extracted with CCl_4. After removal of the solvent, the residue (18.8 g) was analyzed by GLC (Table 1). Crystallization of the reaction mixture from hexane gave 2.5 g of a crystalline substance enriched with isomer V. Repeated recrystallization of it from hexane gave 1.1 g of pure isomer V with mp 95-96°C. The hydrochloride was obtained by neutralization of an alcohol solution of the base with an

ether solution of hydrogen chloride; the colorless crystals had mp 190-192°C (from ethanol). Found: C 51.2; H 7.8; Cl 30.5; N 6.0%. M^+ 201. $C_{10}H_{16}ClNO \cdot HCl$. Calculated: C 50.4; H 7.1; Cl 29.8; N 5.9%. M 201.

The mother solution was treated with an ether solution of HCl, and the resulting precipitate was removed by filtration and washed with ether. Fractional crystallization from acetone gave 1.2 g of the hydrochloride of isomer VII with mp 159-160°C (from acetone). Found: C 43.8; H 7.7; Cl 25.8; N 4.9%. M^+ 201. $C_{10}H_{16}ClNO \cdot HCl \cdot 2H_2O$. Calculated: C 43.8; H 7.7; Cl 25.9; N 5.1%. M 201. The hydrochloride of VII lost two molecules of water when it was dried in vacuo over P_2O_5. The base, which was an oil that was unstable during storage, was obtained by alkalization with Na_2CO_3 of an aqueous solution of the hydrochloride with subsequent extraction with petroleum ether.

Repeated crystallization of the residue from anhydrous ethanol gave 1.0 g of the hydrochloride of isomer VI with mp 172-173°C (from anhydrous ethanol). Found: C 50.5; H 7.1; Cl 29.7; N 5.9%. M^+ 201. $C_{10}H_{16}ClNO \cdot HCl$. Calculated: C 50.4; H 7.1; Cl 29.8; N 5.9%. An aqueous solution of the hydrochloride of isomer VI was decomposed with Na_2CO_3, and the base was extracted with petroleum ether. The oily base that remained after removal of the solvent darkened during storage.

Transformation of N-Chloroamine III in a Solution of 1.5 M HCl in Acetic Acid. An 11.5-g (0.057 mole) sample of N-chloroamine III was added dropwise to 100 ml of a solution of 1.5 M HCl in glacial acetic acid (the starting N-chloroamine was absent in the reaction mixture after 20 min). The mixture was worked up as in the preceding experiment to give 11.03 g of a mixture of isomeric chloro ketones. The results of analysis of the mixture by GLC are presented in Table 1.

Transformation of N-Chloroamine IV in a Solution of 1.5 M HCl in Acetic Acid. A 12-g (0.06 mole) sample of N-chloroamine IV was added gradually to 120 ml of a solution of 1.5 M HCl in glacial acetic acid, and the mixture was maintained at room temperature for 30 min (until it gave a negative reaction for active chlorine), after which it was neutralized and the product was converted to the base by the addition of small portions of sodium carbonate. The mixture was extracted repeatedly with benzene, and the benzene extracts were combined, dried with Na_2SO_4, and evaporated to give 11.8 g (98%) of residue. The results of analysis by GLC are presented in Table 1. Crystallization of the base from ether gave a precipitate consisting primarily of isomer VIII (5.2 g). Repeated crystallization from ethanol gave 3.0 g of α-chloro ketone VIII in the form of colorless crystals with mp 146°C. Found: C 59.6; H 7.8; Cl 17.7; N 6.9%. M^+ 201. $C_{10}H_{16}ClNO$. Calculated: C 59.6; H 7.8; Cl 17.6; N 6.9%. M 201. The hydrochloride was obtained as described above; the colorless crystals had mp 195-196°C (from ethanol). The ether mother liquor was converted to the hydrochloride with an ether solution of HCl. Recrystallization of the resulting precipitate from ethanol gave 2.0 g of the hydrochloride of isomer IX with mp 185-186°C. Found: C 50.6; H 7.1; Cl 30.0; N 6.2%. M^+ 201. $C_{10}H_{16}ClNO \cdot HCl$. Calculated: C 50.4; H 7.1; Cl 29.8; N 5.9%. M 201. The base was an oil that underwent resinification during storage. Crystallization of the residual mixture of isomeric chloro ketones successively from acetone and ethanol gave 0.4 g of the hydrochloride of isomer X in the form of colorless crystals with mp 182-183°C. Found: C 50.5; H 7.4; Cl 29.2; N 5.8%. M^+ 201. $C_{10}H_{16}ClNO \cdot HCl$. Calculated: C 50.4; H 7.1; Cl 29.8; N 5.9%. M 201. The base was obtained as described previously and had mp 70-71°C (from hexane).

Transformation of N-Chloroamine IV in a Solution of 4 M H_2SO_4 in Acetic Acid. An 18-g (0.089 mole) sample of N-chloroamine IV was added slowly dropwise to a solution of 4 M H_2SO_4 in glacial acetic acid. The mixture was worked up as in the preceding experiment to give 17.7 g (98%) of a mixture of isomeric chloro ketones. The results of analysis are presented in Table 1.

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ACETALS OF LACTAMS AND ACID AMIDES.

53.* ENAMIDINES IN THE SYNTHESIS OF PYRIDINE AND PYRIMIDINE

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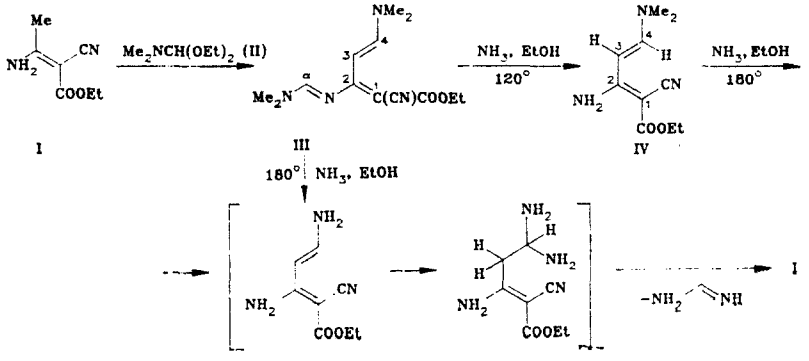
The reaction of α-cyano-β-aminocrotonic ester with DMFA diethylacetal gives 1-ethoxycarbonyl-1-cyano-2-(N-dimethylaminomethylene)-amino-4-dimethylaminobutadiene, the reaction of which with ammonium acetate and amines leads to 4-methylenepyrimidine derivatives. Condensation of α-cyano-β-aminocrotonic ester with dimethylacetamide dieethylacetal gave 2-(ethoxycarbonylcyano)methylene-4-dimethylamino-6-methylpyridine. It was found that in an alkaline medium, 1-benzyl-4-(ethoxycarbonylcyano)methylenepyrimidine recyclizes into 1-benzyl-3-cyano-4-amino-2-pyridone.

It has previously been shown that primary enamines can react with acetals of N-methyllactams to form enamidines, which are very promising starting compounds for the synthesis of various 4-pyridone derivatives [2, 3].

The aim of the present work was to study certain properties of enamidines formed in the reaction of amide acetals with ethyl ester of α-cyano-β-aminocrotonic acid (I). The reaction of the latter with DMFA diethylacetal (II) proceeds in the same way as in the case of lactam acetals [2] (at the amino and methyl groups), as a result of which dienaminoamidine-1-ethoxycarbonyl-1-cyano-2-(N-dimethylaminomethylene)amino-4-dimethylaminobutadiene (III) is formed readily and in a high yield (Table 1).

The reaction of enamidine III with ammonia in alcohol at low temperatures prodeeds very slowly, but when the temperature is increased to 120°C, transamination takes place with splitting of the amidine fragment and formation of a diene-diamine, 1-ethoxycarbonyl-1-cyano-2-amino-4-dimethylaminobutadiene (IV). It can be seen that under these conditions, the nucleophilic attack occurs at the $C_{(2)}$ atom only, without affecting the 4-position. Further increase in temperature not only led to transamination with splitting of the dimethylamino group at the 4-position, but also to rupture of the carbon-carbon bond with formation of a β-aminocrotonic ester derivative I. This unusual splitting probably proceeds by the scheme



*For Communication 52, see [1].

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