NUCLEOPHILIC SUBSTITUTION REACTIONS IN THE SERIES OF PERHALOALKYL β-AMINOVINYL KETONES

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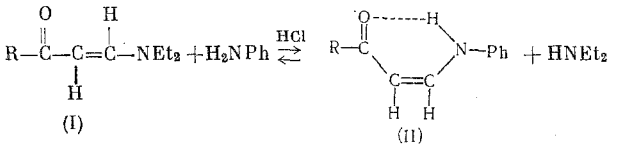
Perhaloalkyl β-aminovinyl ketones (subsequently called aminohaloalkenones) (I) were recently obtained [1] by the scheme:

$$2RCOX + 3NEt_3 \rightarrow \underset{(I)}{RCOCH{=}CHNEt_2} + RCHO + 2NEt_3 \cdot HCl$$

R = CCl_3 (a), C_3F_7 (b), CF_3 (c), $(CF_3)_3C$ etc.

We were interested in the characteristics of these aminoalkenones in nucleophilic substitution reactions of the amino group. Such reactions have been widely investigated for aminoalkenones, not containing the perhaloalkyl radical [2-4]; they are easily accomplished by treating these compounds with amines, water, Grignard reagent, etc. We investigated the reaction of the aminohaloalkenones (I) with primary and secondary amines, and water (acid hydrolysis), and also their reaction with hydroxylamine.

The reaction of diethylaminoalkenones (Ia-c) with aniline in the presence of hydrochloric acid leads to replacement of the diethylamino group by the aniline moiety and the formation of anilinohaloalkenones (IIa-c).



R = CCl_3(a), C_3F_7(b), CF_3(c)

The role of the acid consists in shifting the equilibrium to the right due to the preferential withdrawal of diethylamine (pK_a 10.93 [5]) from the reaction sphere, which is a stronger base than aniline (pK_a 4.58 [5]).

As is known [4], the reaction between aminoalkenones and amines is reversible. And, actually, in a special experiment it was shown that anilinotrichlorobutenone (IIa) readily reacts with diethylamine in the absence of acid to form diethylaminotrichlorobutenone (Ia)

$$\underset{(IIa)}{CCl_3COCH{=}CHNHPh} + HNEt_2 \rightleftarrows \underset{(Ia)}{CCl_3COCH{=}CHNEt_2} + H_2NPh$$

It is interesting to mention that in this reaction the amine does not cause haloform decomposition of aminoalkenones (Ia) and (IIa), whereas with trichloroacetone [6] this decomposition proceeds quite easily.

The structure of the anilinoalkenones (II) was established on the basis of the NMR and IR spectra. A characteristic feature of the NMR spectra of anilinoalkenones (II) is the fact that the signal from the NCH= proton in the AB quartet CH = CH is additionally split into a doublet, with a constant of J 13.5 Hz, by the proton of the NH group.* The value of the constant of this splitting makes it possible to assume a

*In one of the compounds, and specifically in anilinoalkenone (IIc), the HN signal is not detected. Such a phenomenon is encountered quite frequently in the NMR spectra of compounds containing the HN group (cf., for example, with [7]), and is explained by the fact that the signal from the HN proton is markedly broadened.

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trans-configuration for the protons in the fragment NH−CH=C, which is also corroborated by the data of other authors [8] on the example of analogous aminoalkenones. Together with this, the value of the spin−spin coupling constant of the protons in the CH=CH fragment of anilinoalkenones (II), equal to 8 Hz, apparently testifies to their being in the cis-position with respect to the double bond (cf. with [8]). As a result, the geometric structure of the anilinoalkenones is depicted by their structural formula (II).

Since the starting compounds (I) in the above-investigated reaction are most probably trans-aminohaloalkenones [1], it is interesting to mention that inversion of the geometric configuration evidently occurs in this reaction. The inversion of possibly facilitated by the fact that the NH proton of the end product forms an intramolecular hydrogen bond with the carbonyl group.

It should be mentioned that in contrast to aminoalkenones (Ia-c), aminoalkenone (Id), which contains a perfluorotert-butyl group, does not react with aniline, possibly due to steric hindrance by the $(CF_3)_3C$ group to attack by the aniline on the NCH=carbon atom

$$\underset{\text{(Id)}}{(CF_3)_3CCOCH{=}CHNEt_2} + NH_2Ph \xrightarrow{\text{does not go}} (CF_3)_3CCOCH{=}CHNHPh$$

Aminoalkenones (I) readily react with secondary amines. Thus, from aminoalkenones (Ia, b) and piperidine were obtained piperidinoalkenones (IIIa, b)

$$\underset{\text{(I)}}{RCOCH{=}CHNEt_2} + HN\bigcirc \rightleftarrows \underset{\text{(III)}}{RCOCH{=}CHN\bigcirc} + HNEt_2$$

R=CCl_3 (a), C_3F_7 (b)

The addition of hydrochloric acid in this case almost completely suppresses the forward reaction, since the acid primarily binds the more basic piperidine (pK_a 11.22 [5]), and not the diethylamine

$$\underset{\text{(Ia)}}{CCl_3COCH{=}CHNEt_2} + HN\bigcirc \xrightleftharpoons{HCl,\ C_2H_5OH} \underset{\text{(IIIa)}}{CCl_3COCH{=}CHN\bigcirc} + HNEt_2$$

Piperidinotrichlorobutenone (IIIa) can also be obtained from anilinoalkenone (IIa) and piperidine

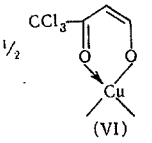
$$\underset{\text{(IIa)}}{CCl_3COCH{=}CHNHPh} + HN\bigcirc \rightleftarrows \underset{\text{(IIIa)}}{CCl_3COCH{=}CHN\bigcirc} + H_2Ph$$

Morpholine also reacts in a similar manner with diethylaminotrichlorobutenone (Ia)

$$\underset{\text{(Ia)}}{CCl_3COCH{=}CHNEt_2} + HN\bigcirc O \rightleftharpoons \underset{\text{(IV)}}{CCl_3COCH{=}CHN\bigcirc O} + HNEt_2$$

We also studied the hydrolysis of aminotrichlorobutenone (Ia) in acid medium and the reaction of aminoalkenones (I) with hydroxylamine. The hydrolysis of diethylaminotrichlorobutenone to the hydroxyalkenone (V) proceeds with great difficulty when it is refluxed with 25% HCl solution for 20 h. This property of diethylaminotrichlorobutenone sharply differentiates it from the hydrogen-containing aminoalkenones, which, as is known [2], are hydrolyzed by mineral acid even at room temperature. Hydroxyalkenone (V) could be isolated only as the inner complex of (V) with the copper salt (VI)

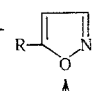
$$\underset{\text{(Ia)}}{CCl_3COCH{=}CHNEt_2} \xrightarrow{[H^+],\ H_2O} \underset{\text{(V)}}{CCl_3COCH{=}CHOH} \xrightarrow{Cu(OCOCH_3)_2} \tfrac{1}{2}$$



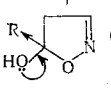
(VI)

The reaction of aminoalkenones (I) with hydroxylamine unexpectedly led to the formation of the stable 5-hydroxy-5-alkylisoxazolines (VII), whereas the hydrogen-substituted aminoalkenones give in this case isoxazoles of the (VIII) type [2, 9]

$$RCOCH{=}CHNEt_2 + NH_2OH \xrightarrow[CH_3OH]{HCl} [RCOCH{=}CHNHOH] \xrightarrow{H_2O} \text{(VIII)}$$



$\xrightarrow{-H_2O}$



(VI)

R=CCl_3 (a), C_3F_7 (b)

The absence of dehydration of isoxazolines (VII) to isoxazoles (VIII) is easily explained by the effect of the perhaloalkyl group (R), which strengthens the bond between the carbon atom and the adjacent oxygen atom. This phenomenon is widely known in the chemistry of other hydroxy derivatives, containing perhaloalkyl groups [10]. One of the characteristics of the studied aminohaloalkenones (I) is specifically manifested in this phenomenon.

In the F^{19} NMR spectrum of isoxazoline (VIIb) is observed a splitting of the signal of the fluorine atom in the $OCCF_2$ group into a doublet with a constant of J 79 Hz, which can be explained by the spin–spin coupling of the fluorine atoms of the CF_2 group with the hydrogen atom of the OH group via the four single bonds or via the space of the molecule. A responsible signal of this same isoxazoline (VIIb) is not seen in the NMR spectrum, but its width (~150 Hz) masks the entire region where the appearance of a responsible triplet of the proton of the OH group could be expected. At the same time, in the NMR spectrum of isoxazoline (VIIa), containing a trichloromethyl group, only the singlet of the proton of the OH group is observed.

EXPERIMENTAL METHOD

The NMR spectra were recorded on a Perkin–Elmer R-12 spectrometer, with an operating frequency of 60 MHz on the protons, while F^{19} NMR spectra were recorded on a Hitachi H-6013 spectrometer, with an operating frequency of 56.64 MHz on the F^{19} nuclei, in either acetonitrile or CCl_4 solutions. The chemical shifts of the protons are given on the δ-scale from HMDS, used as the internal standard, and for the F^{19} atoms on the τ-scale from CF_3COOH, which was used as the external standard. The IR spectra were taken on a UR-10 spectrometer, either as KBr pellets or in CCl_4 solution. The electronic spectra were taken on an SF-4M spectrophotometer in 95% ethanol solution. The thin-layer chromatography (TLC) and the preparative column chromatography were carried out on Al_2O_3 (200-250 mesh) (deactivated with 5% CH_3COOH solution) and on SiO_2 (150 mesh). The given melting points of the compounds are uncorrected.

1-Anilino-4,4,4-trichloro-1-buten-3-one (IIa). A solution of 5 g of aminobutenone (Ia), 5.5 ml of freshly distilled aniline and 5 ml of conc. HCl in 60 ml of absolute alcohol was refluxed for 10 h, after which it was diluted with 100 ml of water and allowed to stand overnight. The crystals were filtered and dried in the air. We obtained 4.9 g (91% of theory) of anilinobutenone (IIa) with mp 107-107.5° (from MeOH) (from [11]: mp 108.3-108.6°). Infrared spectrum (ν, cm^{-1}): 1690, 1654, 1620, 1575. Ultraviolet spectrum (λ,nm): 235 (ε 6100), 345 (ε 3500). NMR spectrum: 5.85 and 7.80 (AB quartet of CH = CH, J 8 Hz. All of the components of the NCH= signal are split in the doublet by NH, J 13.5 Hz); 7.21 (multiplet of Ph); 11.2 (broad NH). Found: C 45.4; H 3.16; Cl 40.4%. $C_{10}H_8Cl_3NO$. Calculated: C 45.4; H 3.05; Cl 40.3%.

The reaction of (Ia) with an equimolar amount of aniline and HCl leads to the formation of a mixture of (Ia) and (IIa) in a 1 : 1 ratio; the yield of (III) was 38%.

1-Anilino-4,4,5,5,6,6,6-heptafluoro-1-hexen-3-one (IIb). A solution of 2 g of aminohexenone (Ib), 0.65 ml of freshly distilled aniline and 0.6 ml of conc. HCl in 40 ml of absolute alcohol was refluxed for 15 h, after which it was diluted with 100 ml of water, extracted with ether, and the ether solution was washed with dilute HCl solution and then dried. The ether was distilled off, and the residue was dissolved in 5 ml of benzene. Chromatographing on Al_2O_3 gave 0.5 g (24% of theory) of anilinohexenone (IIb) with mp 50-51° (from 70% MeOH). Infrared spectrum (ν, cm^{-1}): 1665 (C=O), 1610 (Ph), 1590 (C=C). NMR spectrum: 5.64 and 7.82 (AB quartet of CH = CH, J 8 Hz. All of the components of the NCH= signal are split in the doublet by NH, J 13.3 Hz); 7.1 (Ph); 11.8 (broad NH). Found: C 45.8; H 2.71; F 41.5; N 4.49%. $C_{12}H_8F_7NO$. Calculated: C 45.7; H 2.54; F 42.1; N 4.44%.

From the second fraction, obtained by washing the Al_2O_3 column with benzene, was isolated 0.5 g of starting (Ib).

1-Anilino-4,4,4-trifluoro-1-buten-3-one (IIc). A solution of 2.8 g of aminoalkenone (Ic), 4 ml of freshly distilled aniline and 3.8 ml of conc. HCl in 40 ml of absolute alcohol was refluxed for 15 h, after which it was diluted with 100 ml of water, extracted with ether, and worked up in the same manner as in the preceding experiment. We obtained 0.87 g (28% of theory) of anilinobutenone (IIc) with mp 87-89°. Infrared spectrum (ν, cm^{-1}): 1655 (C=O), 1600 (Ph), 1570 (C=C). NMR spectrum: 5.65 and 7.54 (AB quartet of CH=CH, J 7.5 Hz. All of the components of the NCH= signal are split in the doublet by NH, J 13.5 Hz); 7.25 (Ph); NH was not detected. Found: C 55.8; H 3.84; N 6.44%. $C_{10}H_8F_3NO$. Calculated: C 55.8; H 3.75; N 6.51%.

1-Diethylamino-4,4,4-trichloro-1-buten-3-one (Ia). A solution of 0.8 g of anilinobutenone (IIa) in 2 ml of anhydrous Et_2NH was heated up to the boil, cooled, and diluted with 20 ml of water. The obtained crystals were filtered, and then washed on the filter with 1% HCl solution and water. We obtained 0.52 g (72% of theory) of diethylaminobutenone (Ia) with mp 55-56° (from 50% alcohol), which was identical (mixed melting point, TLC, and NMR) with the known compound [1].

Reaction of Aniline with 1-Diethylamino-5,5,5-trifluoro-4,4-bis(trifluoromethyl)-1-penten-3-one (Id). A solution of 0.76 g of aminoalkenone (Id), 0.6 ml of freshly distilled aniline and 0.6 ml of conc. HCl in 20 ml of absolute alcohol was refluxed for 4 h, after which it was diluted with 50 ml of water and extracted with ether. The ether solution was washed with dilute HCl solution, then with water, and dried. Distillation gave 0.68 g (90%) of diethylaminopentenone (Id) with mp 69-70° (from 50% methanol), which was identical (mixed melting point, TLC, and NMR) with the known compound [1].

1-Piperidino-4,4,4-trichloro-1-buten-3-one (IIIa). Without Acid. A solution of 1 g of aminobutenone (Ia) in 1.5 ml of anhydrous piperidine was refluxed for 30 min, cooled, and washed in succession with 1% HCl solution and water. The obtained crystals were filtered and dried in the air. We obtained 0.77 g (73% of theory) of piperidinobutenone (IIIa) with mp 114-115° (from 40% C_3H_7OH). Infrared spectrum (ν, cm^{-1}): 1670 (C=O), 1580 (C=C). NMR spectrum: 1.67 (multiplet of CH_2); 3.42 (multiplet of CH_2); 5.56 and 7.56 (AB quartet of CH=CH, J 12.7 Hz). Found: C 42.1; H 4.38; Cl 41.2%. $C_9H_{12}Cl_3NO$. Calculated: C 42.1; H 4.71; Cl 41.4%.

In the Presence of Acid. The refluxing for 20 h of a solution of 1 g of aminoalkenone (Ia), 1.5 ml of anhydrous piperidine and 1.2 ml of conc. HCl in 20 ml of absolute alcohol led to the formation of a small amount of aminoalkenone (IIIa), and the mixed melting point of the product was 44-45°. The aminoalkenone (IIIa) obtained in this experiment was also identified by TLC and the NMR spectrum.

1-Piperidino-4,4,5,5,6,6,6-heptafluoro-1-hexen-3-one (IIIb). A solution of 1 g of aminohexenone (Ib) in 0.5 ml of anhydrous piperidine was refluxed for 3 h. Then the mixture was worked up in the same manner as in the preceding experiment. We obtained 0.88 g (84% of theory) of piperidinohexenone (IIIb) with mp 89-90° (from 60% methanol). Infrared spectrum (ν, cm^{-1}): 1660 (C=O), 1580 (C=C). NMR spectrum: 1.45 (multiplet of CH_2); 3.43 (multiplet of CH_2); 5.26 and 7.86 (AB quartet of CH=CH, J 12 Hz). Found: C 42.8; H 3.67; F 43.6; N 4.65%. $C_{11}H_{12}F_7NO$. Calculated: C 43.0; H 3.93; F 43.3; N 4.55%.

1-Morpholino-4,4,4-trichloro-1-buten-3-one (IV). A solution of 1 g of aminoalkenone (Ia) in 0.5 ml of anhydrous morpholine was heated at 60° for 4 h. Then the mixture was worked up in the same manner as in the preceding experiment. We obtained 0.8 g (75% of theory) of morpholinobutenone (IV) with mp 147.5-148.5° (from a 1:1 benzene–cyclohexane mixture). Infrared spectrum (ν, cm^{-1}): 1665 (C=O), 1575 (C=C). NMR spectrum: 3.45-3.65 (multiplet of CH_2); 5.55 and 7.80 (AB quartet of CH=CH, J 12 Hz). Found: C 37.1; H 3.75; N 5.53%. $C_8H_{10}Cl_3NO_2$. Calculated: C 37.2; H 3.89; N 5.41%.

1-Piperidino-4,4,4-trichloro-1-butenone (IIIa). A solution of 0.8 g of anilinobutenone (IIa) in 2 ml of anhydrous piperidine was heated up to the boil and then worked up in the same manner as in the preceding experiment. We obtained 0.6 g (78% of theory) of piperidinobutenone (IIIa) with mp 114-115° (from 40% C_3H_7OH), which was identical (mixed mp 113-115°, TLC, and NMR) with the compound obtained above.

1-Hydroxy-4,4,4-trichloro-1-buten-3-one (V). A mixture of 5 g of diethylaminoalkenone (Ia), 40 ml of 25% HCl solution and 20 ml of chloroform was refluxed for 20 h. Distillation of the chloroform solution gave 1 g (26%) of hydroxybutenone (V) with bp 40-43° (2 mm). The latter is difficultly soluble in water, and when dissolved in either acetone or alcohol it forms yellow solutions. An alcohol solution of (V) when treated with aqueous $FeCl_3$ solution assumes a bright red color (cf. with [2]).

To a solution of 0.5 g of hydroxybutenone (V) in 3 ml of alcohol was added a hot solution of 0.5 g of copper acetate in 7 ml of water, and the obtained greenish crystals were filtered and dried. We obtained 0.54 g (93% of theory) of the inner-complex copper salt (VI) of the hydroxybutenone with mp 163-164° (decomp.) (from a 1:1 CCl_4–benzene mixture). Infrared spectrum (ν, cm^{-1}): 1550 and 1610. Found: C 21.8; H 1.02; Cl 48.2; Cu 14.4%. $C_8H_4Cl_6CuO_4$. Calculated: C 21.8; H 0.92; Cl 48.1; Cu 14.4%.

5-Hydroxy-5-trichloromethylisoxazoline (VIIa). A mixture of 3 g of diethylaminobutenone (Ia) and 1.05 g of hydroxylamine hydrochloride in 20 ml of absolute methanol was refluxed for 8 h. The mixture was diluted with 100 ml of water, extracted with ether, and the ether was dried and distilled. We obtained 1.48 g (92% of theory) of isoxazoline (VIIa) with mp 143-144° (from a 3:7 benzene–cyclohexane mixture).

Infrared spectrum (ν, cm^{-1}): 1630 (C=N), 3150 (OH). NMR spectrum: 3.15 and 3.64 (AB quartet of CH_2, J 19.6 Hz. All of the components of the CH_2 signal are split in the doublet by CH=, J 1.7); 7.3 (double doublet of CH=); 5.65 (OH, when several drops of CF_3COOH is added to an acetonitrile solution of the compound the signal is shifted upfield). Found: C 22.7; H 2.02; Cl 51.9; N 6.96%. $C_4H_4Cl_3NO_2$. Calculated: C 23.5; H 1.97; Cl 52.0; N 6.85%.

5-Hydroxy-5-heptafluoropropylisoxazoline (VIIb). A mixture of 4.9 g of diethylaminoalkenone (Ib) and 1.4 g of hydroxylamine hydrochloride in 20 ml of absolute methanol was refluxed for 8 h, after which it was diluted with 100 ml of water, extracted with ether, and the ether was dried and distilled. We obtained 2.2 g of a red oil. Extraction of the latter with boiling petroleum ether (4 × 10 ml) gave a solution, from which 0.56 g of a crystalline substance deposited on long standing. Recrystallization using a small amount of active carbon gave 0.4 g (10% of theory) of isoxazoline (VIIb) with mp 84-85° (from cyclohexane). Infrared spectrum (ν, cm^{-1}): 1638 (C=N), 3200 (OH). NMR spectrum: 3.1 and 3.5 (AB quartet of CH_2, J 19.2 Hz. All of the components of the CH_2 signal are split in the doublet by CH=, J 1.7 Hz); 7.35 (double doublet of CH=); 5.7 (OH, width ~150 Hz); F^{19} NMR spectrum: $CF_3CF_2{}^bCF_2{}^a$: 3.5 (triplet of CF_3 by $CF_2{}^a$, J 14.5 Hz); 44.5 (doublet of $CF_2{}^a$ by OH, J 79 Hz); 47.5 (multiplet of $CF_2{}^b$). Found: C 28.9; H 1.59; F 51.8%. $C_6H_4F_7NO_2$. Calculated: C 28.3; H 1.58; F 52.1%.

Based on the TLC, the residue from the extraction with petroluem ether represents the starting aminoalkenone (Ib).

CONCLUSIONS

1. A study was made of the nucleophilic substitution reaction of the amino group in diethylaminohaloalkenones. The diethylamino can be replaced by the moieties of aniline, piperidine and morpholine.

2. The reaction of aminohaloalkenones with hydroxylamine leads to the formation of 5-hydroxy-5-perhaloalkylisoxazolines. A characteristic trait of these isoxazolines consists in the fact that they are not dehydrated to isoxazoles.

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