

CHLORINATION OF TETRAHYDROFURAN-2-CARBOXYLIC ACID ESTERS

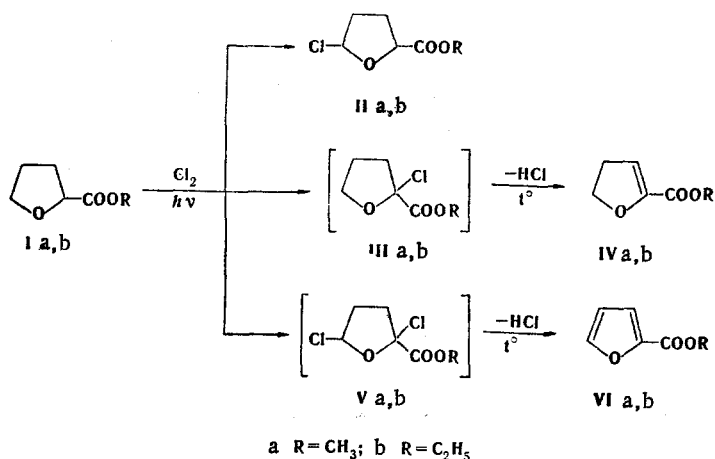
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The photochemical chlorination of tetrahydrofuran-2-carboxylic acid esters with chlorine at -15 to -20°C leads primarily to the formation of 5-chlorotetrahydrofuran-2-carboxylic acid esters (70-80%). 4,5-Dihydrofuran-2-carboxylic acid and furan-2-carboxylic acid esters are formed as side products. The structures of the principal and side products were investigated by PMR and mass spectroscopy.

5-Chlorotetrahydrofuran-2-carboxylic acid esters (IIa, b) are of interest as alkylating agents for the synthesis of analogs of nucleotides [1]. Since esters IIa, b have not been previously described, we studied the possibility of their synthesis by chlorination of tetrahydrofuran-2-carboxylic acid esters (Ia, b). Gross [2] and Kratochvil [3] have shown that the photochemical chlorination of unsubstituted tetrahydrofuran with chlorine at -30 to -40°C leads to 2-chlorotetrahydrofuran or 2,5-dichlorotetrahydrofuran, depending on the amount of chlorine introduced. An increase in the temperature to 0°C leads to the formation of 2,3-dichlorotetrahydrofuran as a result of dehydrochlorination and the addition of chlorine to the double bond.

We studied the photochemical chlorination of tetrahydrofuran-2-carboxylic acid esters in carbon tetrachloride at -15 to -20°C . The reaction mixture was analyzed by means of PMR spectroscopy. We were unable to use gas-liquid chromatography as an analytical method or for the preparative isolation of the individual compounds, since the α -chloro esters underwent decomposition during chromatographic separation to give dehydrochlorination products (IV, VIa, b). Partial decomposition of the reaction products was also observed during vacuum fractionation ($1 \cdot 10^{-2}$ mm of Hg).



Two doubled doublets at 6.35 and 6.46 ppm are observed in the PMR spectrum of the reaction mixture formed in the chlorination of methyl ester Ia (Fig. 1). Calculation with the use of the Shooley additivity increment for chlorine [4] makes it possible to assign them to the 5-H proton of the cis and trans isomers of ester IIa. From an analysis of the PMR spectra of a number of 2,5-disubstituted tetrahydrofurans it was previously [5] concluded

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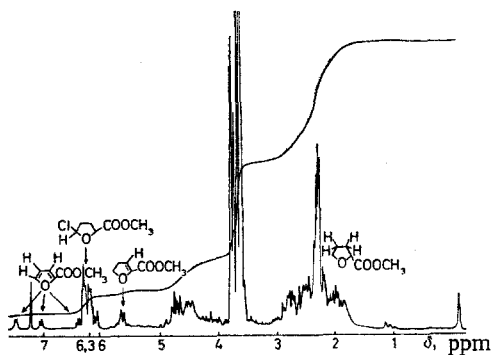


Fig. 1. PMR spectrum of the reaction mixture obtained in the chlorination of methyl tetrahydrofuran-2-carboxylate.

that the signals of the trans isomers are shifted 0.1-0.15 ppm to weak field as compared with the signals of the cis isomers. Since tetrahydrofuran derivatives with substituents that differ markedly with respect to their anisotropic properties (CH_3 , CH_2OH , and COOR) were studied in [5], it may be assumed that the shift of the signals of the cis and trans isomers is not due to the effect of the anisotropy of the substituent attached to C_5 on the 2-H proton (or of the substituent attached to C_2 on the 5-H proton) but rather to the different geometries of the tetrahydrofuran rings in the two isomers. On the basis of a comparison of the data that we obtained with the results in [5] it may be concluded that in our case also the signal of the trans isomer is observed at weaker field and that a mixture of cis and trans isomers of IIa in a ratio of 2:3 is formed during chlorination.

The triplet at 5.8 ppm (Fig. 1) can be assigned to the 3-H proton in 4,5-dihydrofuran-2-carboxylic acid ester IVa, which is formed as a side product as a result of dehydrochlorination of methyl-2-chlorotetrahydrofuran-2-carboxylate (IIIa). In individual cases signals at 7.60, 7.20, and 6.55 ppm, which are characteristic for furan compounds and constitute evidence for the formation of a small amount of methyl furan-2-carboxylate (VIa) as a side product, were observed in the spectra.

The spectrum of the reaction mixture also contains multiplets centered at δ 2.1 ppm (3-H, 4-H in Ia), 2.5 ppm (3-H, 4-H in IIa), and 4.7 ppm (2-H in IIa, 2-H and 5-H in Ia, and 5-H in IVa) and a singlet at 3.75 ppm (3H in OCH_3).

Calculation of the ratio of the reaction products in the mixture on the basis of the integral intensities of the signals of the protons in the PMR spectrum showed that ester IIa constitutes 80% of the mixture, IVa and VIa constitute \sim 8 and 2%, respectively, and unchanged starting ester Ia constitutes 10% of the mixture (average values for 10 experiments).

Thus the principal reaction pathway is replacement of a hydrogen in the free α position of the tetrahydrofuran ring by chlorine to give esters II. The structure of ester IIa was confirmed by its mass spectrum: m/e 164 (M^+); 163 ($\text{M} - 1$)⁺; and 105 ($\text{M} - \text{COOCH}_3$)⁺.

The reaction mixture containing \sim 80% ester IIa and IIb can be used as the alkylating agent, since the side products do not react in this case.

Esters IIa, b are considerably more stable than unsubstituted 2-chlorotetrahydrofuran, since the presence of an electron-acceptor substituent in the 5 position of the tetrahydrofuran ring hinders splitting out of halogen in the anionic form.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in carbon tetrachloride were recorded with a Perkin-Elmer R 12A spectrometer (60 MHz) with tetramethylsilane as the internal standard. The mass spectra were obtained with an MS-905 spectrometer (AEI) with direct introduction of the samples into the ionization chamber; the ionizing-electron energy was 70 eV.

Methyl Tetrahydrofuran-2-carboxylate (Ia). The reaction was carried out in an R-A5-3 isothermal reactor-autoclave with steam heating and vigorous stirring ($\text{Re} = 40000$). The free volume of the reactor was 2190 ml. The autoclave was charged with 50 g (0.4 mole) of methyl furan-2-carboxylate, 45 g of finely ground KD industrial catalyst (1.7% Pd-C), and 900 ml of dry ethyl acetate, and the autoclave was sealed and flushed successively three times with nitrogen and three times with hydrogen. Hydrogenation was carried out at $80 \pm 5^\circ\text{C}$ and an initial hydrogen pressure of 50 atm. The calculated amount of hydrogen (13.5 liters) was absorbed in 30 minutes. The excess hydrogen pressure (35 atm) was then released, and the

autoclave was flushed with nitrogen. The reaction mass was filtered to remove the catalyzate, the ethyl acetate was removed from the filtrate by distillation, and the residue was subjected to vacuum distillation to give 50 g (92%) of ester Ia in the form of a colorless liquid with bp 68°C (17 mm) and n_D 1.4355 [bp 177-183°C (680 mm) [6]].

Ethyl Tetrahydrofuran-2-carboxylate (Ib). This compound was similarly obtained. The hydrogenation of ethyl furan-2-carboxylate was carried out at $90 \pm 5^\circ\text{C}$ and an initial hydrogen pressure of 60 atm. The product had bp 95°C (11 mm) and n_D 1.4340.

Methyl 5-Chlorotetrahydrofuran-2-carboxylate (IIa). A solution of 32.5 g (0.25 mole) of ester Ia in 100 ml of dry carbon tetrachloride was placed in a quartz flask, the flask was cooled to -20°C , and a mixture of dry nitrogen and chlorine was introduced with stirring and illumination with a PRK-4 UV lamp. A total of 25.4 g (0.36 mole) of chlorine was introduced in the course of 2 h while maintaining the temperature at -20 to -15°C . Illumination was continued for another hour, after which the mixture was flushed with nitrogen to remove the hydrogen chloride, and the solvent was removed by vacuum distillation. The residue (40 g) contained, according to the PMR data, 80% ester IIa (from the intensity of the signal of the 5-H protons at δ 6.3 ppm), 10% unchanged starting ester Ia (3-H and 4-H, δ 2.1 ppm), and dehydrochlorination products: 8% IVa (3-H, δ 5.8 ppm) and 2% VIa (5-H, δ 7.55 ppm).

Ethyl 5-Chlorotetrahydrofuran-2-carboxylate (IIB). The reaction was carried out as in the chlorination of ester Ia. A total of 44 g of reaction products containing 33 g (75%) of IIB was obtained from 36 g (0.25 mole) of Ib.

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