Chem. Pharm. Bull. 30(5)1876—1879(1982)

The Fujiwara Reaction: Isolation and Structural Investigation of the Reaction Product from Chloroform

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(Received October 23, 1981)

The structure of the red product of the Fujiwara reaction was investigated by using chloroform as a *gem*-polyhalogen compound. Isolation of the product followed by nuclear magnetic resonance and mass spectroscopic analysis revealed the red chromophore to be the sodium salt of N^1,N^2-bis[(1*E*,3*E*)-4-formyl-1,3-butadien-1-yl] formamidine. The structure of the red products formed from trichloroacetic acid and chloral hydrate were also investigated. High-performance liquid chromatography analysis and mass spectra showed that both products have the same structure as that from chloroform. Since the red product from benzotrichloride has an analogous spectrum, it is concluded that the structure of the red products formed from the series of trichloroalkyl compounds ($RCCl_3$) is the nitrogenated polyene produced by the ring cleavage of two pyridine rings.

Keywords——Fujiwara reaction; chloroform; trichloroacetic acid; chloral hydrate; nitrogenated polyene; ^{1}H NMR spectrum

When a mixture of a *gem*-polyhalogen compound and pyridine is heated for a few minutes in a strongly alkaline medium, an intense red color develops.[1] This reaction is called the Fujiwara reaction. In the previous paper, we used benzotrichloride as a *gem*-polyhalogen compound, and isolated **1** (see Figure 1) which is responsible for the red color.[2] Furthermore, we investigated the mechanism of color development and determined the structure of the product in alkaline media to be **1′**, which is the anionic form of **1**. In the ^{1}H nuclear magnetic resonance (^{1}H NMR) spectrum of **1**, the overlap of the signals due to four olefinic protons (Hc, Hc′, He, and He′) with those due to the benzene ring protons makes the assignments of these signals difficult. If chloroform were used in place of benzotrichloride, a compound which has a hydrogen atom instead of the benzene ring would be obtained. It should be simpler to obtain accurate information regarding the olefinic signals and structure with this product. However, this compound, which is presumed to be the red chromophore formed from chloroform, has not yet been obtained because it is extremely difficult to isolate.

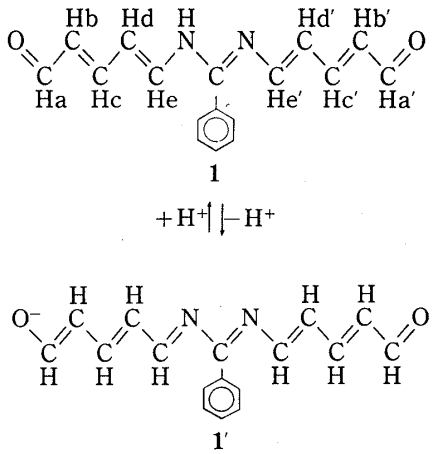


Fig. 1. Structure of the Red Chromophore formed from Benzotrichloride

The structural change from **1** (yellow) to **1′** (red) is due to deprotonation.

In order to clarify the structure of the red product formed from chloroform and to confirm that the nitrogenated polyene is always responsible for the red color when a trichloroalkyl compound is used as a *gem*-polyhalogen compound for this reaction, we isolated the red product from chloroform and determined its structure by means of NMR and mass spectrometry. Further, since both trichloroacetic acid and chloral hydrate yield chloroform in caustic solution,[3] we attempted to confirm by means of high-performance liquid chromatography (HPLC) analysis and mass spectrometry that the structure of the red products formed from them is identical with that from chloroform.

Experimental

Reagents and Materials——Pyridine and chloroform of analytical reagent grade (Wako Pure Chemical Industries Ltd.) were further purified by distillation, and were protected against light and moisture. Trichloroacetic acid, chloral hydrate, and other chemicals of analytical reagent grade were used as supplied.

General Methods——^{1}H NMR spectra were measured on a Varian XL-200 NMR spectrometer using 5 mm spinning tubes at ambient temperature and employing the deuterium field/frequency lock system. The sample was dissolved in DMSO-d_6. The chemical shifts are given in parts per million from internal tetramethylsilane and are reported in δ values. Field-desorption mass spectra were taken with a JEOL JMS-01SG spectrometer (JEOL, Tokyo) equipped with a field desorption ion source, operating at an accelerating voltage of 10 kV and an emitter heating current of 5—12 mA. Column chromatography was carried out on a Lobar column size B LiChroprep RP-8 (Merck) with 1: 1 water–methanol. The purity of the isolated compounds was checked by means of Shimadzu LC-3A liquid chromatograph (Shimadzu, Kyoto) equipped with a variable wavelength UV detector (SPD-2A, Shimadzu) over Nucleosil $10C_{18}$ (M. Nagel) packed in 25 cm × 4.6 mm i.d. stainless steel tubing with 1: 1 water–methanol. The flow rate was maintained at 1.0 ml/min, and the measuring wavelength was 250 nm.

Isolation of the Colored Product from Chloroform (I)——Chloroform (0.4 ml) was mixed with 4 ml of pyridine and 4 ml of aqueous 20% sodium hydroxide. The mixture was stirred for 30 s at 100°C. The pyridine layer was separated from the reaction mixture and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in 1 ml of 1: 1 water–methanol and 1 N HCl was added (1—2 drops) until a yellow color developed. The precipitate was removed by filtration and the filtrate was subjected to column chromatography. The yellow fraction was collected. Evaporation of the solvent gave a pale yellow oil. Field-desorption mass spectrum, m/z 204.

Isolation of the Colored Product from Trichloroacetic Acid——Trichloroacetic acid (0.5 g) was added to a mixture of 4 ml of pyridine and 4 ml of aqueous 20% sodium hydroxide. The subsequent procedure is identical with that for the isolation of the colored product from chloroform. Field-desorption mass spectrum m/z 204.

Isolation of the Colored Product from Chloral Hydrate——Chloral hydrate (0.4 g) was added to a mixture of 4 ml of pyridine and 4 ml of aqueous 20% sodium hydroxide. The subsequent procedure is identical with that described above. Field-desorption mass spectrum, m/z 204.

Results and Discussion

The Structure of the Red Chromophore formed from Chloroform.

Figure 2 shows the ^{1}H NMR spectrum of I in DMSO-d_6. The ^{1}H NMR spectrum consists of six resonances of 2: 1: 2: 2: 2: 2 area ratio: three groups of doublets at around δ 9.4 (Ha), a

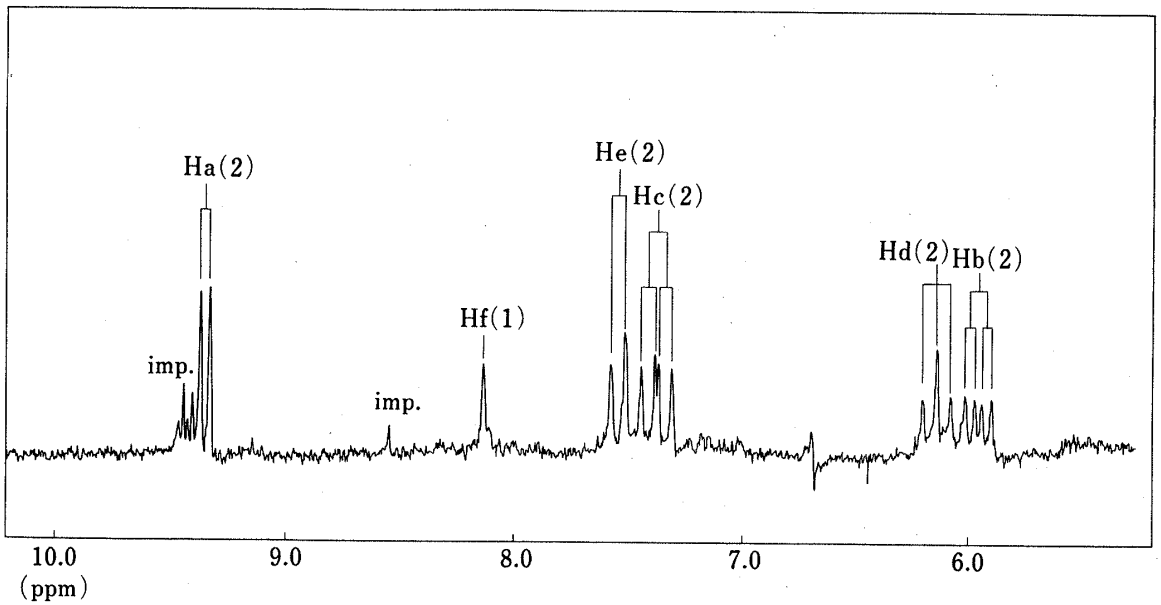
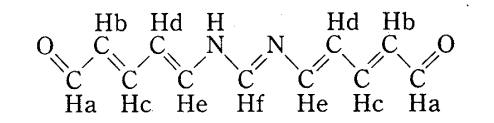


Fig. 2. ^{1}H NMR Spectrum of I (5 mM Solution in DMSO-d_6)

The numbers in parentheses are integrated area ratios.



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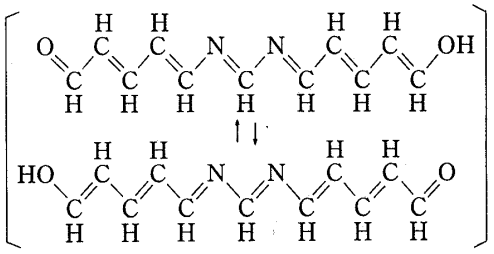

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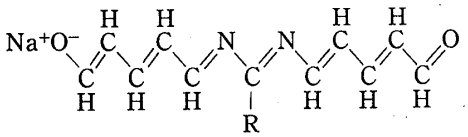

(4 : R=H) 5

singlet at δ 8.13 (Hf), a doublet at δ 7.56 (He), a double doublet at δ 7.46 (Hc), a triplet at δ 6.12 (Hd), and a double doublet at δ 5.97 (Hb). The aldehydic proton Ha at around δ 9.4 is spin coupled to the olefinic proton Hb at δ 5.97 (J_{HaHb}=8.2 Hz), the olefinic proton Hc at δ 7.46 is coupled to Hb (J_{HbHc}=14.4 Hz) and also to Hd at δ 6.12 (J_{HcHd}= 12 Hz), and Hd is coupled to He at δ 7.56 (J_{HdHe}= 12.1 Hz). The close resemblance of this ^{1}H NMR spectrum with that of **1** implies that the structure of the red product formed from chloroform is similar to that of **1**. Thus, Hf at δ 8.13 may be the proton attached to the central carbon intercepted by two nitrogens. The integrated areas of the protons other than Hf (*i.e.*, Ha, Hb, Hc, Hd, and He) are twice that of Hf. Consequently, these protons are considered to be distributed symmetrically on both sides of this carbon, as in **2**.

According to the field-desorption mass spectrum of I, the molecular formula and molecular weight are $C_{11}H_{12}N_2O_2$ and 204, respectively. These values exactly coincide with those of **2**. From the magnitudes of J values (J_{HbHc}=14.4 Hz and J_{HdHe}=12.1 Hz), the arrangement of the protons attached to C=C double bonds can be considered as *trans*.[2,4]

In DMSO solution, I showes a red color (λ_{max}, 530 nm), so the structure **3**, in which the conjugated system is approximately twice as long as in **2**, can be expected. This structure may explain why we could not detect the signal due to the NH proton in DMSO solution.

In Figure 2, the signals due to aldehydic protons at around δ 9.4 indicate the presence of three kinds of proton which occupy magnetically somewhat different positions. Since I is unstable at room temperature, degradation products may be responsible for the minor signal.

Thus, the structure of I is determined as **2**, *i.e.*, N^1,N^2-bis[(1*E*, 3*E*)-4-formyl-1,3-butadien-1-yl] formamidine, and the development of an intense red color when I is dissolved in an alkaline medium should thus be due to deprotonation of the NH proton of **2** to give **4**, which is almost identical with **3**.

The Structure of Red Chromophores formed from Trichloroacetic Acid and Chloral Hydrate

On HPLC, I gives a peak at 28.6 min. The chromatograms of the reaction solutions with trichloroacetic acid and chloral hydrate also show peaks at around 28.6 min. The products corresponding to this peak were isolated by HPLC. Field-desorption mass spectra indicated that M^+ of both the isolated compounds was 204.

Thus, the structure of the red chromophore formed from trichloroacetic acid and chloral hydrate is considered to be identical to that formed from chloroform.

Conclusion

The sodium salt of N^1,N^2-bis[(1*E*, 3*E*)-4-formyl-1,3-butadien-1-yl] formamidine (**4**) has been found to be responsible for the red color in the Fujiwara reaction, when chloroform, trichloroacetic acid, or chloral hydrate was used as the chromogenic reagent. All trichloroalkyl compounds ($RCCl_3$) presumably yield analogous chromophores, having the structure represented by **5**.

Acknowledgement We thank Dr. N. Akimoto for the measurements of MS, and Miss J. Fujiki for her technical assistance.

References and Notes

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