[Chem. Pharm. Bull. 25(5)1101—1103(1977)]

UDC 547.568.1.03.04 : 542.944

Rearrangement in Halogenation of 2-Phenylethanol[1]

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(Received July 22, 1976)

The halogenation of 2-phenylethanol-1-^{14}C and -1-^{13}C was carried out with halogen-phosphorus or phosphorus trihalide under various conditions. The resulting 2-phenylethyl halides showed isotopic scrambling of the ^{14}C and ^{13}C label from C-1 to C-2. The degree of rearrangement increased with the rise of reaction temperature. In a given temperature, the rearrangement in iodination was more than that found in bromination or chlorination.

Keywords——rearrangement; isotopic scrambling; halogenation; 2-phenylethanol; ^{14}C-labeled compound; ^{13}C-nuclear magnetic resonance; ethylenephenonium ion; nucleophilic substitution

The halogenation of 2-phenylethanol-1-^{14}C with various reagents has given rise to rearrangement of the ^{14}C label from C-1 to C-2.[3] However, no detailed study on the rearrangement has been carried out.

In this paper, we describe the data of the isotopic scrambling which occurs in the reaction of 2-phenylethanol-1-^{14}C(I) and -1- ^{13}C(II) with halogen-phosphorus or phosphorus trihalide. In ^{14}C labeled experiments, the isotopic scrambling was determined by the measurement of radioactivity of benzoic acid obtained from 2-phenylethyl halide(III) by an alkaline permanganate oxidation. On the other hand, the ^{13}C distribution was decided on the basis of the signal intensities of C-1 and C-2 in ^{13}C Fourier transform nuclear magnetic resonance (FT-NMR) spectra. The results are summarized in Table I and II. The data indicate that the extent of rearrangement increases with the rise of reaction temperature, and that in a given reaction temperature, it varies with the halogen species. Since it is thought that a reaction *via* ethylenephenonium ion (IV) (pathway A) and a direct displacement (pathway B) are involved in this system,[4] an increase in the reaction

Table I. Rearrangements in the Reaction between 2-Phenylethanol and Iodine in the Presence of Red Phosphorus

Run	Reaction temperature (°C)	Reaction time (hr)	Yield (%)	Rearrangement from C-1 to C-2 (%)	
				^{14}C	^{13}C
1	room temperature	168	72.2	4.3	—
2	50	2	80.0	—	9.6
3	100	0.5	84.1	13.2	—
4	150	0.5	78.0	15.2	—
5	150	0.5	90.8	14.4	16.3
6	200	0.5	79.4	18.3	—
7	200	0.5	75.0	—	17.7

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[1] This work was presented at The 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, Apr. 1974. Contribution TMIG-I No. 5.

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temperature seems to be of advantage to pathway A. In our condition, iodine increases the proportion of rearrangement relative to bromine and chlorine. However, it has been found that the reaction of I with hydrobromic acid resulted in a greater extent of rearrangement than the corresponding reaction with hydroiodic acid.[3] Presumably, the reverse of relative reactivity between iodine and bromine would depend on a degree of solvation effect for the attacking species and the leaving group, because the order of nucleophilicity might be changable with the solvent used.[5]

TABLE II. Rearrangements in 2-Phenylethyl Halides from 2-Phenylethanol

Run	Reagents	Reaction Temperature (°C)	Reaction time (hr)	Yield (%)	^{13}C Rearrangement from C-1 to C-2 (%)
1	P, Br_2	150	1	89.7	11.4
2	P, Br_2	200	1	56.2	12.4
3	PBr_3	150	1	75.3	6.4
4	PBr_3	200	1	70.5	8.5
5	PCl_3	150	1	58.9	7.2
6	PCl_3	200	1	65.2	7.6

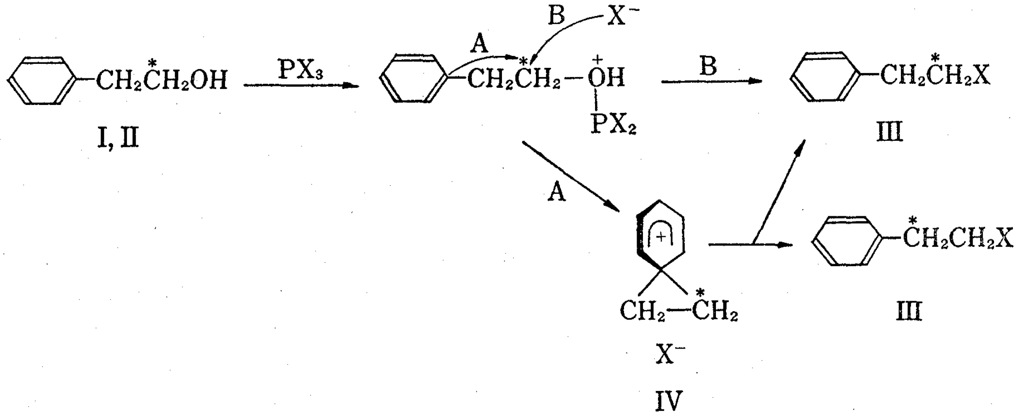

Chart 1

Experimental

All ^{13}C FT-NMR spectra were taken at 25.16 MHz on a Varian XL-100-12 spectrometer, equipped with a Varian 620/L computer. The measurement was carried out in $CDCl_3$ solution (1 mmol/ml) by use of 10 mm sample tubes and TMS as an internal standard. On the determination of ^{13}C rearrangement, the spectra were recorded under the condition in which the signal intensities of C-1 and C-2 in III were equal in the natural abundance ^{13}C FT-NMR spectrum. The chemical shifts of C-1 and C-2 in II and III are as follows; II: C-1 (63.7 ppm), C-2 (39.3). III: X=I, C-1 (5.3), C-2 (40.4). X=Br, C-1 (32.8), C-2 (39.5). X=Cl, C-1 (44.9), C-2 (39.0). The measurements of radioactivity were done with an Intertechnique SL-30 liquid scintillation spectrometer. The counting was corrected by an external standard ratio method. A total of 10 ml of a toluene scintillator containing PPO (40 mg) and POPOP (1 mg) was used for each counting vial. By $LiAlH_4$ reduction, I was prepared from methyl phenylacetate-1-^{14}C which was derived on esterification of phenylacetic acid-1-^{14}C (sp. act. 45 mCi/mmol; The Radiochemical Centre, Amersham, U.K.).[6] II was synthesized from phenylacetic acid-1-^{13}C (90 atom %; The British Oxygen Co., Ltd., London, U.K.).

Halogenation of 2-Phenylethanol——The halogenation was attained by usual methods.[7] The typical procedures are as given below.

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a) Reaction with Red Phosphorus and Halogen: To a mixture of I (255 mg) and red phosphorus (20 mg) in a 5 ml round-bottomed flask fitted with a reflux condenser holding a calcium chloride tube was added iodine (272 mg) at room temperature. The mixture was heated on an oil bath at 150° for 30 min. After purification, the yield of 2-phenylethyl iodide-1-^{14}C was 378 mg (78.0%).

b) Reaction with Phosphorus Trihalide: In a 5 ml two-necked flask with a reflux condenser holding a calcium chloride tube and a separatory funnel was placed II (122 mg). With stirring, the vessel was heated on an oil bath maintained at 150°. Phosphorus tribromide (298 mg) was added dropwise to it. After its addition, the mixture was allowed to stand at 150° for 1 hr. The yield of 2-phenylethyl bromide-1-^{13}C was 139 mg (89.5%).

Degradation to Benzoic Acid——A mixture of 2-phenylethyl iodide (382 mg), $KMnO_4$ (965 mg) and 1% NaOH solution (17 ml) was refluxed for 3 hr, and then MnO_2 precipitated was removed by filtration. The filtrate was acidified with conc. HCl. After removal of the precipitate resulted, the solution was concentrated *in vacuo* to give benzoic acid, 159 mg (79.7%). This product was repeatedly recrystallized and sublimed until a constant specific activity was obtained.

Acknowledgement We thank Dr. M. Kaneda for the preparation of several raw materials and Mrs. Y. Tamura for her technical assistance.

[Chem. Pharm. Bull. 25(5)1103—1106(1977)]

UDC 547.546-033.03.04: 546.33-36.03.04

Mechanism of the Color Reaction of Active Methylene Compounds with 1,3,5-Trinitrobenzene Derivatives. VIII.[1] Interaction of Mono- and Dihydroxylated Species (1:1 and 1:2 Complexes) derived from 1,3,5-Trinitrobenzene and Hydroxide Ion with Acid

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(Received July 26, 1976)

By use of stopped flow rapid scan spectrophotometric technics, it was demonstrated that the backward reaction from dihydroxylated anion (1:2 complex) derived from 1,3,5-trinitrobenzene with sodium hydroxide to monohydroxylated anion (1:1 complex) did not occur when the alkaline solution of 1,3,5-trinitrobenzene was neutralized or acidified with acids.

Keywords——1,3,5-trinitrobenzene; 1,3,5-trinitrobenzene monohydroxylated anion; 1,3,5-trinitrobenzene dihydroxylated anion; absorption spectral changes with time; stopped flow rapid scan analyser

In the improved sensitive method of detecting active methylene compounds with 1,3,5-trinitrobenzene (TNB),[3] the alkaline color reaction mixtures were neutralized with sodium dihydrogen phosphate solution in order to diminish the intensive red color of excessive TNB and to intensify and stabilize the colors produced by the reactions of active methylene compounds with TNB in alkaline medium. In the previous study on the color reaction of acetophenone with TNB by use of stopped flow rapid scan spectrophotometric technics,[1] it was reported that 1:1 complex (I) and 1:2 complex (II) shown in Chart 1 were succes-

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