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The Reaction of Optically Active Silver β-Phenylisobutyrate with Halogen

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The Hunsdiecker reaction of optically active silver β-phenylisobutyrate with bromine was carried out, and racemic β-phenylisopropyl bromide and optically atcive 3-methyl-7-bromohydrocoumarin were obtained as the major products. Meanwhile, the Simonini reaction was also performed with the same optically active acid and iodine; 1-phenyl-2-propyl β-phenylisobutyrate was obtained as the product here. Upon the hydrolysis of the ester, the resulting alcohol, β-phenylisopropyl alcohol, was found to be racemic. From these observations, the mechanisms involving the formation of the incipient free radical during the reactions were suggested for both the reactions.

There are two different pathways for the reaction between silver carboxylate and halogen, depending mainly upon the molarity of halogen used. One is known as the Hunsdiecker reaction[1]; it gives an alkyl halide, carbon dioxide and silver halide, when a silver carboxylate is treated with a one mole equivalent of halogen, usually bromine; the other pathway, known as the Simonini reaction,[1] gives an ester, carbon dioxide and silver halide, using two moles of halogen and generally employing iodine.

As for the Hunsdiecker reaction, a few stereochemical studies have been carried out using various optically active silver carboxylates. Bell and

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[1] a) R. G. Johnson and R. K. Ingham, *Chem. Revs.*, **56**, 219 (1956). b) C. V. Wilson, *Org. Reactions*, **9**, 332 (1957).

Smyth[2] reported that the Hunsdiecker reaction of optically active silver benzylethylacetates gave an almost completely inactive 2-bromo-1-phenylbutane. A similar racemization was reported by Arnold and Morgan[3] and also by Heintzeler[4]; they favored a radical process for this reaction. Meanwhile, there has been a report by Arcus, Campbell and Kenyon[5] that the Hunsdiecker reaction of silver (+)-α-phenylpropionate gave (+)-α-phenylethyl bromide to the extent of a 43.1% inversion of the configuration. On the other hand, no stereochemical study has been reported of the Simonini reaction.

During our recent studies of the thermal decompositions of diacyl peroxides,[6] we have had occasion to synthesize a few optically active carboxylic acids; thus we have extended the mechanistic investigation into the nature of these two reactions using an optically active silver carboxylate, namely silver β-phenylisobutyrate, in the hope of accumulating additional supporting evidence for the free radical nature of these reactions.

Results and Discussion

The Hunsdiecker Reaction.—A mixture of optically active silver β-phenylisobutyrate and bromine (in a one-to-one molar ratio) was refluxed in carbon tetrachloride for about 11 hr. The products obtained were practically racemized β-phenylisopropyl bromide, carbon dioxide, an optically active lactone (identified as 3-methyl-7-bromohydrocoumarin), silver bromide, and optically active β-phenylisobutyric acid. The yields and optical rotations of these products will be shown in the Experimental section.

The expected product of the Hunsdiecker reaction, β-phenylisopropyl bromide (obtained in about an 18% yield) was almost completely racemized within the range of experimental error. This result agreed well with the previous results reported[2-4] for similar reactions using other optically active carboxylic acids. The present stereochemical outcome can serve to support the free radical mechanism suggested for the formation of the bromide, as has been suggested by previous workers.[2-4,7]

β-Phenylisobutyric acid could be a reaction product, formed via the acyl hypobromite; however, the stereochemical outcome (retention) does not indicate whether β-phenylisobutyric acid is the recovered material or the reaction product.

It is interesting to note here that the formation of a substantial amount of 3-methyl-7-bromohydrocoumarin was obtained in this reaction. Although the formation of lactone in the Hunsdiecker reaction has rarely been reported, it may not be particularly unusual when the Hunsdiecker reaction is applied to a carboxylic acid that bears a phenyl group at the β-position. In fact, Pandit and Dirk[8a] reported that 4-phenylcoumarin and 4-phenylhydrocoumarin were obtained in 43 and 25% yields respectively in the reaction of silver salt of 3, 3-diphenylpropionic acid with bromine, while similar formations of lactones were reported by Berr[1a] and Wilt[8b]. The structure of the lactone, 3-methyl-7-bromohydrocoumarin, was confirmed from the information on infrared spectra, and NMR spectra and from an elemental analysis.

The Simonini Reaction.—The reaction of iodine in ether or a carbon tetrachloride solution with optically active silver β-phenylisobutyrate at a boiling temperature yields optically active 1-phenyl-2-propyl β-phenylisobutyrate, carbon dioxide, silver iodide, and optically active β-phenylisobutyric acid. In this case, however, no detectable amount of the lacton was formed. The ester obtained was then subjected to alkaline hydrolysis in order to examine the stereochemical change in the alcohol moiety. The results will be shown in the Experimental section.

The β-phenylisopropyl alcohol thus obtained from the hydrolysis of the ester was completely racemized, indicating that the ester was formed via a symmetrical intermediate, probably the 1-phenyl-2-propyl radical, at the initial stage of the formation of 1-phenyl-2-propyl iodide; this iodide eventurally would react with the silver salt to form the ester in the following stage of the ionic process.[9]

Experimental

(+)- and (−)-Silver β-Phenylisobutyrate.—Optically active β-phenylisobutyric acid was prepared following DeTar's method.[10] The optically active acid ($[\alpha]^{17}_{\rm D}$ +21.7, *c* 0.0559 and $[\alpha]^{15}_{\rm D}$ −9.8, *c* 0.0254) was neutralized with aqueous potassium hydroxide, and the hot solution was treated with a one-equivalent amount of aqueous silver nitrate. The preciptated silver salt was washed with water and acetone, and then dried on phosphorous pentoxide in vacuo.

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2) F. Bell and I. F. B. Smyth, *J. Chem. Soc.*, **1949**, 2372.

3) R. T. Arnold and P. Morgan, *J. Am. Chem. Soc.*, **70**, 4248 (1948).

4) M. Heintzeler, *Ann.*, **569**, 102 (1950).

5) C. L. Arcus, A. Campbell and J. Kenyon, *J. Chem. Soc.*, **1949**, 1510.

6) S. Oae, T. Kashiwagi and S. Kozuka, *Chem. & Ind.*, **1965**, 1694.

7) a) C. C. Price, "Mechanisms of the Reaction of Carbon-Carbon Double Bonds," Interscience, Publishers, New York (1946), p. 55. b) W. T. Smith, Jr., and R. L. Hull, *J. Am. Chem. Soc.*, **72**, 3309 (1950).

8) a) U. K. Pandit and I. P. Dirk, *Tetrahedron Letters*, No. 14, 891 (1963). b) J. W. Wilt and J. A. Lundquist, *J. Org. Chem.*, **29**, 921 (1964).

9) a) J. D. Roberts and H. E. Simmons, Jr., *J. Am. Chem. Soc.*, **73**, 5487 (1951). b) R. N. Haszeldine and A. G. Sharpe, *J. Chem. Soc.*, **1952**, 993. c) H. Wielland and F. G. Fischer, *Ann.*, **446**, 49 (1926).

10) D. F. DeTar and C. Weis, *J. Am. Chem. Soc.*, **79**, 3045 (1957).

The Hunsdiecker Reaction.—Silver salt (6 g.) was suspended with stirring in boiling dry carbon tetrachloride (54 ml.), to which bromine (3.6 g.) was then added. The solution was heated under refluxing for about 8 hr., allowed to stand overnight, and then refluxed with stirring for 3 hr. During this period, the evolution of a detectable amount of carbon dioxide was noticed by passing the gas through a saturated barium hydroxide solution. The reaction mixture was filtered. The filtrate was washed with 30 ml. of 10% sodium bicarbonate and then with water, and then the aqueous layer was extracted with carbon tetrachloride. The carbon tetrachloride layers were then combined and dried over sodium sulfate. There were thus obtained 0.8 g. of β-phenylisopropyl bromide (b. p. 90°C/10 mmHg) and 150 mg. of 3-methyl-7-bromohydrocoumarin (b. p. 126—130°C/1 mmHg; m. p. 127—128°C) by fractional distillation, and 0.75 g. of the tarry residue was left. β-Phenylisopropyl bromide, which was identified by comparing its infrared spectrum with that of an authentic sample, was practically all racemized; $[\alpha]_D^{20}$ +1.3, *c* 0.0365 (using (−)-silver salt), +0.88, *c* 0.0756 (using (+)-silver salt). 3-Methyl-7-bromohydrocoumarin was in the form of colorless crystalline plates, m. p. 127—128°C (from ethyl alcohol), Found: C, 50.22; H, 4.11. Calcd. for $C_{10}H_9O_2Br$: C, 49.82; H, 3.76; spectral peaks appeared at: IR: 1760 cm^{-1} and 1715 cm^{-1}; UV: λ_{max}^{EtOH} 275, 283, 321 mμ; λ_{min}^{EtOH} 298 mμ; 60 MC. NMR (Deuterochloroform): a doublet at 1.36 τ, a multiplet at 2.87 τ, and a multiplet at 7.12 τ. The peak areas are in the ratio of 1 : 1 : 1. The position of bromine on the benzene ring was assigned from the NMR spectra, thus, 5-H; multiplet at 6.88 τ, 6-H; doublet at 7.43 τ, 8-H; singlet at 7.29 τ, (intensities 1 : 1 : 1). $[\alpha]_D^{22}$ +12.0, *c* 0.029 (using (+)-silver salt). Meanwhile, 1 g. of optically active β-phenylisobutyric acid ($[\alpha]_D^{20}$ +21.2, *c* 0.0636 (using (+)-silver salt), −9.8 (using (−)-silver salt), b. p. 122°C/2 mmHg) was obtained by acidifying the water layer with conentrated sulfuric acid.

The Simonini Reaction.—Optically active silver β-phenylisobutyrate (8 g.) was suspended in dry ether (50 ml.), into which was then stirred iodine (3.7 g). in dry ether (17 ml.). The solution immediately turned light yellow. It was then refluxed for 3 hr. under a nitrogen stream. The carbon dioxide (about 0.18 g.) evolved was trapped through an aqueous barium hydroxide solution. The silver iodide was separated from the reaction mixture by filtration; the filtrate was washed initially with a 5% aqueous potassium hydroxide solution, then with aqueous sodium thiosulfate, and finally with water, and then dried over sodium sulfate. Only 2.3 g. of optically active 1-phenyl-2-propyl β-phenylisobutyrate ($[\alpha]_D^{15}$ +30.8, *c* 0.0635 (using (+)-silver salt), −12.9, *c* 0.0416 (using (−)-silver salt), b. p. 145°C/1 mmHg) was obtained from the ether layer. One gram of optically active β-phenylisobutyric acid ($[\alpha]_D^{13}$ +21.7, *c* 0.0584 (using (+)-silver salt), −9.8 (using (−)-silver salt)) was obtained from the water layer.

By using carbon tetrachloride instead of ether as a solvent, a similar result was also obtained.

The hydrolysis of the optically active ester (1.3 g.) was performed by allowing it to dissolve in a mixture of potassium hydroxide (0.5 g.), water (0.2 g.), and methyl alcohol (12 ml.) at room temperature for 3 hr. Optically inactive β-phenylisopropyl alcohol (b. p. 74—76°C/3 mmHg, $[\alpha]_D^{15}$ +0.5, *c* 0.054 (using the (+)-ester), +0.7, *c* 0.0353 (using the (−)-ester)) and optically active β-phenylisobutyric acid ($[\alpha]_D^{13}$ +21.7, *c* 0.0431 (using the (+)-ester), −9.8, *c* 0.0254 (using the (−)-ester)) were obtained. In a separate experiment, it was confirmed that there was no change in optical rotation for this and a similar alcohol under the same conditions as in the hydrolysis.

The optical rotations of all the above samples were measured in absolute ethyl alcohol.

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