REARRANGEMENT STUDIES WITH C^{14}

II. THE PREPARATION OF 2-PHENYLETHYL HALIDES[1]

By C. C. Lee and J. W. T. Spinks

ABSTRACT

The 2-phenylethyl halides were prepared from the treatment of 2-phenylethanol-1-C^{14} with thionyl chloride alone, thionyl chloride in pyridine, 48% hydrobromic acid, 55% hydroiodic acid, or phosphorus and iodine. Except for the reaction with thionyl chloride in pyridine, these reactions gave rise to some rearrangement of the C^{14} activity from the C-1 to the C-2 position. It appears probable that these rearrangements resulted from reactions having the S_N1 type of mechanism with the phenylethyl cation as reaction intermediate. The fact that the thionyl chloride in pyridine treatment leads to a product without rearrangement is of interest in that this method may have further applications in synthetic tracer chemistry.

INTRODUCTION

Among the most common methods for the preparation of an alkyl halide is the replacement of the hydroxyl group of an alcohol by a halogen through the reaction of the alcohol with a hydrohalic acid or a halide of sulphur or phosphorus. That the mechanism of such a replacement reaction may be bimolecular involving Walden inversion (S_N2) or unimolecular with a carbonium ion as intermediate (S_N1) has been pointed out by Hughes, Ingold, and co-workers (1). If the S_N1 mechanism were involved, typical carbonium ion-type rearrangements (2*b*) would be observed if conditions were favorable for rearrangement. For example, extensive structural changes occurred when pinacolyl alcohol was treated with hydrochloric acid (15) while less pronounced rearrangements were observed when *n*-amyl alcohol or pentanol-2 were heated with $ZnCl_2$ and HCl (13, 14).

It has previously been pointed out that the use of C^{14} as a tracer makes possible studies of rearrangements otherwise unobservable (5). In an attempt to convert cyclopentanol-1-C^{14} to cyclopentyl bromide with phosphorus tribromide, Loftfield (6) found that 20% of the total radioactivity had become rearranged to positions other than C-1. He pointed out that this reaction likely involved a carbonium ion "sufficiently free" to permit a "hydride ion" migration. On the other hand, Roberts *et al.* (10) observed no rearrangement of the C^{14} activity when 2-methyl-2-propanol-2-C^{14}, 2-methyl-2-butanol-1-C^{14}, and 2-methyl-2-butanol-2-C^{14} were converted to the corresponding chlorides by treatment with concentrated hydrochloric acid. In these cases, rearrangement of the C^{14} activity is unlikely because it would require the transformation of tertiary carbonium ions to the energetically less favorable secondary and/or primary carbonium ions. In the present paper, rearrangements observed in the preparation of 2-phenylethyl halides from the reaction between 2-phenylethanol-1-C^{14} and thionyl chloride, hydrobromic acid, hydroiodic acid, or phosphorus and iodine are reported.

---

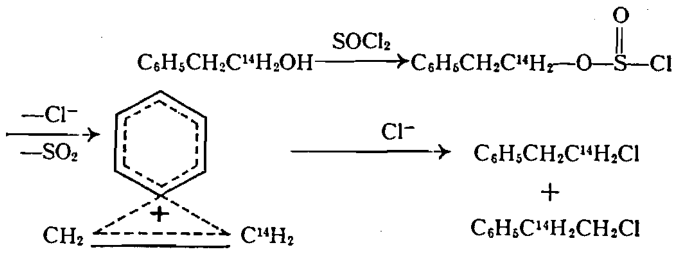
[1] *Manuscript received May 27, 1954.*
Contribution from the Department of Chemistry, University of Saskatchewan, Saskatoon, Sask. For Paper I, see Reference 5.

RESULTS AND DISCUSSION

The degrees of rearrangement in the various preparations of 2-phenylethyl halides studied are summarized in Table I. The labeled 2-phenylethanol was synthesized by the lithium aluminum hydride reduction of phenylacetic acid carboxyl-C^{14} (8) obtained from carbonation, with $C^{14}O_2$, of the corresponding Grignard (5). That all the radioactivity was in the C-1 position was shown by oxidation of the labeled alcohol to non-radioactive benzoic acid. All the samples of 2-phenylethyl halides obtained were treated with magnesium in dry ether and then reacted with dry ice to give crystalline hydrocinnamic acid for radioactivity determination.

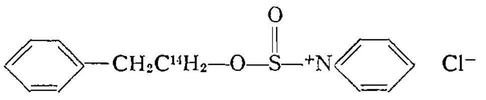
Subsequent oxidation of the hydrocinnamic acid to benzoic acid and measurement of its activity gave the amount of rearrangement from the C-1 to the C-2 position. It may be noted that the direct oxidation of the 2-phenylethyl halides to benzoic acid is also possible. Trials with inactive materials, however, showed that the conditions required to effect such an oxidation are quite drastic, and the yields attainable are low compared to that obtained from the oxidation of hydrocinnamic acid. Consequently, only one active sample of 2-phenylethyl iodide was oxidized directly, and the degree of rearrangement observed agreed very well with that found by the oxidation of hydrocinnamic acid derived from the same sample.

Except for the reaction of 2-phenylethanol-1-C^{14} with thionyl chloride in pyridine, all reactions studied gave rise to some rearrangement of the C^{14} activity from the C-1 to the C-2 position. Most probably, these rearrangements resulted from reactions having the S_N1 type of mechanism with the phenylethyl cation as reaction intermediate. The possible nature of the phenylethyl cation and how it might cause the rearrangement of C^{14} from C-1 to C-2 has previously been discussed (5, 11). It is noteworthy that in the treatment of the labeled alcohol with thionyl chloride alone, the resulting 2-phenylethyl chloride has its C^{14} activity practically equally distributed in the C-1 and C-2 positions. Such a finding is as would be expected if the phenylethyl cation has the symmetrical "non-classical" structure I.



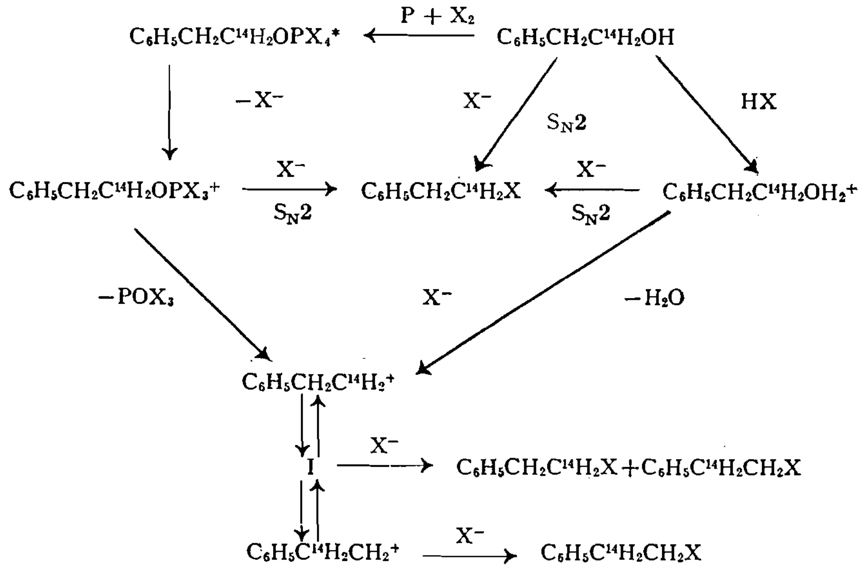
I

When the reaction with thionyl chloride is carried out in pyridine, a pyridinium chloride complex, II, (4) may be formed which, on decomposition, gives 2-phenylethyl-1-C^{14} chloride without rearrangement since no carbonium ion intermediate is likely to be formed with the organic base, pyridine, as solvent.



II

The degree of rearrangement found in the 2-phenylethyl bromide or iodide prepared from the treatment of the labeled alcohol with 48% hydrobromic acid, 55% hydroiodic acid, or phosphorus and iodine ranged from 2.5 to 7.4%. (Table I). In these instances, only a fraction of the reaction proceeds through the unimolecular mechanism involving rearrangement of the intermediate phenylethyl cation. The major portion of the reaction follows a process or processes which lead to no rearrangement. Such a process may be of the S_N2 type, or it may involve the rapid interaction between the unrearranged phenylethyl cation and the conjugate base of the reaction medium as previously suggested (5, 11).



It is of interest to note that the reaction of 2-phenylethanol-1-C^{14} with hydrobromic acid resulted in a greater degree of rearrangement than the corresponding reaction of the labeled alcohol with hydroiodic acid. Apparently the protonating power of 48% hydrobromic acid, as measured by Hammett's acidity function, H_0 (2*a*), is greater than that of 55% hydroiodic acid. That such a deduction is a reasonable one is further supported by the fact that the electron affinity of bromine is greater than that of iodine (9).

**Complex* $ROPX_4$ *has been suggested by Kenyon and co-workers (4) as intermediate in the reaction between ROH and* PX_5. *No attempt was made in the present study to definitely establish the structure of complex* $C_6H_5CH_2CH_2OPX_4$. *Another possible intermediate may be* $C_6H_5CH_2CH_2OPX_2$.

In view of the finding that the reagents frequently employed for the preparation of alkyl halides may give rise to rearranged products, it is of utmost importance that in the syntheses of C^{14}-labeled compounds, whenever the use of alkyl halides is involved, the positions of the labeled atoms in the final products be unequivocally established. In order to obtain a cyclopentyl-1-C^{14} halide for further synthetic applications, Loftfield (6) prepared the *p*-bromobenzenesulphonate of cyclopentanol-1-C^{14} and then treated this sulphonate with sodium iodide in acetone, a typical S_N2 reaction, to give the iodide without rearrangement. The observation that the replacement of a hydroxyl group with chlorine effected by thionyl chloride in pyridine eliminated the possibility of rearrangement (14) is here extended and shown to be applicable for C^{14}-labeled 2-phenylethanol. It is our belief that the thionyl chloride in pyridine method is much less time consuming and likely to give higher over-all yields than the sulphonate – sodium iodide in acetone method for the preparation of unrearranged alkyl halides, though both of these methods will most likely find further applications in the syntheses of C^{14}-labeled compounds.

TABLE I

REARRANGEMENTS IN 2-PHENYLETHYL HALIDES FROM 2-PHENYLETHANOL-1-C^{14}

Reagents used	Compound counted†	Specific activity, counts/min./mM. Run I	Run II	% rearrangement Run I	Run II
	Phenylurethan of 2-phenylethanol-1-C^{14}	1133 ±16			
	Benzoic acid‡	0.6± 3.6		0.0	
$SOCl_2$ alone	Hydrocinnamic acid	902 ±12	1134 ±13		
	Benzoic acid	453 ± 7	551 ±10	50.3	48.6
$SOCl_2$ in pyridine	Hydrocinnamic acid	1152 ±14	1132 ±13		
	Benzoic acid	−0.1± 3.2	−0.2± 3.2	0.0	0.0
48% HBr	Hydrocinnamic acid	1170 ±14	1143 ±13		
	Benzoic acid	82.0± 3.2	60.6± 2.5	7.0	5.3
55% HI	Hydrocinnamic acid	1158 ±13	1190 ±14		
	Benzoic acid	28.3± 2.5	32.7± 3.0	2.5	2.7
	Benzoic acid§	32.3± 3.0		2.8	
$P+I_2$	Hydrocinnamic acid	702 ±10	715 ±10		
	Benzoic acid	38.3± 3.6	531 ± 4.5	5.5	7.4

†*As "infinitely thick" samples of constant geometry in a windowless Q-gas counter.*
‡*From oxidation of 2-phenylethanol-1-C^{14}.*
§*From direct oxidation of active 2-phenylethyl iodide.*

EXPERIMENTAL

Reaction with Thionyl Chloride

In a 100 ml. round-bottomed flask, cooled in an ice bath and fitted with a reflux condenser, was placed 5.00 gm. of 2-phenylethanol-1-C^{14}. Fifteen milliliters of thionyl chloride was added slowly. The mixture was removed from the ice bath and refluxed gently for one half hour. The excess thionyl chloride was distilled off and the residue fractionated under reduced pressure. The yields of 2-phenylethyl chloride, b.p. 85–87°C. at 17 mm. (lit.(16) b.p. 81–84°C. at 14 mm.), for the duplicate runs were 4.64 and 4.40 gm. (81 and 77%, respectively).

Reaction with Thionyl Chloride in Pyridine

To a solution of 5.00 gm. of 2-phenylethanol-1-C^{14} in 20 ml. of pyridine in a 250 ml. Erlenmeyer flask cooled in an ice-bath was added portionwise 10 ml. of thionyl chloride. When the mixture was shaken and then heated on a steam bath for about five minutes (prolonged heating will cause extensive decomposition) a black solution resulted. The mixture was then allowed to stand at room temperature for one half hour before it was poured into ice water. The product was extracted with ether, the extract being washed successively with distilled water, dilute hydrochloric acid, 10% sodium bicarbonate solution, and distilled water. After the extract was dried over anhydrous sodium sulphate, the ether was removed from the extract and the residue distilled under reduced pressure. The yields of 2-phenylethyl chloride for the duplicate runs were 3.72 and 3.86 gm. (65 and 67%, respectively).

Reaction with Hydrobromic Acid

A mixture of 5.00 gm. of 2-phenylethanol-1-C^{14} and 28 gm. of 48% hydrobromic acid was heated under reflux, with occasional shaking, for two hours. After the resulting mixture was cooled to room temperature, it was poured into ice water and extracted with ether. The extract was washed with water and 10% sodium bicarbonate solution and dried over anhydrous sodium sulphate. The ether was evaporated off and the residue distilled under reduced pressure. The yields of 2-phenylethyl bromide, b.p. 110–113°C. at 17 mm. (lit.(7) b.p. 108–112°C. at 17 mm.), for the duplicate runs were 6.30 and 6.05 gm. (83 and 80%, respectively).

Reaction with Hydroiodic Acid

2-Phenylethanol-1-C^{14} (5.00 gm.) and 55% hydroiodic acid (38 gm.) were refluxed for two hours. The resulting mixture was worked up as described in the reaction with hydrobromic acid. The yield of 2-phenylethyl iodide, b.p. 115–118°C. at 14 mm. (lit.(12) b.p. 114–116°C. at 12 mm.), was 8.75 gm. (92%). In a duplicate preparation using 4.00 gm. of the labeled alcohol, the yield of the iodide was 6.88 gm. (90%).

Reaction with Phosphorus and Iodine

To a mixture of 4.00 gm. of 2-phenylethanol-1-C^{14} and 0.35 gm. of red phosphorus in a 100 ml. round-bottomed flask fitted with a reflux condenser was added 4.40 gm. of iodine in small portions with shaking at room temperature. A slight warming up of the reaction mixture resulted. After the addition of iodine had been completed, the mixture was heated over a steam bath for one hour. After the mixture was cooled, ether was introduced to dissolve the product. The ether solution was filtered through glass wool, washed with dilute sodium hydroxide solution and distilled water, dried over anhydrous sodium sulphate, and evaporated over a steam bath to give a residue which on fractionation under reduced pressure gave 2-phenylethyl iodide, b.p. 115–118°C. at 14 mm. The yields for duplicate runs were 6.14 and 6.46 gm. (81 and 85%, respectively).

Hydrocinnamic Acid from 2-Phenylethyl Halides

The phenylethylmagnesium halide was prepared in the conventional way and treated with excess solid carbon dioxide. The resulting reaction mixture was acidified and extracted with ether. After the solvent was evaporated off from the ethereal extract, the residue was taken up in dilute sodium hydroxide solution and washed with ether to remove any unreacted organic halide. The product was then precipitated by acidifying the washed sodium hydroxide solution and again recovered by extraction with ether. After the extract was dried over anhydrous sodium sulphate, the ether was removed from this final extract and the residue was crystallized from petroleum ether (b.p. 40–60°C.). Colorless needles of hydrocinnamic acid were obtained which melted alone, or on admixture with an authentic sample, at 48–49°C. (lit.(3) m.p. 48.6°C.). The yields based on the various samples of 2-phenylethyl halides used ranged from 70 to 80%.

Oxidation to Benzoic Acid

2-Phenylethanol-1-C^{14} or hydrocinnamic acid was oxidized to benzoic acid with potassium permanganate in sodium hydroxide solution according to a method previously described (5). The yields obtained generally exceeded 80%.

The oxidation of 2-phenylethyl iodide to benzoic acid was effected as follows. Three grams of 2-phenylethyl iodide was heated under reflux until it was nearly boiling. A saturated aqueous solution of potassium permanganate was added gradually whereby a very vigorous reaction took place. After a total of about 10 gm. of potassium permanganate, as a saturated solution, was added, the reaction mixture was allowed to reflux for one half hour. The product was worked up as previously described (5). It was further purified by dissolution in sodium hydroxide and washed with ether as indicated in the preparation of hydrocinnamic acid. The final yield of benzoic acid, crystallized from water, was 0.54 gm. (34%).

ACKNOWLEDGMENT

We are grateful for the financial support given by the National Research Council of Canada.

REFERENCES

1. Cowdrey, W. A., Hughes, E. D., Ingold, C. K., Masterman, S., and Scott, A. D. J. Chem. Soc. 1252. 1937.
2. Hammett, L. P. Physical organic chemistry. 1st ed. McGraw-Hill Book Company, Inc., New York. 1940. (*a*) pp. 267–271. (*b*) pp. 315–325.
3. Handbook of chemistry and physics. 31st ed. Chemical Rubber Publishing Co., Cleveland, Ohio. 1949. p. 888.
4. Kenyon, J., Lipscomb, A. G., and Philips, H. J. Chem. Soc. 415. 1930.
5. Lee, C. C. and Spinks, J. W. T. Can. J. Chem. 31: 761. 1953.
6. Loftfield, R. B. J. Am. Chem. Soc. 73: 4077. 1951.

7. Norris, J. F., Watt, M., and Thomas, R. J. Am. Chem. Soc. 38: 1071. 1916.
8. Nystrom, R. F. and Brown, W. G. J. Am. Chem. Soc. 69: 2548. 1947.
9. Pauling, L. The nature of the chemical bond. Cornell Univ. Press, Ithaca, New York. 1939. p. 66.
10. Roberts, J. D., McMahon, R. E., and Hine, J. S. J. Am. Chem. Soc. 72: 4237. 1950.
11. Roberts, J. D. and Regan, C. M. J. Am. Chem. Soc. 75: 2069. 1953.
12. Vogel, A. I. British Patent 565,452. Nov. 10, 1944. Chem. Abstr. 40: 5066. 1946.
13. Whitmore, F. C. and Karnatz, F. A. J. Am. Chem. Soc. 60: 2536. 1938.
14. Whitmore, F. C., Karnatz, F. A., and Papkin, A. H. J. Am. Chem. Soc. 60: 2540. 1938.
15. Whitmore, F. C. and Rothrock, H. S. J. Am. Chem. Soc. 55: 1106. 1933.
16. Whitmore, F. C. and Thorpe, M. A. J. Am. Chem. Soc. 55: 782. 1933.