Isotopic Evidence for an Aryl-Group Migration during Chromic Acid Oxidation of 1,1-Di(*p*-iodophenyl)ethane

H. HARRY SZMANT,[1] JAIME COLÓN, AND JOSÉ CASTRILLÓN*[2]

Puerto Rico Nuclear Center,[3] San Juan, Puerto Rico 00935,
and University of Puerto Rico, Río Piedras, Puerto Rico 00928

Received July 8, 1970

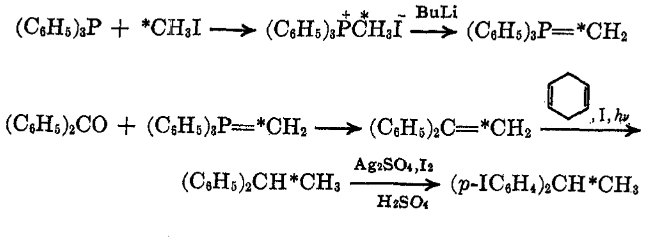
The use of 1,1-di(*p*-iodophenyl)ethane-*2*-^{14}C allows the unequivocal assignment of the source of *p*-iodobenzoic acid obtained in the course of oxidation by means of chromic acid. At room temperature, and in acetic acid, a 11.2 molar excess of chromic acid produces 25% of oxidation with a 1,2 migration of the *p*-iodophenyl group, while the oxidative rearrangement is decreased to 17% at reflux temperatures.

In 1956 Szmant and Yoncoskie[4] reported the formation of an unexpected product, *p*-iodobenzoic acid, in addition to the expected benzophenone, during the oxidation of 1,1-di(*p*-iodophenyl)ethane and 1-*p*-iodophenyl-1-phenylethane with chromic acid. This result, plus the fact that the *p*-nitro- and *p*-cyano-substituted 1,1-diarylethanes behaved similarly while the *p*-methoxy derivative and the parent hydrocarbon did not, led to the suggestion[5] of a homolytic reaction mechanism.

Since unsubstituted benzophenone is slowly oxidized by chromic acid to benzoic acid,[6] the action of chromic acid at high concentration on *p,p'*-diiodobenzophenone was examined, and it was found that this compound is indeed degraded to *p*-iodobenzoic acid. Thus, it became highly desirable to determine unequivocally the contributions of both processes, rearrangement and oxidative degradation, to the yield of the benzoic acid in the oxidation of 1,1-di(*p*-iodophenyl)ethane. The reaction is complicated by the fact that the solvent, glacial acetic acid, is oxidized by chromic acid even in the cold. Since variable amounts of carbon dioxide are generated in this way, the stoichiometric approach is inconvenient and, therefore, ^{14}C labeling becomes the most practical way of establishing the extent of rearrangement.

The labeled reactant was synthesized by means of the Wittig reaction, followed by photochemical reduction of the 1,1-diphenylethylene, and iodination of the diphenylethane, according to Scheme I.

SCHEME I



The iodination was performed at the end rather than at the beginning of the synthesis due to the difficulty in preserving the iodine substituents during the reduction of the diphenylethylene. The position of the label was confirmed by degradation with potassium permanganate.

The oxidation of 1,1-di(*p*-iodophenyl)ethane-*2*-^{14}C allows one to distinguish neatly the different mechanistic possibilities. (a) Degradative oxidation of the initial oxidation product involves the destruction of one aryl group and leads to the formation of inactive benzoic acid.

$$(p\text{-IC}_6\text{H}_4)_2\text{CH}^*\text{CH}_3 \longrightarrow (p\text{-IC}_6\text{H}_4)_2\text{CO} \longrightarrow \text{IC}_6\text{H}_4\text{COOH}$$

(b) Oxidation with migration of an aryl group is expected to give a molar activity of the benzoic acid that is half of that of the starting material.

$$(p\text{-IC}_6\text{H}_4)_2\text{CH}^*\text{CH}_3 \longrightarrow \text{IC}_6\text{H}_4{}^*\text{COOH} + \text{IC}_6\text{H}_4\text{CO}_2\text{H}$$

If both processes a and b are operative, as turns out to be the case, the respective contributions of processes a and b can be easily ascertained from the molar activities of the diarylethane (m) and benzoic acid (n) according to the expression

$$\%\text{ acid from rearrangement} = \frac{2 \times n \times 100}{m} \qquad (1)$$

In either case the benzophenone should be inactive unless there is an unlikely scrambling of the aryl groups, and, indeed, in all experiments the activity of purified benzophenone was undistinguishable from background radioactivity.

The activity of the liberated carbon dioxide was also determined and a good activity balance was established. This indicates that material losses should be attributed only to those of the benzophenone. This seems reasonable since the benzophenone yield is given after purification by recrystallization, while the isolation of *p*-iodobenzoic acid is practically quantitative because of its low solubility in water. Table I shows the results of the oxidation with a chromic acid–diarylethane molar ratio of 11.2 at both room and reflux temperatures. The stoichiometric amount of chromic acid required for either process is 3.33 mol to 1 mol of the diarylethane.

Table II reports the contributions of processes a and b to the observed yield of the iodobenzoic acid. The origin of the acid is calculated on the basis of the molar activities according to the previously given expression, and from these values, and assuming a quantitative recovery of the acid, the percentages of "normal" oxidation and that involving a migration of the aryl group rearrangement are derived. "Normal" oxidation represents oxidation according to pro-

---

[1] Department of Chemistry, University of Detroit, Detroit, Mich. 48221.

[2] Author to whom correspondence should be addressed at the Puerto Rico Nuclear Center.

[3] The Puerto Rico Nuclear Center is operated by the University of Puerto Rico for the U. S. Atomic Energy Commission under Contract AT-(40-1)-1833.

[4] H. H. Szmant and R. Yoncoskie, *J. Org. Chem.*, **21**, 78 (1956).

[5] H. H. Szmant and J. F. Deffner, *J. Amer. Chem. Soc.*, **81**, 958 (1959).

[6] R. Slack and W. A. Waters, *J. Chem. Soc.*, 1666 (1948).

TABLE I

OXIDATION OF 2.32 MMOL OF DI(p-IODOPHENYL)ETHANE OF MOLAR SPECIFIC ACTIVITY 0.1955 μCi WITH 26.0 MMOL OF CrO_3[a]

	Reflux temperature			Room temperature		
Products	Yield, mmol	Yield, %	Molar sp act., μCi/mmol	Yield, mmol	Yield, %	Molar sp act., μCi/mmol
Diiodobenzophenone	0.50	21.6	0.0000	0.80	34.5	0.000
Iodobenzoic acid	1.21	26.1[b]	0.0613	1.45	31.2[b]	0.0793

[a] Each value is an average of two determinations. [b] % yield of iodobenzoic acid based on eq 1.

TABLE II

"NORMAL" OXIDATION *vs.* OXIDATIVE REARRANGEMENT OF 1,1-DI(p-IODOPHENYL)ETHANE WITH CHROMIC ACID

	Acid origin, %		"Normal" oxidation, %	Oxidation with rearrangement, %
	Rearrangement	Degradation		
Reflux	63	37	83	17[a]
Room temp	81	19	75	25

[a] Example of the calculation: 0.63 (fraction of benzoic acid originating from rearrangement) × 26.1 (% yield of benzoic acid; see Table I) = 17 (% oxidation with rearrangement at reflux temperature).

cess a regardless of whether the diaryl ketone survives or is further oxidized to the benzoic acid.

As expected, the percentage of acid derived from degradation of the benzophenone is larger at the higher temperature, and it is clear that rearrangement is favored at the lower temperature.

In the "normal" oxidation process, the activity at C-2 is retained in the liberated carbon dioxide, and a further check of the contributions of the two oxidation paths can be obtained by examining the total activity of carbon dioxide collected in the form of barium carbonate. These results are shown in Table III.

TABLE III

% "NORMAL" OXIDATION BASED ON THE TOTAL ACTIVITY OF CARBON DIOXIDE

	$BaCO_3$ yield, mmol	Molar sp act., μCi/mmol	Total activity recovered as $BaCO_3$ μCi	"Normal" oxidation, %
Reflux	17.52	0.0218	0.382	84
Room temp	10.83	0.0316	0.342	75

It can be seen that the yield of carbon dioxide is much higher at the reflux temperature as a consequence of increased normal oxidation and degradation. The measure of the total activity provides values for the relative contribution of "normal" oxidation that agree well with those given in Table II that are derived from the yield of p-iodobenzoic acid and its specific activity.

Experimental Section

Radioactivity Determinations.—A Beckman liquid scintillation spectrometer, Model LS-II, without refrigeration, was used for counting by means of the ^{14}C plug-in module. With two exceptions, all the samples (about 10 mg) were prepared and counted under air in toluene solution containing 0.5% PPO. Efficiencies were determined by the external standard, double channel method. Methyltriphenylphosphonium iodide is insoluble in toluene and, although it can be incorporated into a dioxane-based scintillator by dissolving it first in a very small volume of methanol and then adding the scintillating solution, the samples turn intensely yellow. It was finally successfully counted in solution by using the new scintillation solvent, benzonitrile.[7] Barium carbonate was finely ground in an agate mortar and counted in 100-mg portions as a suspension in the scintillation solution already mentioned containing also 4.0% of the thixotropic agent Cab-O-Sil. The efficiency was determined by the internal standard method.

Preparation of Methyltriphenylphosphonium Iodide-^{14}C.—Triphenylphosphine, 45 g (0.172 mol), was dissolved in 250 ml of anhydrous ether in a three-necked, round-bottomed flask provided with a magnetic stirrer, a condenser, and an addition funnel. Methyl iodide, 24.4 g (0.172 mol, 0.37 mCi), was added slowly. The reaction was allowed to proceed for 96 hr. The resulting *solid was filtered and recrystallized from isopropyl alcohol to give* 59.3 g of the product melting at 179–181°.[8] The chemical and radiochemical yield was based on methyl iodide, 94%.

Preparation of 1,1-Diphenylethylene-2-^{14}C.—Methyltriphenylphosphonium iodide, 44.8 g (0.111 mol), plus 10.1 g (0.025 mol) of the previously labeled iodide and 500 ml of anhydrous ether were placed in a three-necked, round-bottomed flask fitter with a condenser, stirrer, nitrogen inlet, and septum cap. Butyllithium, 8.71 g (0.136 mol), as a 20% heptane solution was injected and the mixture stirred for 1 hr. Benzophenone, 24.8 g (0.136 mmol), was rapidly added under increased flow of nitrogen and the reaction continued for 24 hr. The resulting suspension was filtered and the solid washed with ether. The ether solution and washings were evaporated in a rotary evaporator; the resulting oil was distilled under reduced pressure [123–128° (3.9 mm)] to yield the 1,1-diphenylethylene-2-^{14}C. The product was redistilled [90.5° (1.0 mm)] to give 19.0 g (78%).

Preparation of 1,1-Diphenylethane-2-^{14}C.—The ethylene was reduced to the ethane photochemically.[9]

1,1-Diphenylethylene-2-^{14}C, 18.0 g (0.100 mol), 45.8 g (0.572 mol) of 1,4-cyclohexadiene, and 6.0 g (0.024 mol) of iodine were mixed and exposed to sunlight for 24 hr. Analysis of the reaction products by gas chromatography on a silicone column showed the presence of 1,4-cyclohexadiene, iodocyclohexane, 4-iodocyclohexene, 1,1-diphenylethane, and a trace of 1,1-diphenylethylene. The first three products were removed by distillation at atmospheric pressure. The 1,1-diphenylethane was distilled under reduced pressure [91–95° (0.5 mm)], yield 16.1 g (88%).

Preparation of 1,1-Di(p-iodophenyl)ethane-2-^{14}C.—The technique of Szmant and Yoncoskie[4] was followed with a slight modification in order to improve the yield of the diiodo derivative. A mixture of 50 ml of water, 75 ml of concentrated sulfuric acid, 23.4 g (0.075 mol) of silver sulfate, 7.1 g (0.050 mol) of anhydrous sodium sulfate, and 38.4 g (0.151 mol) of iodine was cooled with mechanical stirring to −5°. 1,1-Diphenylethane-2-^{14}C, 11.4 g (0.063 mol), was added over the period of 1 hr. The mixture was stirred for an additional 48 hr and poured over crushed ice, and, finally, filtered. Both the solution and the solid were extracted repeatedly with ether. The combined ethereal extracts were washed with 5% sodium hydroxide to eliminate the excess iodine, then with water, and dried over anhydrous calcium chloride. The clear yellowish solutions were taken to dryness and the resulting oil was kept in a desiccator for several days in order to crystallize the diiodo compound. Seeding accelerates this process. The oil was separated by decantation and the crystals were dissolved in hot heptane, treated with activated charcoal, filtered, and allowed to crystallize to give 8.5 g (31%) of colorless crystals melting at 85–86° (lit.[5] mp 87–87.5°). The overall yield based on methyl iodide was 20%. The yield can be improved considerably if the separated oil (essentially the monoiodo compound plus a trace of the diiodo compound as well as some starting material) is recycled. The product's activity was 0.365 μCi/mmol, and, since this was ample for the tracer experiments, it was diluted with 7.40 g of inactive diiodophenylethane in order to obtain an activity of 1000 dpm/mg.

---

(7) E. Gómez, J. Freer, and J. Castrillón, *Int. J. Appl. Radiat. Isotopes*, to be published.

(8) All melting points are uncorrected.

(9) M. K. Eberhardt, *Tetrahedron*, **23**, 3029 (1967).

Oxidation of 1,1-Di(*p*-iodophenyl)ethane-2-^{14}C with Potassium Permanganate.—1,1-Di(*p*-iodophenyl)ethane-2-^{14}C, 1.06 g (2.44 mmol), and 1.45 g (9.18 mmol) of potassium permanganate were refluxed in 50 ml of glacial acetic acid for 4 hr. Water was added to the reaction mixture and the solution was filtered. The solid was extracted with 10 ml of a 10% solution of sodium hydroxide. The extract was acidified with concentrated hydrochloric acid, but no precipitate was formed. Since *p*-iodobenzoic acid is very insoluble in water, it can be concluded that no rearrangement can be detected on oxidation of the diarylethane with potassium permanganate. The remaining solid was repeatedly washed with water, dried, and recrystallized from toluene to yield 0.927 g (87%) of *p,p'*-diiodobenzophenone, mp 229–230°. Three more recrystallizations from toluene yielded a product melting at 240–241° whose activity was undistinguishable from background showing that the label was indeed at C-2.

Oxidation of *p,p'*-Diiodobenzophenone with Chromic Acid.—*p,p'*-Diiodobenzophenone, 1.01 g (2.33 mmol), and 2.61 g (26.1 mmol) of chromic acid were refluxed for 4 hr in 25 ml of acetic acid. The products were isolated according to the procedure described in the next paragraph. *p*-Iodobenzoic acid, 0.11 g, mp 268–268, was obtained in a 19% yield (0.112 g).

General Procedure for the Oxidation of 1,1-Di(*p*-iodophenyl)ethane with Chromic Acid.—1,1-Di(*p*-iodophenyl)ethane, 1.00 g (2.30 mmol), 2.60 g (26.0 mmol) of chromic acid, and 25 ml of glacial acetic acid were placed in a three-necked, round-bottomed flask fitted with a nitrogen inlet, a condenser, and either a magnetic stirrer for reactions at room temperature or boiling stones for reactions at reflux temperature. The condenser was connected to three traps containing 50 ml of 5% sodium hydroxide in each. Pure, dry nitrogen was bubbled through the system in order to sweep the carbon dioxide into the traps. Reflux time was 4 hr, while the reactions at room temperature were allowed to run for 24 hr. After the reaction time was completed, water was added to the mixture and it was filtered. The solid was extracted three times with 10% sodium hydroxide and the mother liquor was extracted with benzene. The benzene solution was also extracted with 10% sodium hydroxide. The combined sodium hydroxide extracts were acidified to precipitate the *p*-iodobenzoic acid. The benzene solution was washed with water, dried over calcium chloride, and taken to dryness. This residue was combined with the previously mentioned solid fraction and recrystallized from toluene to yield *p,p'*-diiodobenzophenone. The yields reported are for the crude precipitated acid and for the recrystallized benzophenone. For counting, the products were recrystallized until constant activity (zero, in the case of the ketone) and melting point [240–241° for the ketone, and 268–269° for the acid (lit.[5] mp 237–238° and 268–270°, respectively)] were attained. The contents of the traps were combined, 15 g of NH_4Cl was added, and then 90 ml of a 10% solution of $BaCl_2$. The carbonate was filtered on a tared, sintered glass funnel, dried in the oven at 100°, and kept in a desiccator.

Registry No.—Chromic acid, 7738-94-5; 1,1-di(*p*-iodophenyl)ethane, 5216-55-7; 1,1-di(*p*-iodophenyl)ethane-2-^{14}C, 27067-11-4.

Synthesis of 6,6-Difluoronorethindrone[1]

GEORGE A. BOSWELL, JR.,* ALEXANDER L. JOHNSON, AND JOSEPH P. MCDEVITT

Contribution No. 1719 from the Central Research Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received July 31, 1970

Two syntheses of 6,6-difluoronorethindrone (**13**) are described, utilizing the reactions of NOF and SF_4 with steroids. The more direct approach from norethindrone (**20**) was less satisfactory than the longer route from 19-nortestosterone (**1**). Some of the chemistry of 6,6-difluoro-4-estrene-3,17-dione (**7**), a useful intermediate, is also discussed.

The enhancement of endocrine activity of steroids by fluorine substitution has been studied extensively.[2] We have recently described[3] the application of nitrosyl fluoride as a useful fluorinating agent for steroids, and, together with sulfur tetrafluoride,[3-5] it may be used in the key stages of a multistep steroid synthesis. In the present work, two synthesis of 6,6-difluoronorethindrone (**13**) are described, suitable starting materials being 19-nortestosterone (**1**) and norethindrone (**20**). The more direct route from norethindrone (Scheme III) was less satisfactory than the longer route from 19-nortestosterone (Scheme I) because the 17α-ethynyl group of **20** is sensitive both to NOF and to acidic oxidizing conditions.

The preferred synthesis (Scheme I) starts with the conversion of 19-nortestosterone to 3β,17β-dihydroxy-5-estrene-3,17-diacetate (**2**) by the procedure of Villotti, Djerassi, and Ringold.[6] This step protects the 3 and 17 positions and shifts the double bond from the 4 to the 5 position, for the introduction of 5 and 6 substituents by means of NOF and SF_4. Treatment of the Δ^5-diacetate **2** with NOF in dichloromethane[3] gave two major products in addition to unreacted starting material (Scheme II). When excess NOF was used, the major product was the 5α-fluoro-6-nitrimino steroid **17**, which was hydrolyzed to 3β,17β-dihydroxy-5α-fluoroestran-6-one-3,17-diacetate (**3**) on hydrated alumina chromatography.[3] The second product, which is more abundant when insufficient NOF is used, is 3β,17β-dihydroxy-5α-fluoro-6-nitrosoestrane-3,17-diacetate dimer[7] (**18**). **18** was also converted to ketone **3** in 70% overall yield by allowing it to tautomerize in methanol solution to 3β,17β-dihydroxy-5α-fluoro-6-oximinoestrane-3,17-diacetate[3f] (**19**), which was then deaminated to **3** with nitrous acid. The conversion of **2** to **3**, by combining the two procedures, was 40%.

---

(1) Presented in part at the Fifth Middle Atlantic Regional Meeting of the American Chemical Society, Newark, Del., April 2, 1970.

(2) (a) J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.*, **76**, 1455 (1954); (b) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y. 1959, pp 593, 682–686; (c) C. Djerassi, "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, pp 155–177; (d) A. A. Akhrem, I. G. Reshetova, and Yu. A. Titov, *Russ. Chem. Rev.*, **34**, 926 (1965); (e) V. M. Khutoretskii, L. V. Okhlobystina, and A. A. Fainzilberg, *ibid.*, **36**, 145 (1967); (f) G. Schiemann and B. Cornils, "Chemie und Technologie Cyclischer Fluorverbindungen," Ferdinand Enke Verlag, Stuttgart, 1969, pp 114–127.

(3) (a) G. A. Boswell, Jr., *Chem. Ind. (London)*, 1929 (1965); (b) U. S. Patent 3,219,673 (1965); (c) *J. Org. Chem.*, **31**, 991 (1966); (d) U. S. Patent 3,235,571 (1967); (e) S. Andreades and G. A. Boswell, Jr., U. S. Patent 3,320,291 (1967); (f) G. A. Boswell, Jr., *J. Org. Chem.*, **33**, 3699 (1968).

(4) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **82**, 543 (1960).

(5) (a) J. S. Tadanier and J. W. Cole, German Patent 1,183,077 (1961); (b) D. G. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962); (c) D. G. Martin and J. E. Pike, *ibid.*, **27**, 4086 (1962).

(6) R. Villotti, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 4566 (1959).

(7) In ref 3f, Table II, footnote 1, we stated that this product arose from excess NOF, but the reverse situation now appears to be true.