The Decomposition of Methyl N-Nitroso-p-acetamidobenz[^{14}C]oate in Benzene. The Determination of the Products by the Isotopic Dilution Method

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Nitrosoacylarylamines decompose in a liquid aromatic compound (Ar′H) to yield biaryls (Ar-Ar′) as follows¹⁾:

$$\mathrm{ArN(NO)COR + Ar'H} \longrightarrow \mathrm{Ar\text{-}Ar' + N_2 + RCOOH}$$

The homolytic nature of this reaction is now widely accepted²⁾; the biaryl is thought to be formed by substitution of Ar′H by aryl radicals (Ar·) homolytically produced from the nitroso compound. However, the yield of the biaryl is far from quantitative, and an appreciable quantity of tar is usually formed. In some cases a compound (ArH) resulting from abstraction of a hydrogen atom by the aryl radical was isolated³⁾. Further, it was observed that about 3% of azobenzene was formed in the decomposition of *N*-nitrosoacetanilide in benzene⁴⁾. In view of the complex nature of this reaction, it seemed of interest to determine the yields of various by-products from the decomposition of *N*-nitrosoacylarylamines. We report the results of isotopic dilution analysis of the products from decomposition of labelled methyl *N*-nitroso-*p*-acetamidobenzoate in benzene.

Methyl *N*-nitroso-*p*-acetamidobenz[^{14}C]oate (4.48 mmol.) was dissolved in benzene (405 mmol.) and left to stand for four days at 17∼18°C; by the end of this period 76 cc. (0°, 1 atm., 76% of the theoretical amount) of nitrogen had been evolved. The reaction mixture was then worked up, and the yields of methyl benzoate, methyl *p*-acetoxybenzoate, methyl 4-biphenylcarboxylate etc. were determined by isotopic dilution analysis as will be described in the experimental part. The results are summarized in Table I.

Methyl 4-biphenylcarboxylate is obviously the product of the homolytic substitution of benzene by 4-methoxycarbonylphenyl radicals, although the detailed mechanism of this reaction is still obscure. Its yield, viz., 53.3%, definitely precludes the possibility, which has already come to be regarded as unlikely, that methyl 4-biphenylcarboxylate is formed exclusively by combination of 4-methoxycarbonylphenyl with phenyl radicals produced from benzene by hydrogen abstraction by the former radical. The low yield of methyl benzoate, which is formed by this abstraction, also supports this conclusion.

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1) W. S. M. Grieve and D. H. Hey, *J. Chem. Soc.*, **1934**, 1798; H. France, I. M. Heilbron and D. H. Hey, ibid., **1940**, 369.

2) G. H. Williams, " Homolytic Aromatic Substitution ", Pergamon Press, Oxford (1960), p. 29.

3) I. M. Heilbron, D. H. Hey and A. Lambert, *J. Chem. Soc.*, **1940**, 1279; J. W. Haworth and D. H. Hey, ibid., **1940**, 361; H. France, I. M. Heilbron and D. H. Hey, ibid., **1939**, 1284; J. Elks and D. H. Hey, ibid., **1943**, 441.

4) D. F. DeTar and H. J. Scheifele, *J. Am. Chem. Soc.*, **73**, 1442 (1951).

Dimethyl 4, 4′-biphenyldicarboxylate may have been produced by homolytic substitution of the methyl benzoate formed during the reaction by *p*-methoxycarbonylphenyl radicals. The extent of this substitution can be estimated as follows: The concentration of methyl benzoate may be assumed to be $0.013\times4.48\times0.5/405=7.2\times10^{-5}$ mol. per mole of benzene throughout the reaction, and as the partial rate factor of the para position of the methyl benzoate for the homolytic phenylation should be about 5[5] and the yield of methyl 4-biphenylcarboxylate was 53%, the yield of dimethyl 4, 4′-biphenyldicarboxylate by the substitution mechanism is expected to be of the order of $53\times7.2\times10^{-5}\times5/6=0.0032\%$. The experimentally found value of 0.024% therefore suggests that dimethyl 4, 4′-biphenyldicarboxylate must have been afforded largely by dimerization of *p*-methoxycarbonylphenyl radicals. But the possibility of induced decomposition by these radicals of the original *N*-nitroso-compound or of the rearranged diazoacetate could not be ruled out.

TABLE I. YIELDS OF VARIOUS PRODUCTS FROM THE DECOMPOSITION OF METHYL *N*-NITROSO-*p*-ACETAMIDOBENZ[^{14}C]OATE IN BENZENE

Product	yield, %
Methyl 4-biphenylcarboxylate	53.3
Methyl 4-acetoxybenzoate	0.046
Methyl benzoate	1.30
Dimethyl 4, 4′-biphenyldicarboxylate	0.024
Dimethyl 4, 4′-azobenzenedicarboxylate	0.46
Methyl 2-biphenylcarboxylate	<0.0074

The yields of dimethyl 4, 2′- and 4, 3′-biphenylcarboxylate, although no attempt was made at their determination, must have been small, since the homolytic arylation usually gives three isomerides in comparable amounts.

Methyl benzoate is thought to have been formed by hydrogen abstraction by *p*-methoxycarbonylphenyl radicals. Some of it must have reacted with *p*-methoxycarbonylphenyl radicals, giving three isomeric dimethyl biphenyldicarboxylates, but the extent of this reaction seems to have been exceedingly small, as is indicated by the low yield of dimethyl 4, 4′-biphenyldicarboxylate. The same is true of the substitution of methyl benzoate by any phenyl radicals to be generated from benzene by hydrogen abstraction by radicals, methyl 2-biphenylcarboxylate, one of the anticipated products of the phenylation, being formed in a negligible quantity, if at all. The yield of the meta isomeride would have been shown to be virtually nil, too. The conclusion is therefore drawn that the observed yield of methyl benzoate gives a practical estimate of the extent of the hydrogen abstraction by *p*-methoxycarbonylphenyl radicals.

Experimental

Methyl *p*-Acetamidobenz[^{14}C]oate. — *p*-Aminobenz[^{14}C]oic acid was prepared according to the procedure described by Murry et al.[6] The labelled acid (0.357 g.) was dissolved in 37 cc. of anhydrous methanol and 1 cc. of acetyl chloride, the solution left to stand overnight, and the solvent removed on a water bath. The remaining methyl *p*-aminobenz[^{14}C]oate hydrochloride was dissolved in water; the solution was treated with a little active charcoal, filtered, made slightly alkaline with sodium carbonate and stirred with acetic anhydride. The resulting precipitate was collected on a filter paper to give 0.352 g. of methyl *p*-acetamidobenz[^{14}C]oate, m. p. 129.7~130.5°C. A specimen of the non-labelled acid (Found: N, 7.25. Calcd. for $C_{10}H_{11}\cdot NO_3$: N, 7.25%) which was similarly prepared had the same melting point[7]. The labelled methyl ester was diluted with the inactive specimen and recrystallized from hot water containing 10% of methanol to give 990 mg. of methyl *p*-acetamidobenz[^{14}C]oate (activity, 27.25 ± 0.545 mc./mol.), which was used for the preparation of the *N*-nitroso compound.

Methyl *N*-Nitroso-*p*-acetamidobenz[^{14}C]oate.— The above methyl *p*-acetamidobenz[^{14}C]oate (943.5 mg.) was dissolved in 6 cc. of a mixture (1 to 1 by volume) of acetic anhydride and acetic acid, containing 1.8 g. of potassium acetate and a little phosphorus pentoxide; this mixture was cooled with ice and water and nitrosated by adding dropwise 3 cc. of a solution of nitrosyl chloride (1 cc.) in acetic anhydride (4.3 cc.). The reaction mixture was stirred into 30 cc. of water, and the yellow precipitate was filtered off, washed with water and dried on a porous plate for 2 hr. and a half in an evacuated desiccator (3 mmHg) containing concentrated sulphuric acid, to give 1.004 g. of methyl *N*-nitroso-*p*-acetamidobenz[^{14}C]oate, m. p. 73~74°C with decomposition. This was immediately assayed for purity and subjected to decomposition in benzene. The purity of this specimen was estimated at $94.8\pm2.5\%$, as is described below. On the addition of 8.59 mg. of the labelled nitroso compound to a solution of 14 mg. of β-naphthol in 5 cc. of methanol, labelled 1-(*p*-methoxycarbonylphenylazo)-2-naphthol began to precipitate. The reaction mixture was allowed to stand for two days, 102.15 mg. of inactive 1-(*p*-methoxycarbonylphenylazo)-2-naphthol and 150 cc. of methanol were added, and the mixture was heated on a water bath to effect dissolution and then cooled. The precipitated azo compound was filtered off and repeatedly crystallized from methanol to a constant

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[5] A value estimated from the partial rate factors of ethyl benzoate for phenylation (unpublished work).

[6] A. Murray, W. W. Foreman and W. Langham, *J. Am. Chem. Soc.*, **70**, 1037 (1948).

[7] N. W. Hirwe and P. Y. Kulkarni (*Proc. Indian Acad. Sci.*, **16A**, 294 (1942); *Chem. Abstr.*, **37**, 4061 (1943)) reported a m. p. of 114°C, but G. W. K. Cavill and J. M. Vincent (*J. Soc. Chem. Ind.* (London), **67**, 25 (1948); *Chem. Abstr.*, **42**, 4701b (1948)) reported a m.p. of 128°C.

activity of 2.70±0.043 mc./mol. The non-radioactive azo compound used as a carrier for the dilution analysis was prepared by coupling methyl *N*-nitroso-*p*-acetamidobenzoate with β-naphthol in methanol, m. p. 185.3∼186.8°C (from methanol) (Found: N, 9.37. Calcd. for $C_{18}H_{14}N_2O_3$: N, 9.15%).

Decomposition of Methyl *N*-Nitroso-*p*-acetamidobenz$[^{14}C]$oate in Benzene.—The labelled nitroso compound (994.5 mg., 4.48 mmol.) was dissolved in 36 cc. of benzene (405 mmol.) containing a little anhydrous sodium sulphate and allowed to decompose at 17∼18°C; at the end of four days the nitrogen evolved had amounted to 76 cc. (0°C, 1 atmosphere).

The solution was decanted from the sodium sulphate, which was then washed with benzene. To the combined benzene solutions, 753.35 mg. of methyl benzoate was added, and the benzene was removed on a water bath. The residue, after addition of 496.20 mg. of methyl *p*-acetoxybenzoate, m. p. 82.9∼83.9°C, (lit.8) m. p. 85°C), and 941.73 mg. of methyl 4-biphenylcarboxylate, m. p. 117∼118°C, (lit.9) m. p. 116∼117°C), was subjected to distillation under diminished pressure. The following fractions were obtained: Methyl benzoate, b. p. 90.6∼90.9°C at 21 mmHg, methyl *p*-acetoxybenzoate, b. p. 144∼160°C at 9 mmHg, and methyl 4-biphenylcarboxylate, b. p. 179∼180°C at 9 mmHg.

The methyl benzoate was hydrolyzed with alkali, and the resulting benzoic acid was repeatedly crystallized from hot water to a constant activity of 0.283±0.0099 mc./mol. The yield of methyl benzoate from the decomposition of the nitroso compound in benzene was therefore 7.91 mg., or 1.30% based on the nitroso compound.

The methyl 4-biphenylcarboxylate was purified by repeated crystallizations from methanol; the activity was found to be 9.55±0.191 mc./mol., corresponding to a yield of 53.3%.

It was found difficult to purify the methyl *p*-acetoxybenzoate by recrystallization from methanol on account of the contamination with methyl 4-biphenylcarboxylate. Accordingly, the fraction containing methyl *p*-acetoxybenzoate was dissolved in benzene, and the solution was washed with dilute aqueous alkali to remove any phenolic substance which might have been formed owing to unknown causes, washed with water, dried with anhydrous sodium sulphate and filtered through a column of alumina. Methyl 4-biphenylcarboxylate passed through, and on elution with ether 0.2 g. of methyl *p*-hydroxybenzoate was recovered. It was ascertained by a separate experiment that methyl *p*-acetoxybenzoate is deacetylated on alumina under those experimental conditions. The eluted methyl *p*-hydroxybenzoate was dissolved in benzene and extracted with dilute aqueous alkali, and the extract was washed with benzene and acidified with dilute sulfuric acid to precipitate methyl *p*-hydroxybenzoate, m. p. 131°C, (lit.8) m. p. 131°C). Two crystallizations from water afforded a specimen with an activity of 0.0223 mc./mol. We were unable to pursue the purification to a constant activity on account of the dearth of the material. The activity of 0.0223 mc./mol. corresponds to a yield of 0.046%.

The mother liquors from the purification of methyl 4-biphenylcarboxylate were combined, and methanol was removed. The residue was combined with that from evaporation of the fraction containing 4-biphenylcarboxylate from the above chromatographic separation, and 750.15 mg. of methyl 2-biphenylcarboxylate, b. p. 173.5°C (18 mmHg), was added. The whole was dissolved in benzene and the solution washed with 0.05 N sodium hydroxide solution and then with water, dried with calcium chloride and filtered through a column of alumina to remove most of the methyl 4-biphenylcarboxylate. Benzene was removed from the filtrate, the remaining ester hydrolyzed by boiling for about five hours with sodium hydroxide in dilute alcohol, and hydrochloric acid added. The precipitated 2-biphenylcarboxylic acid was filtered off, dried (706 mg.), and heated for ten minutes with 4 cc. of concentrated sulphuric acid on a water bath. The reaction mixture was added to water, the precipitate filtered off and dissolved in ether, the solution washed thoroughly with dilute sodium carbonate and dried with anhydrous calcium chloride, and the ether removed on a water bath to give 0.50 g. of fluorenone. Repeated crystallizations from petroleum ether gave a specimen, m. p. 84°C (lit.10) m. p. 84∼86°C), with an activity of 1.1 μc./mol. with a reliable error of ±1.6 μc./mol. Therefore, the yield of methyl 2-biphenylcarboxylate is estimated to be less than 0.0074%.

The upper part of the chromatographic column for the separation of methyl 4-biphenylcarboxylate and methyl *p*-acetoxybenzoate showed an orange color. This part was extracted three times with hot 94% alcohol, and the combined extracts were evaporated. The residue was added, together with 175.5 mg. of dimethyl 4, 4′-azobenzenedicarboxylate, m.p. 242∼242°C (lit.11) m.p. 242°C), 365.1 mg. of methyl 4-azobenzencarboxylate, m.p. 123∼124°C (lit.12) m.p. 123∼124°C), and 115.1 mg. of dimethyl 4,4′-biphenyldicarboxylate, m.p. 213∼214°C (lit.13) m.p. 212∼213°C), to a benzene solution of the residue from the fractional distillation. The benzene solution was heated, and, on concentration to about 40 cc., dimethyl 4, 4′-azobenzenedicarboxylate crystallized out in small scales. This was filtered off and recrystallized from benzene to a constant activity of 0.947±0.018 mc./mol., corresponding to a yield of 0.46%. The mother liquor was chromatographed on alumina in order to effect a further separation. But, as no substances were eluted owing to strong adsorption, the alumina was boiled with methanol and 17.0 mg. of dimethyl 4, 4′-biphenyldicarboxylate recovered. This was diluted with 176 mg. of inactive ester and recrystallized from benzene to a constant activity of 0.0060±0.0006 mc./mol., corresponding to a yield of 0.024%. Purification of methyl 4-azobenzenecarboxylate failed owing to its greater

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8) C. H. V. Hoessle, *J. prakt. Chem.*, (2), **49**, 502 (1894).

9) R. L. Dannley and B. Zaremsky, *J. Am. Chem. Soc.*, **77**, 1588 (1955).

10) J. Schmidt and H. Wagner, *Ber.*, **43**, 1797 (1910).

11) F. Meyer and K. Dahlem, *Ann.*, **326**, 338 (1903).

12) P. Jacobson and A. Steinbrenk, ibid., **303**, 387 (1898).

13) M. Weiler, *Ber.*, **32**, 1061 (1899).

solubility than those of the other compounds added as carriers.

Radioactivity Determination.—Radiocarbon assays were carried out by oxidizing samples according to the method of Van Slyke and Folch[14] and by converting the resulting carbon dioxide into barium carbonate, the activity of which was counted with an end-window Geiger-Müller counter on an " infinitely thick " layer with a surface area of 4.9 cm^2, the counts being all corrected for background and compared with the count of a standard barium carbonate with a known activity.

Summary

Methyl *N*-nitroso-*p*-acetamidobenz[^{14}C]oate was decomposed in benzene, and the product was analyzed by the isotopic dilution method. The results are shown in Table I, and the mechanistic implication is discussed.

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[14] D. D. Van Slyke and J. Folch, *J. Biol. Chem.*, **136**, 509 (1940).