C^{14} in the general manner described[4] by Burr and Ciereszko. The material had m.p. 125–126° and showed a radioactive assay of 0.977 ± 0.003 mc./mole.

Ozonization of Stilbene.—Stilbene (0.200 g.) was dissolved in ethanol (8 ml.) and treated with a hot solution of 2,4-dinitrophenylhydrazine (0.7 g.) and sulfuric acid (3 ml.) in ethanol (10 ml.). The mixture was diluted with ethanol (10 ml.), cooled to room temperature ozonized in a semimicro ozonizer[5] after seeding with a crystal of benzaldehyde 2,4-dinitrophenylhydrazone. Formation of the solid derivative was almost instantaneous, though in the absence of seed precipitation did not begin for about five minutes. Ozonization was continued for 25 minutes, when the solid was filtered, rinsed with ethanol and dried, 0.603 g. (95%), m.p. 237–238°. Recrystallization of 0.20 g. of the product from 5 ml. of dioxane gave 0.16 g. of red needles, m.p. 238–239°.

To establish further that the reaction of 2,4-dinitrophenylhydrazine sulfate with stilbene ozonide was "instantaneous and quantitative," stilbene (0.3604 g.) was suspended in ethanol (15 ml.) and ozonized until dissolved (*ca.* 30 minutes). A seed of benzaldehyde 2,4-dinitrophenylhydrazone was added, followed by a solution of 2,4-dinitrophenylhydrazine (1 g.) and sulfuric acid (5 ml.) in ethanol (15 ml.). Formation of a heavy precipitate was instantaneous. This was filtered, rinsed and dried, 1.042 g. (92%). When this reaction was repeated with the above stilbene-α-C^{14}, the benzaldehyde 2,4-dinitrophenylhydrazone, recrystallized from dioxane, showed a radioactivity assay of 0.4915 ± 0.0025 mc./mole.

Fractional Ozonization of Stilbene-α-C^{14}.—The above stilbene-α-C^{14} (1.0000 g.) was dissolved in hot ethanol (35 ml.) and treated with a solution of 2,4-dinitrophenyldrazine (3.2 g., 18% excess) and sulfuric acid (10 ml.) in ethanol (40 ml.). The mixture was diluted with ethanol (15 ml.) cooled to room temperature, seeded with benzaldehyde 2,4-dinitrophenylhydrazone, and ozonized for several minutes. The ozonization was stopped and the accumulated derivative filtered on a tared sintered-glass funnel, rinsing with a little ethanol. The filtrate was returned to the ozonizer, and the process repeated. A series of successive fractions was collected in this manner until further ozonization of the filtrate produced no additional derivative. The sum of the weights of the twelve fractions collected represent a 92.4% yield. Each fraction was recrystallized from purified dioxane[6] (2.5 ml./0.1 g. derivative) to obtain an analytical sample suitable for radioactivity assay.

Assay of Radioactive Benzaldehyde 2,4-Dinitrophenylhydrazone Fractions.—The above purified fractions were assayed for C^{14}-content by a modification of the previously described wet combustion procedure.[7] For assaying large (30–40 mg.) samples of compounds such as the present ones containing a large percentage of nitrogen, it was found necessary to include a heated (175–180°) lead peroxide cartridge (1 × 5 cm.) in the combustion line to remove oxides of nitrogen. In the absence of such a lead peroxide cartridge highly erratic radioactive assays resulted and the wet combustion procedure was unreliable.

The assays of the successive fractions are given in Table I, along with the average deviation from the mean obtained on duplicate assays. The estimated over-all precision of *ca.* ±1% for the wet combustion method is taken into account in the vertical line over each of the data points in Fig. 1. An over-all radiochemical balance between our product fractions and the starting stilbene-α-C^{14} gives agreement within about 1%.

---

[4] J. G. Burr, Jr., and L. S. Ciereszko, THIS JOURNAL, **74**, 5426 (1952).

[5] W. A. Bonner, *J. Chem. Educ.*, in press.

[6] L. F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath & Company, New York, N. Y., 1941, p. 368.

[7] O. K. Neville, THIS JOURNAL, **70**, 3501 (1948).

OAK RIDGE, TENNESSEE

[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF OAK RIDGE NATIONAL LABORATORY]

Studies[1] of Some Carbon-14 Isotope Effects in Organic Chemistry

BY GUS A. ROPP, VERNON F. RAAEN AND ARTHUR J. WEINBERGER

RECEIVED MARCH 20, 1953

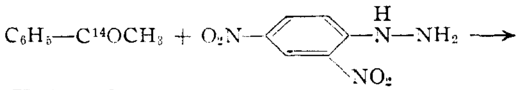
Isotope fractionation was shown to occur in the decomposition of mercurous formate-C^{14} and in some of the keto group reactions of acetophenone-α-C^{14} and benzophenone-α-C^{14}. No isotope fractionation was found in addition of bromine to the carbon-14-labeled ethylenic bonds of styrene or methyl cinnamate. No isotope effect was found in the Diels–Alder addition of 2,3-dimethylbutadiene to β-nitrostyrene-α-C^{14}. No isotope effect was found in absorption of carbon-14 dioxide in two alkaline media.

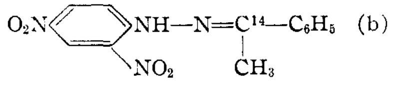
A significant number of carbon isotope effects in organic reactions have been reported recently in the literature.[2] Because such isotope fractionations are of particular interest as sources of error in quantitative tracer studies, it seems desirable to report reaction studies in which no isotope effects were found, as well as those in which isotope effects were discovered. In this paper the results of a series of examinations of organic reactions for isotope effects are reported; in a number of these no isotope fractionation was indicated.

The following is a list of reactions studied:

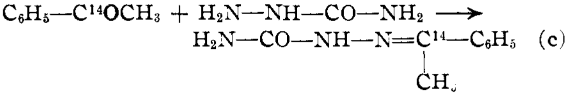
With isotope effects:

$$2Hg\ OOC^{14}H \xrightarrow{80°} C^{14}O_2 + 2Hg + HC^{14}OOH \quad (a)$$

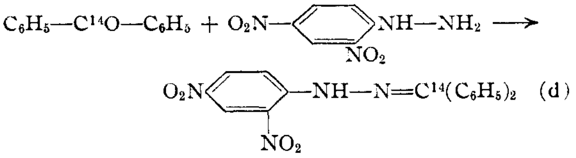




(b)



$$C_6H_5-C^{14}OCH_3 + H_2N-NH-CO-NH_2 \longrightarrow H_2N-CO-NH-N{=}\underset{\displaystyle CH_3}{C^{14}}-C_6H_5 \quad (c)$$



(d)

Without isotope effects:

$$C_6H_5-C^{14}H{=}CH_2 + Br_2 \xrightarrow{-80°} C_6H_5-C^{14}HBr-CH_2Br \quad (e)$$

$$C_6H_5-CH{=}C^{14}H_2 + Br_2 \xrightarrow{-80°} C_6H_5-CHBr-C^{14}H_2Br \quad (f)$$

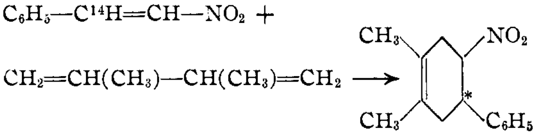
$$C_6H_5-CH{=}C^{14}H_2-COOCH_3 + Br_2 \xrightarrow{25°} C_6H_5-CHBr-C^{14}HBr-COOCH_3 \quad (g)$$

---

[1] This paper is based on work performed under contract Number W-7405-eng-26 for the Atomic Energy Commission at Oak Ridge National Laboratory.

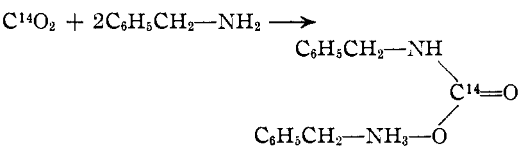
[2] For a review, see G. A. Ropp, *Nucleonics*, **10**, 22 (1952).

$$C_6H_5—C^{14}H=CH—COOCH_3 + Br_2 \xrightarrow{25°} C_6H_5—C^{14}HBr—CHBr—COOCH_3 \qquad (h)$$



(i)

$$C^{14}O_2 + NaOH \xrightarrow{H_2O} NaHC^{14}O_3 \qquad (j)$$



(k)

$$C^{14}O_2 + 2C_6H_5CH_2—NH_2 \longrightarrow (C_6H_5CH_2—NH)(C_6H_5CH_2—NH_3—O)C^{14}=O$$

In isotopic tracer studies involving organic systems molar activities of labeled organic compounds are often most readily measured after converting the compounds concerned to easily purified solid derivatives. The presence of isotope fractionation in the derivative formation could therefore introduce errors into such tracer studies. Since several of the reactions listed above are frequently used in preparing derivatives, the presence or absence of isotope effects in these reactions could be of considerable interest.

Discussion of Results

I. The cause of the appreciable carbon isotope effect found (Table I, below) in the mercurous formate-C^{14} decomposition is rather difficult to explain since the reaction as written seems to involve only the breaking of a carbon to hydrogen bond. The frequency of the carbon–hydrogen vibration should be relatively insensitive to the 17% change in the mass of the carbon atom resulting from isotopic substitution; hence only a very small isotope effect would be expected. Thus the experimentally observed isotope fractionation might be taken to suggest some intermediate with a carbon–oxygen bond or carbon–mercury bond which is broken in the rate controlling step. The work of Miller and Murphy[3] also indicates that the mechanism of reaction is complex since water appears to be involved and the reaction is said to be heterogeneous.

II. In the cases of carbon isotope fractionation in the reaction of carbonyl-C^{14}-ketones, the ratio, k_{14}/k_{12}, of the rate constants can be calculated[2] approximately from the data of Table II. For the acid-catalyzed formation of the 2,4-dinitrophenylhydrazone of acetophenone-α-C^{14}, the approximate value of k_{14}/k_{12} is found to be 0.946 (average) at 25° and 0.909 at $-75°$. Using these isotope effect values at two temperatures and assuming the Arrhenius equation holds over this range of temperatures, the value of ΔE, the difference between the Arrhenius activation energies for the two species is calculated[4] to be approximately 50 cal. per mole. Benzophenone-α-C^{14} gives at 25° approximately the same isotope effect ($k_{14}/k_{12} = 0.934$) as that given by acetophenone-α-C^{14} in the formation of the 2,4-dinitrophenylhydrazone and the semicarbazone (see Table II).

III. There seems to be no obvious explanation for the lack of isotope fractionation in addition reactions of the type listed in Table III. Other studies of addition of bromine to carbon-14-labeled unsaturated compounds and the Diels–Alder reaction are in progress. Preliminary results indicate that appreciable isotope fractionation occurs in the catalytic addition of hydrogen to acetophenone-α-C^{14}.

IV. The lack of appreciable isotope fractionation in the two cases of absorption of carbon-14 dioxide (Table IV) could be due to exchange of carbon dioxide between the gas phase and the solution. Such an exchange might well mask any rate isotope effect which would otherwise appear. An alternative explanation might be that each reaction is diffusion controlled with the rate of diffusion of the carbon dioxide molecules being essentially independent of their isotopic composition.

Methods and Experimental

The general methods of detecting the presence of carbon-14 isotope effects have been discussed in detail.[2] As a rule isotope fractionation was indicated in the present studies if the product of complete reaction of the labeled compound had a substantially different specific activity from the product formed by only partial reaction of the labeled compound. There was considered to be no isotope effect in those processes in which the products of partial and complete reaction had the same specific activities within approximately 2%. Products of the partial reactions were separated from unchanged reactants by crystallization, sublimation, and/or distillation. In all cases solid reaction products were prepared for radioassay by several recrystallizations. The compounds radioassayed melted sharply at the temperature recorded in the literature.

I. Demonstration of the Isotope Fractionation in the Decomposition of Mercurous Formate-C^{14}.—Labeled mercurous formate (10 mmoles, 2.50 g.) was permitted to decompose[3] over an eight-hour period in a 25-ml. reaction bulb at 70–75°. The bulb was continuously swept with nitrogen which was previously passed through Drierite–Ascarite mixture and through aqueous potassium hydroxide to saturate the gas with water. Gases leaving the reaction bulb were passed through a series of nine absorption bottles which were equipped with fritted bubble tubes. The bottles were filled with saturated aqueous barium hydroxide. When the barium hydroxide in the first bottle was exhausted, that bottle was by-passed and the gas was passed through the succeeding eight bottles. In this manner each of the first eight bottles was in turn by-passed to prevent possible exchange of the carbon dioxide with previously precipitated barium carbonate. When the reaction was complete, the barium carbonate samples were collected, washed thoroughly with water by decantation, filtered, and dried 15 hours at 120° in a stream of nitrogen. The washing and drying procedures were critical in obtaining reproducible assays of the barium carbonate-C^{14}. The barium carbonate-C^{14} samples were weighed. Collectively they represented 91% recovery of carbon dioxide. Weighed samples were decomposed with 85% phosphoric acid, and each carbon-C^{14} dioxide sample released was collected in a stainless steel ion chamber for radiochemical assay using the vibrating reed electrometer.[5] Table I presents the results of these assays. In this instance an isotope effect was

TABLE I

ISOTOPE FRACTIONATION OF CARBON-C^{14} DIOXIDE PRODUCED IN THE DECOMPOSITION OF MERCUROUS FORMATE-C^{14}

Sample $BaC^{14}O_3$	1	2	3	4	5	6	7
Reaction represented, %	5	5	5	15	36	16	9
Specific activity, μc./mg.	0.0998	0.0999	0.100	..	0.104	0.106	0.112

---

(3) G. A. Miller and G. Murphy, THIS JOURNAL, **73**, 1871 (1951).

(4) G. A. Ropp, A. J. Weinberger and O. K. Neville, *ibid.*, **73**, 5573 (1951).

(5) Neville, *ibid.*, **70**, 3501 (1948).

shown by the fact that increments of reaction product increased in specific activity as the reaction proceeded.

II. Demonstration of Isotope Effects in Reactions of C^{14}-Labeled Keto Groups in Ketones.—The reactions which fall in this group were usually carried out at 25° under the conditions used to prepare derivatives of ketones. For each reaction the specific activity of the ketone was determined by radioassaying the derivative prepared by adding excess reagent to the ketone in ethanol. The radioassay[5] so obtained was compared with the radioassay of the derivative prepared by adding 0.05 to 0.20 mmole of reagent per millimole of ketone. For each reaction an isotope effect was indicated by the fact that the derivative prepared by 5 to 20% conversion of the ketone had a lower specific activity than the derivative prepared by use of excess reagent. Derivative samples were burned[5] using Van Slyke solution and radioassayed[5] using the vibrating reed electrometer. The resulting data are presented in Table II.

TABLE II

ISOTOPE EFFECTS IN THE PREPARATION OF DERIVATIVES OF KETONES

Ketone	Derivative	Reaction temp., °C.	Conversion of ketone, %	Specific activity of derivative (μc./mg.)
Acetophenone-α-C^{14}	2,4-Dinitrophenylhydrazone	25	100	0.00894
			10	.00850
Acetophenone-α-C^{14}	2,4-Dinitrophenylhydrazone	25	100	.00897
			5	.00848
Acetophenone-α-C^{14}	2,4-Dinitrophenylhydrazone	−75	100	.00909
			5	.00827
Acetophenone-α-C^{14}	Semicarbazone	25	100	.01530
			10	.01440
Benzophenone-α-C^{14}	2,4-Dinitrophenylhydrazone[a]	25	100	.004403
			10	.004125

[a] This isotope effect also has been reported by F. Brown and D. Holland, *Can. J. Chem.*, **30**, 438 (1952).

Preparation of 2,4-Dinitrophenylhydrazones from Acetophenone-α-C^{14} and Benzophenone-α-C^{14}.—Acetophenone-α-C^{14} was prepared by Friedel–Crafts reaction from acetyl-1-C^{14} chloride and benzene. Benzophenone-α-C^{14} was prepared similarly[6] from a mixture of benzoyl chloride with benzoic-α-C^{14} acid.

These derivatives were prepared according to Procedure 15 of Shriner and Fuson[7] except that a constant temperature bath at 25° was used and just sufficient reagent was added to give the desired per cent. reaction of the ketones. For the formation of the acetophenone-α-C^{14} 2,4-dinitrophenylhydrazone at −75°, Dry Ice–acetone cooling was used while the desired amount of reagent was added dropwise over 90 minutes with stirring. The mixture was kept at −75° overnight, then worked up. The 2,4-dinitrophenylhydrazones were recrystallized from ethanol and ethyl acetate and melted at the temperature recorded in the literature.

Preparation of Acetophenone-α-C^{14} Semicarbazone.—This derivative was also prepared by using the method of Shriner and Fuson,[8] Procedure 13B, and adding only enough reagent to give the desired per cent. reaction. A constant temperature bath at 25° was used. The derivatives were recrystallized from aqueous methanol and dried at 50° over phosphorus pentoxide *in vacuo*. They melted at the temperature recorded in the literature.

Test for Reversibility of the Semicarbazone Formation.—To determine whether the semicarbazone formation involved an equilibrium, equimolar amounts of acetophenone-α-C^{14} and unlabeled acetophenone semicarbazone were stirred 20 hours in aqueous ethanol solution under the same conditions as those used to form the semicarbazone from the ketone. About half the semicarbazone added remained undissolved and rapid stirring was used to keep it suspended. The semicarbazone was then recovered and recrystallized. No activity was found. It was thus shown that acetophenone did not exchange with acetophenone semicarbazone and that the isotope effect reported here was a rate effect.

III. Examination of Addition Reactions for Isotope Effects in the Bromination of Styrene-α-C^{14} and Styrene-β-C^{14}.—The styrenes were prepared with sodium acetate-1-C^{14} and sodium acetate-2-C^{14}. The reactions involved the preparation of labeled acetyl chloride, Friedel–Crafts reaction with benzene, catalytic reduction of the acetophenone, and dehydration of the resulting alcohol by the method of Brooks.[9] For bromination of the styrenes, a three-necked, 200-ml. flask equipped with stirrer, dropping funnel and drying tube was placed in a freezing mixture of chloroform, carbon tetrachloride and Dry Ice. A solution in 100 ml. of dry chloroform of 3.0 g. (29 mmoles, 2–3 μc. per mmole) of styrene was added. The drying tube was replaced by a thermometer and after the temperature reached −70°, a solution of 0.46 g. (2.9 mmoles) of bromine in 10 ml. of chloroform was added in the dark over a period of ten minutes. Excess solvent and styrene were then removed at reduced pressure so that the temperature never became higher than 30°. Two 3-ml. portions of 95% ethanol were added and vacuum distilled to ensure complete removal of styrene. The remaining white crystalline styrene dibromide was twice recrystallized from 95% ethanol and dried at room temperature over phosphorus pentoxide in a vacuum desiccator at 2 mm. pressure to give a product of m.p. 73–74°. A second sample of styrene dibromide was prepared in the same manner except for the use of excess bromine above the amount necessary to completely saturate the double bond. Samples of the dibromide representing 10% reaction of the styrene and complete reaction of the styrene were thus prepared. These were combusted[5] using Van Slyke mixture and assayed[5] using the vibrating reed electrometer. The entire reaction and assaying were carried out first with styrene-α-C^{14}, then repeated with styrene-β-C^{14}. The resulting data are presented in Table III.

TABLE III

DATA INDICATING NO ISOTOPE FRACTIONATION IN CERTAIN ADDITION REACTIONS

Labeled cpd.	Reagent added	Reaction temp., °C.	Labeled cpd. reacted, %	Specific act. of product (μc./mg.)
Styrene-α-C^{14}	Bromine	−70	100	0.00919
			10	.00911
Styrene-β-C^{14}	Bromine	−70	100	.01240
			10	.01241
Methyl cinnamate-α-C^{14}	Bromine	25	100	.00140
			40	.00141
			10	.00139
Methyl cinnamate-β-C^{14}	Bromine	25	100	.00229
			10	.00232
β-Nitrostyrene-α-C^{14}	2,3-Dimethylbutadiene	80–100	100	.00421
			30	.00418

Test for Exchange of Bromine between Labeled and Unlabeled Styrene.—In an attempt to prove that the failure to detect any isotope effect in styrene bromination at −70° was not caused by rapid exchange of bromine between the styrene dibromide formed and unreacted styrene, an additional experiment was performed.

A sample of unlabeled styrene dibromide (1.00 g., 3.8 mmoles) was dissolved in a solution of labeled styrene (500 mg., 4.8 mmoles, 5 μc. per mmole) in 100 ml. of dry chloroform. The solution was carried through the same operations as those used in the recovery of the styrene dibromide produced by bromination above: excess styrene and solvent were removed at room temperature in vacuum over a 50-minute period. Since the styrene dibromide recovered was inactive, the possibility of exchange was ruled out.

Bromination of Methyl Cinnamate-α-C^{14} and Methyl Cinnamate-β-C^{14}.—By the use of the Perkin reaction the methyl cinnamates were prepared from sodium acetate-1-

---

[6] J. G. Burr, THIS JOURNAL, **75**, 1990 (1953).

[7] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 171.

[8] Reference 7, p. 170.

[9] L. A. Brooks, THIS JOURNAL, **66**, 129 (1944).

C^{14} and sodium acetate-2-C^{14}. Samples of the labeled esters were brominated at 25° in carbon tetrachloride with sufficient bromine to give 10, 40 and essentially 100% reaction. In the cases of partial reaction, the unreacted methyl cinnamate was vacuum-distilled from the dibromo ester and the residue was recrystallized from methanol to give methyl dibromocinnamate having a melting point of 119°. For the 100% reaction purification was by recrystallization only. Product samples were oxidized using Van Slyke solution and assayed using the vibrating reed electrometer.

Diels–Alder Reaction[10] of β-Nitrostyrene-α-C^{14} and 2,3-Dimethylbutadiene.—The choice of this Diels–Alder reaction for isotope fractionation study was based partially on the fact that it gives relatively high yields at 80 to 100° of a crystalline, easily purified adduct. The β-nitrostyrene-α-C^{14} was synthesized[11] from benzaldehyde-α-C^{14} and nitromethane. To obtain the labeled adduct from complete reaction of the labeled dienophile, 30 mmoles of 2,3-dimethylbutadiene, 20 mmoles of β-nitrostyrene-α-C^{14} and 20 ml. of dry toluene were heated to reflux temperature overnight. Excess diene and toluene were distilled off *in vacuo* and the adduct, m.p. 91.5–92.5°, was obtained by recrystallization from aqueous ethanol and vacuum sublimation. To obtain the labeled adduct representing 30% reaction of the dienophile the same procedure was repeated using 50 mmoles of β-nitrostyrene-α-C^{14} and 15 mmoles of 2,3-dimethylbutadiene. The adduct was separated from unreacted dienophile (after distilling the solvent) by fractional extraction of the concentrate with 95% ethanol. The product thus separated was further purified to m.p. 91–92° by recrystallization from aqueous ethanol and vacuum sublimation. The purified products from 100% reaction and 30% reaction were burned[5] using Van Slyke solution and assayed[5] using the vibrating reed electrometer.

Test for Reversibility of the Diels–Alder Reaction.—Since certain Diels–Alder reactions are considered to be reversible, it was of interest to demonstrate that even at 130° (30 to 50° above the temperature at which the Diels–Alder reaction was run in this case) there was no appreciable rate of exchange between the adduct and uncombined dienophile. This demonstration was effected by heating β-nitrostyrene-α-C^{14} with an equimolar amount of unlabeled adduct as a melt for 24 hours at 130°. The adduct was isolated and after careful purification, showed only background activity. The possibility was thus eliminated that a rate isotope effect actually existed in this Diels–Alder reaction studied but was masked by rapid exchange between the adduct and unreacted dienophile.

IV. Examination of Carbon-14 Dioxide Absorption in Alkaline Media for Isotope Fractionation.—In experiments to determine whether isotope fractionation occurs in carbon-14 dioxide absorption, the gas was passed through (a) dilute sodium hydroxide and (b) benzylamine[12] in dibenzyl ether in such fashion as to give 80% absorption of the gas in each case. The extent of reaction was determined by the pressure and volume in the manometric system used. In each case the specific activity of the original gas was compared with the specific activity of the unabsorbed gas after reaction. Specific activity measurements were performed, always at the same temperature and pressure, in a 10-ml. stainless steel ion chamber[4] which was sealed into the manometric system. The sample data of Table IV indicate no isotope fractionations for these reactions.

TABLE IV

DATA INDICATING NO ISOTOPE FRACTIONATION IN CARBON-14 DIOXIDE ABSORPTION

Absorbent	Original sp. act. $C^{14}O_2$ (as millivolts)	Absorption of $C^{14}O_2$, %	Sp. act. of unabsorbed $C^{14}O_2$ (as millivolts)
200 ml. of C.P. dibenzyl ether and 1.7 ml. of C.P. benzylamine	986	80	987
200 ml. of 0.1 *N* aqueous sodium hydroxide	980	80	980

---

(10) C. F. H. Allen, A. Bell and J. W. Gates, *J. Org. Chem.*, **8**, 373 (1943).

(11) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 2nd Ed., 1947, p. 413.

(12) A. B. Wright and M. B. Moore, THIS JOURNAL, **70**, 3865 (1948).

OAK RIDGE, TENN

[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH, UNIVERSITY OF CHICAGO]

Preparation and Reactions of 2-Methoxythiophene

BY JEAN SICÉ

RECEIVED MARCH 23, 1953

2-Methoxythiophene was obtained by a copper-catalyzed Williamson synthesis. The ether function was found to overcome appreciably the directive influence of the hetero-atom in orienting some attack by electrophilic reagents on the 3-position; radical reagents reacted only with the 5-position. The readily available 5-methoxy-2-thienyllithium is a convenient material for the introduction of the 5-alkoxy-2-thienyl group into a molecule. A modification of the aldehyde synthesis of Bouveault is described.

2-Thienol and its methyl ether have recently been characterized; 3-thienol and its ethers have not yet been isolated. These two series of substances are important for the study of directive influences on nuclear substitutions of thiophene. Moreover, they would render available compounds of potential biological interest[1] containing an isostere of the phenyl ether group. But the free hydroxy substances exhibit an hemimercaptenol–thiolactone tautomerism or a keto–enol prototropy[2,3] and are unstable. A more satisfactory[2] preparation of 2-methoxythiophene and a study of its behavior in characteristic reactions are presented in this communication.

Iodothiophene reacted readily, bromothiophene slowly, chlorothiophene did not react with sodium alkoxides. The addition of minute quantities of sodium iodide accelerated the reaction of bromothiophene, but did not affect that of chlorothiophene. Cupric oxide[4] was more satisfactory as catalyst than cuprous oxide or copper. The concentration and the ratio of halide to sodium alkoxide and cupric oxide, and the quality of the latter, influenced the rate of the reaction. The yields were good and the products easily purified.

The strongly *ortho-para* orienting alkoxy group on carbon atom-2 increased the directive influence of the sulfur atom to the 5-position, but competed with it to induce some attack by electrophilic reagents (mercuration, nitration, acylation, in de-

---

(1) *Cf.* J. Sicé and M. Mednick, THIS JOURNAL, **75**, 1628 (1953).

(2) C. D. Hurd and K. L. Kreuz, *ibid.*, **72**, 5543 (1950).

(3) P. Friedlaender and St. Kielbasinski, *Ber.*, **45**, 3389 (1912).

(4) B. B. Dey, *et al.*, *J. Sci. Ind. Research* (*India*), **5B**, 25 (1946).