[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TENNESSEE]

Irreversibility of the Benzilic Ester Rearrangement

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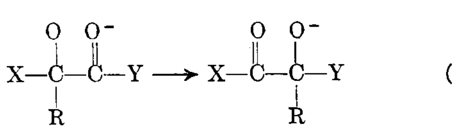
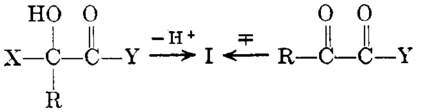
The benzilic acid and benzilic ester rearrangements are classified with a number of related molecular rearrangements, each of which occurs through formation of a key intermediate (I) of a structural type common to all of these base-induced rearrangement. Although this key intermediate can be formed from a benzilic acid ester, formation of it (XI in this case) does not lead to a molecular rearrangement which would constitute reversal of the benzilic ester rearrangement discovered by Doering and Urban. Demonstration of this irreversibility of the benzilic ester rearrangement was done by showing the positional stability of labeling in methyl anisilate-1-C^{14} (VI) in the presence of strong base. Synthesis of the labeled ester involved the first successful alcoholysis of an aroyl cyanide to an imino ether.

A variety of systems, represented by the general structure I, are known to undergo molecular rearrangement (Equation 1). Ions like I, the conjugate base of an α-keto alcohol, are attained (Equation 2) either by the removal of a proton from the alcohol itself or by attack of base on an α-diketone. Thus, α-phenyl-2-methylbenzoin (III) results either from the treatment of α-o-tolylbenzoin (II) with alkali,[1] or from the addition of o-tolyllithium to benzil (IV) (see Experimental). In either case the rearranging intermediate is I with R = Y = phenyl and X = o-tolyl. A better known system I, which has R = Y = phenyl but X = hydroxyl, is attained by the attack of hydroxyl ion on benzil and is the intermediate in the benzilic acid rearrangement.

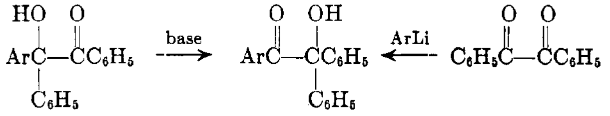


$$X-\underset{\underset{R}{|}}{\overset{\overset{O}{|}}{C}}-\overset{\overset{O^-}{\|}}{C}-Y \longrightarrow X-\overset{\overset{O}{\|}}{C}-\underset{\underset{R}{|}}{\overset{\overset{O^-}{|}}{C}}-Y \qquad (1)$$

I



$$X-\underset{\underset{R}{|}}{\overset{\overset{HO}{|}}{C}}-\overset{\overset{O}{\|}}{C}-Y \xrightarrow{-H^+} I \xleftarrow{\mp} R-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-Y \qquad (2)$$

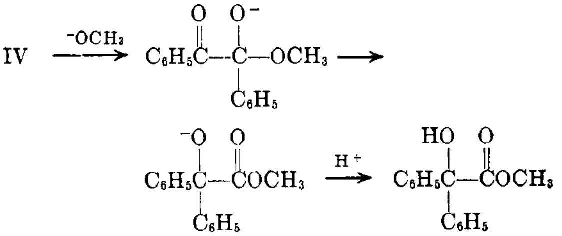


$$Ar\underset{\underset{C_6H_5}{|}}{\overset{\overset{HO}{|}}{C}}-\overset{\overset{O}{\|}}{C}C_6H_5 \xrightarrow{\text{base}} Ar\overset{\overset{O}{\|}}{C}-\underset{\underset{C_6H_5}{|}}{\overset{\overset{OH}{|}}{C}}C_6H_5 \xleftarrow{ArLi} C_6H_5\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}C_6H_5$$

II III IV

Ar = o-tolyl

The intermediacy of system I can be recognized in many other base induced rearrangements, including the formation of methyltartronic acid from ethyl α,β-diketobutyrate[2] (wherein X = OH, R = $CO_2C_2H_5$, Y = CH_3), the rearrangement of 4-methoxybenzilaldehyde to 4-methoxybenzoin[3] (wherein X = anisyl, R = C_6H_5, Y = H), the conversion of diphenyl triketone into α-benzoylmandelic acid[4] (wherein X = OH, R = C_6H_5CO, Y = C_6H_5), and the benzilic ester rearrangement[5] (wherein X = OCH_3, R = Y = C_6H_5), a transformation of benzil (IV) found by Doering and Urban[5] to be effected by methoxide ion in methanol (Chart One).



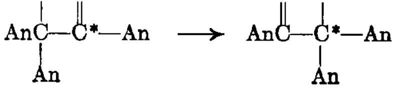
$$IV \xrightarrow{^-OCH_3} C_6H_5\overset{\overset{O}{\|}}{C}-\underset{\underset{C_6H_5}{|}}{\overset{\overset{O^-}{|}}{C}}-OCH_3 \longrightarrow$$

$$C_6H_5\underset{\underset{C_6H_5}{|}}{\overset{\overset{^-O}{|}}{C}}-\overset{\overset{O}{\|}}{C}OCH_3 \xrightarrow{H^+} C_6H_5\underset{\underset{C_6H_5}{|}}{\overset{\overset{HO}{|}}{C}}-\overset{\overset{O}{\|}}{C}OCH_3$$

V

Chart One

From an examination of these and numerous other examples of the rearrangement in Equation 1,[6] one is struck by the wide variety of groups X, R, and Y which may be involved, particularly by the various migrating groups R, which may be hydrogen, alkyl, aryl, or carbonyl. The three groups may in fact be the same, for example X = R = Y = anisyl, in which case the rearrangement proceeds (Equation 3) without free energy change and is detected by isotopic tracer technique.[1a] It has been suggested that all of the different reactions correlated with Equation 1 might be called "α-oxo-alcohol rearrangements."[6]



$$An\underset{\underset{An}{|}}{\overset{\overset{^-O}{|}}{C}}-\overset{\overset{O}{\|}}{C}{}^*-An \longrightarrow An\overset{\overset{O}{\|}}{C}-\underset{\underset{An}{|}}{\overset{\overset{O^-}{|}}{C}}{}^*-An \qquad (3)$$

It seemed of interest to determine if the system X = R = aryl and Y = methoxyl would undergo

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[1] (a) J. F. Eastham, J. E. Huffaker, V. F. Raaen, and C. J. Collins, *J. Am. Chem. Soc.*, **78**, 4323 (1956); (b) R. Roger and A. McGregor, *J. Chem. Soc.*, 442 (1934); (c) D. B. Sharp and E. L. Miller, *J. Am. Chem. Soc.*, **74**, 5643 (1952).

[2] W. Denis, *Am. Chem. J.*, **38**, 587 (1907); H. W. Davis, E. Grovenstein, and O. K. Neville, *J. Am. Chem. Soc.*, **75**, 3304 (1953).

[3] D. Y. Curtin and A. Bradley, *J. Am. Chem. Soc.*, **76**, 5777 (1954).

[4] J. D. Roberts, D. R. Smith, and C. C. Lee, *J. Am. Chem. Soc.*, **73**, 618 (1951).

[5] W. von E. Doering and R. S. Urban, *J. Am. Chem. Soc.*, **78**, 5938 (1956).

[6] S. Selman and J. F. Eastham, *Quart. Revs.*, **14**, 221 (1960).

a base catalyzed rearrangement which would constitute a reversal of the benzilic ester rearrangement. Because of resonance stabilization of the carbomethoxy group, one might expect that a benzilic ester (V) would be more stable than the corresponding benzil (IV) and, hence, that even if the changes in Chart One were reversible, only the ester would be isolable. Rearrangement could still be detected, however, by isotopic tracer technique. In this work methyl anisilate-1-C^{14} (VI) has been prepared, subjected to conditions which effect the benzilic ester rearrangement, and analyzed for mixing of the position of labeling.

The method of synthesis utilized in the preparation of methyl anisilate-1-C^{14} (VI) is outlined in Chart Two. Anisoyl chloride was treated with cuprous cyanide-C^{14} to give anisoyl cyanide-1-C^{14} in 62% yield. Treatment of anisoyl cyanide-1-C^{14} with anhydrous methanol and hydrogen chloride in ether gave 4-methoxyphenylglyoxylimino methyl ether hydrochloride (VII), which was immediately hydrolyzed to obtain methyl 4-methoxyphenylglyoxylate-1-C^{14} (VIII) in 48% yield from the anisoyl cyanide. Addition of anisylmagnesium bromide to VIII gave methyl anisilate-1-C^{14} in 22% yield.

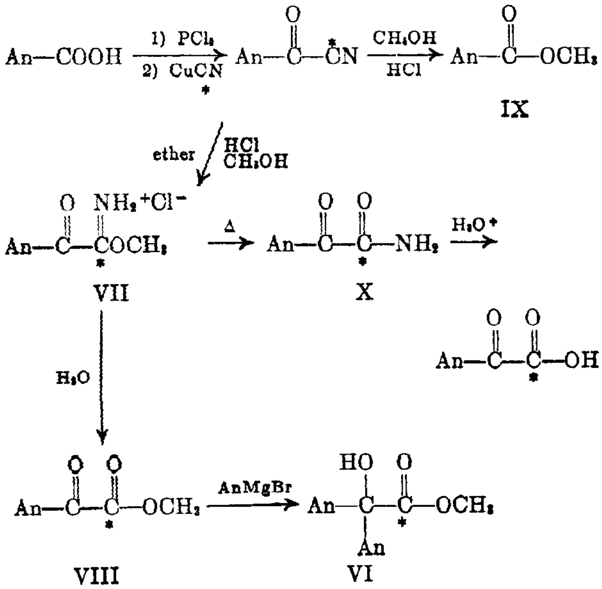
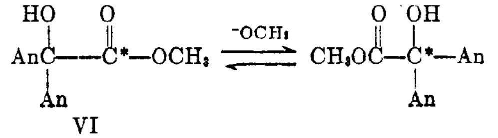


Chart Two

The critical step in the synthesis shown in Chart Two was the preparation of 4-methoxyphenylglyoxylimino methyl ether hydrochloride (VII), and a variety of conditions were tried for its preparation. Although VII was not purified, it was isolated in a crystalline form whose solubility characteristics and chemical reactions establish its structure. Compound VII is apparently the first imino ether hydrochloride to be obtained from an aroyl cyanide. The principal difficulty encountered in preparing compounds like VII is the formation of decarbonylation products, ester IX in this case, and decomposition products, amide X in this case. Thus Migrdichian[7] has reported that benzoyl cyanide does not form an imino ether but reacts with alcohols in the presence of hydrogen chloride to form benzoic acid esters. This was found to be the case when anisoyl cyanide was treated with a large excess of methanol in the presence of hydrogen chloride; methyl anisate (IX) was obtained in 88% yield. The obtaining of the imino ether (VII) was facilitated by the use of anhydrous ether as a solvent, a stoichiometric amount of methanol, low temperatures, and strictly anhydrous conditions throughout the reaction. When the ethereal reaction solution was allowed to remain for prolonged periods, even at 10°, without inducing crystallization, or when the temperature of the solution was allowed to rise, the product was 4-methoxyphenylglyoxylamide (X). The formation of amides by decomposition of imino ethers is a known reaction.[7]

The base induced transformation of ester VI sought in this work is illustrated in Equation 4.



$$\mathrm{An\overset{HO}{\underset{An}{C}}-\overset{O}{\overset{\|}{C}}{}^{*}-OCH_3 \xrightleftharpoons{^{-}OCH_3} CH_3O\overset{O}{\overset{\|}{C}}-\overset{OH}{\underset{An}{C}}{}^{*}-An} \quad (4)$$

The steps to effect the transformation are shown in Chart Three. The first step, reversible removal of a proton by base from the ester, would yield an equilibrium concentration of ion XI. The last step, removal of methoxide ion from XII, should also be reversible; hydroxide ion attack on benzil has been proved reversible,[8] and the reversible attack of methoxide ion on a carbonyl should be even more rapid than that of hydroxide ion.[9] The step designated by k_2 is the one demonstrated by Doering and Urban to occur in the benzilic ester rearrangement. Effecting the transformation of Equation 4 hinged then on whether the step designated by k_1 in Chart Three could occur. The dimethoxybenzilic ester

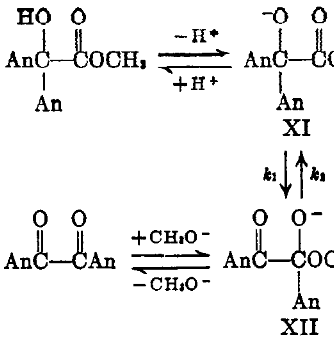


Chart Three

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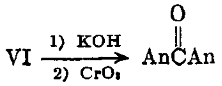
[7] V. Migrdichian, *The Chemistry of Organic Cyanogen Compounds*, Rheinhold Publishing Corp., New York, N. Y., 1947, Chap. 5.

[8] F. H. Westheimer, *J. Am. Chem. Soc.*, 58, 2209 (1938); I. Roberts and H. C. Urey, *J. Am. Chem. Soc.*, 60, 880 (1938).

[9] M. Bender and W. Glasson, *J. Am. Chem. Soc.*, 81, 1590 (1959).

(VI) was chosen for study to take advantage of the high migratory aptitude on the anisyl group and of any resonance stabilization of the incipient anisil. The probability of the occurrence of the step designated k_1 seemed real in view of the demonstrated occurrence of the reaction in Equation 3.[6]

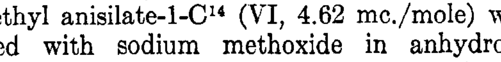
In an experiment with unlabeled methyl anisilate (VI), it was shown that an 80% recovery of the ester could be made after it was heated with sodium methoxide in anhydrous methanol for two days. In an experiment with labeled VI, it was shown that the ester could be degraded (Equation 5) by saponification and oxidation to unlabeled 4,4′-dimethoxybenzophenone. If the ester VI could be rearranged by Equation 4, this degradation would yield labeled dimethoxybenzophenone.



$$\mathrm{VI} \xrightarrow[\text{2) CrO}_3]{\text{1) KOH}} \mathrm{An}\overset{O}{\overset{\|}{C}}\mathrm{An} \qquad (5)$$

Methyl anisilate-1-C^{14} (VI, 4.62 mc./mole) was treated with sodium methoxide in anhydrous methanol at 99° for two days. An aqueous solution of potassium hydroxide was added to saponify the ester remaining in solution. The anisilic acid obtained was oxidized to dimethoxybenzophenone devoid of radioactivity; therefore, no rearrangement was detected.

Rearrangement of the ester was then attempted under more vigorous conditions. Methyl anisilate-1-C^{14} (4.62 mc./mole) was treated with sodium methoxide in anhydrous methanol at 200° for two days. The crude anisilic acid, which constituted the majority of the reaction product, was isolated and oxidized to dimethoxybenzophenone whose activity was about 0.03 mc./mole. The extent of rearrangement detected was no more than 0.5% and probably was within experimental error. These results at 200° are not unequivocal since at this temperature the rate of the displacement reaction (Equation 6),



$$\mathrm{VI} + CH_3O^- \longrightarrow \mathrm{An}\overset{HO}{\underset{An}{C}}\!-\!\overset{O}{\overset{\|}{C}}O^- + CH_3OCH_3 \qquad (6)$$

which probably gave rise to the acid analyzed, could be much greater than that of the rearrangement. That is, the lack of activity in the dimethoxybenzophenone resulting from the oxidation of the acid fraction may have been due to the fact that the acid was formed *via* the displacement reaction before any ester could rearrange. The neutral fraction remaining after treatment of methyl anisilate-1-C^{14} with methoxide ion at 200° was small and was not analyzed.

The only difference between the rearrangement in Equation 4, which does not occur at all in two days at 99°, and that of Equation 3, which occurs extensively in a few hours at 65°, is that in the latter a benzene ring is interposed between methoxyl and carbonyl. Apparently direct attachment of methoxyl as Y in system I so decreases the electronegativity of the carbonyl carbon that it cannot serve as a migration terminus. Yet there are apparent instances of reversal of the benzilic acid rearrangement itself,[10] for which, under the basic conditions employed, the migration terminus would be even more strongly deactivated, having an oxide ion attached as the Y group.

Considering the variety of groups in system I which have been observed to rearrange, it is surprising that no rearrangement has been found where X = R = anisyl and Y = methoxyl.

EXPERIMENTAL[11]

Reaction of benzil and o-tolyllithium. A solution of *o*-tolyllithium prepared from *o*-bromotoluene (8.6 g.) and lithium (0.7 g.) in 53 ml. of anhydrous ether was added dropwise to a stirred solution of benzil (10.5 g.) in anhydrous ether in a nitrogen atmosphere. The reaction mixture was hydrolyzed with dilute hydrochloric acid and ethereal layer was isolated, dried, and evaporated to an oil. The oil was vacuum distilled and the fraction with b.p. 200–225° (1.0 mm.) was crystallized from hexane and recrystallized from absolute ethanol. The yield of α-phenyl-2-methylbenzoin (III) was 1.8 g., m.p. 116–117° with or without admixture of an authentic sample.

Anisoyl cyanide-1-C^{14}. Anisoyl chloride (9.50 g., 0.056 mole) and cuprous cyanide-C^{14} (5.0 g., 0.056 mole, previously dried *in vacuo* over phosphorus pentoxide for 2 days) were placed in a 50-ml., one-necked flask equipped with a reflux condenser and drying tube. The flask was placed in a Wood's metal bath which was maintained at 120–130° for 3.5 hr. During this heating period the flask was removed from the bath and vigorously shaken at 30-min. intervals. Crude product was vacuum distilled (0.7 mm.) from the reaction mixture until the flask contained no more liquid. The solid distillate was crystallized and recrystallized from benzene-ligroin. The yield of anisoyl cyanide-1-C^{14} was 5.70 g. (62%) of colorless needles, m.p. 57–59° (lit.,[12,13] m.p. 60° and 63–64°).

Alcoholysis of anisoyl cyanide-1-C^{14}. (a) *Methyl p-methoxyphenylglyoxylate-1-C^{14}* (VIII). A solution of anisoyl cyanide-1-C^{14} (3.00 g., 0.0187 mole, dried *in vacuo* over phosphorus pentoxide for 1 day) and anhydrous methanol (0.60 g., 0.0187 mole, freshly distilled from magnesium methoxide) in 40 ml. of anhydrous ether was cooled to 0°. The solution was kept at this temperature by means of an ice bath while anhydrous hydrochloric acid (previously passed through concentrated sulfuric acid) was passed through it for 45 min. The solution was then seeded (with seeds obtained from a previous run on unlabeled material) and placed in the refrigerator for 3 hr. The crystals of *p*-methoxyphenylglyoxylimino methyl ether hydrochloride (VII) were collected, washed twice with anhydrous ether, and added to 50 ml. of water. The aqueous mixture was stirred for 5 min. and filtered. The precipitate was washed with water and re-

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(10) W. Huckel, *Theoretical Principles of Organic Chemistry*, Elsevier Publishing Co., New York, N. Y, Vol. 1, 1955, p. 463.

(11) Melting points and boiling points are reported uncorrected. In addition to the properties reported, spectroscopic properties (ultraviolet and infrared) and elemental analyses were determined to characterize the compounds prepared in this work. Carbon-14 analyses were made by the dry combustion and ionization chamber techniques.

(12) D. Vorlander, *Ber.*, **44**, 2465 (1911).

(13) F. Mauthner, *Ber.*, **42**, 191 (1909).

crystallized from dilute ethanol. The yield of methyl *p*-methoxyphenylglyoxylate-1-C^{14} (VIII) was 1.74 g. (48%), m.p. 50–51°, (lit.,[14] m.p. 54°), 8.80 mc./mole.

The imino ether hydrochloride had an indefinite melting point above 100°, after which the resolidified material remelted around 145–150°, *i.e.*, the melting point of 4-methoxyphenylglyoxylamide (X).

(b) *4-Methoxylphenylglyoxylamide* (X). A solution of anisoyl cyanide (9.0 g., 0.056 mole) and anhydrous methanol (2.24 g., 0.070 mole) in 60 ml. of anhydrous ether was cooled to 0°. The solution was kept at this temperature by means of an ice bath while anhydrous hydrochloric acid was passed through it for 60 min. The solution was then placed in the refrigerator (without seeding) for 3 days and the crystals which appeared were filtered, m.p. 147–150°, and added to 60 ml. of $2N$ hydrochloric acid. After being stirred for 30 min. at room temperature, the acidic mixture was heated to boiling, cooled, and filtered. The precipitate was dissolved in ether and the ethereal solution was extracted with 5% sodium carbonate. Acidification of the basic aqueous extract yielded 4-methoxyphenylglyoxylic acid, m.p. 91–93° (lit.,[15] m.p. 93°) and evaporation of the ethereal solution yielded 4-methoxyphenylglyoxylamide (X), m.p. 148–149° (lit.,[13] m.p. 151–152°).

(c) *Methyl anisate* (IX). A solution of anisoyl cyanide (10.0 g., 0.062 mole) in 100 ml. of anhydrous methanol (distilled from magnesium methoxide) was cooled to 0°. The solution was kept at this temperature by means of an ice bath while anhydrous hydrochloric acid (previously passed through concentrated sulfuric acid) was passed through it for 10 min. The solution was placed in a refrigerator for 8 days, diluted with 300 ml. of water, and extracted with ether. The ethereal extract was washed with 5% sodium bicarbonate—acidification of which yielded no acid—dried, and evaporated. The solid residue was recrystallized from aqueous methanol. The yield of methyl anisate (IX) was 9.0 g. (88%), m.p. 46–48° alone or admixed with an authentic sample.

Hydrolysis of anisoyl cyanide. A mixture of 200 ml. of concd. hydrochloric acid and anisoyl cyanide (9.0 g., 0.049 mole) was stirred for 2 weeks at room temperature. The mixture was extracted five times with 100-ml. portions of ether. The combined ethereal extract was washed with 50-ml. portions of 10% sodium carbonate until no precipitate appeared upon acidification of the sodium carbonate solution. The combined acidified sodium carbonate solution yielded approximately 7.0 g. of solid material, which was recrystallized twice from benzene-hexane to yield 4.0 g. of product, m.p. 88–90° (lit.,[16] for *p*-methoxyphenylglyoxylic acid, m.p. 93°). When more vigorous hydrolytic conditions were applied to the anisoyl cyanide, anisic acid was obtained.

Methyl anisilate-1-C^{14} (VI). The Grignard reagent prepared from *p*-bromoanisole (4.00 g., 0.021 mole) and magnesium (0.52 g., 0.021 mole) in 25 ml. of anhydrous ether was added to a solution of methyl *p*-methoxyphenylglyoxylate-1-C^{14} (3.20 g., 0.017 mole, 8.80 mc./mole) in 100 ml. of anhydrous ether. A heavy yellow precipitate appeared during addition; stirring was continued for 15 min. after addition was complete. After hydrolysis with dilute hydrochloric acid, the ether layer was separated, dried, and evaporated. The residue, a yellow oil which solidified, was recrystallized from benzene-ligroin to yield 1.1 g. of methyl anisilate, m.p. 109–110°. To the supernatant liquid from the recrystallization was added 1.1 g. of unlabeled methyl anisilate and a recrystallization carried out in the usual manner; the recovery was 0.85 g., m.p. 106–108°, 2.56 mc./mole, from which it may be calculated that another 0.45 g. of reaction product had been isolated. The total yield of methyl anisilate was thus 1.55 g. (22%). The labeled product was mixed with 0.5 g. of unlabeled material and the entire amount recrystallized from benzene-ligroin to obtain 1.9 g. of methylanisilate-1-C^{14} (VI), 4.62 mc./mole, m.p. 110.0–111.5° (lit.,[16] m.p. 110.0–110.5°).

Degradation of methyl anisilate-1-C^{14} to benzophenone. Two and one half milliliters of freshly boiled water was added to 0.6 mole of sodium methoxide in 10 ml. of methanol solution. One and one quarter milliliters of this solution was added to methyl anisilate-1-C^{14} (100 mg., 4.62 mc./mole) contained in a small glass vial. The vial was sealed and placed in a steam bath for 50 min. The contents of the vial were poured into 10 ml. of water and the aqueous solution was washed with ether, acidified with hydrochloric acid, cooled, and extracted with two 25-ml. portions of ether. The combined ethereal extract was dried and evaporated to leave 71.5 mg. (75%) of crude anisilic acid-1-C^{14}. To a solution of the crude acid in 3 ml. of warm glacial acetic acid was added a solution of chromium trioxide (25 mg., 0.25 mmole) in 2 ml. of glacial acetic acid containing 2 drops of water. The resulting solution was heated on a steam bath for 30 min. and poured into 15 ml. of water. The aqueous mixture was extracted with three 20-ml. portions of ether. The combined ethereal extract was washed with aqueous sodium carbonate, dried, and evaporated until 4 ml. remained. The residual solution was cooled and the ether decanted from the crystals which appeared, which were washed with ether and dried *in vacuo*. The yield was 26.5 mg. of 4,4'-dimethoxybenzophenone, m.p. 142–144° (lit.[17] 144–145°), <0.02 mc./mole.

Treatment of methyl anisilate-1-C^{14} with sodium methoxide at 99°. To 10 ml. of anhydrous methanol (distilled from magnesium methoxide) contained in a nitrogen filled 50-ml., round bottomed flask, was added 70 mg. of sodium metal. One milliliter of the resultant solution was added to methyl anisilate-1-C^{14} (100 mg., 4.62 mc./mole) contained in a small, carefully dried vial, previously flushed with nitrogen. The vial was sealed and placed in a 99° oven for 2 days. The tube was opened and 0.25 ml. of $1.25N$ potassium hydroxide added; the tube was sealed again and placed in a steam bath for 50 min. The contents of the tube were processed in the manner described in the preceding experiment to obtain 4,4'-dimethoxybenzophenone, m.p. 140–141.5°, <0.02 mc./mole.

Treatment of methyl anisilate-1-C^{14} with sodium methoxide at 200°. To 10 ml. of anhydrous methanol (distilled from magnesium methoxide) contained in a nitrogen filled 50-ml., round bottomed flask was added 70 mg. of sodium metal. Two milliliters of the resultant solution was added to methyl anisilate-1-C^{14} (200 mg., 4.62 mc./mole) contained in a carefully dried nitrogen filled Carius tube. The tube was sealed and placed in an oven at 200 ± 6° for 2 days. The tube was opened and its contents poured into 15 ml. of water. The aqueous mixture was extracted three times with ether, filtered, acidified with hydrochloric acid, and extracted three more times with ether. The combined ethereal extract from the acid solution was dried and evaporated to leave 163 mg. of impure anisilic acid-1-C^{14}. The combined ethereal extract from the basic solution was dried and evaporated to leave 50 mg. of brownish semisolid, which was not further examined. The crude acid was oxidized with 60 mg. of chromic acid by the procedure described above to obtain 4,4'-dimethoxybenzophenone, m.p. 142–144°, ~0.03 mc./mole.

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[14] F. Kogl and H. Becker, *Ann.*, **465**, 236 (1928).

[15] L. Bouveault, *Bull. soc. chim. France*, [3], **17**, 943 (1897).

[16] W. E. Bachmann and H. R. Sternberger, *J. Am. Chem. Soc.*, **56**, 170 (1934).

[17] M. Bosler, *Ber.*, **14**, 328 (1881).