Advances in
Physical Organic Chemistry

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VOLUME 2

1964

Academic Press, London and New York

ACADEMIC PRESS INC. (LONDON) LTD.
Berkeley Square House,
Berkeley Square, London, W.1.

U.S. Edition published by
ACADEMIC PRESS INC.
111 Fifth Avenue
New York 3, New York

Library of Congress Catalog Card Number: 62-22125

PRINTED IN GREAT BRITAIN BY
WILLMER BROTHERS AND HARAM LIMITED, BIRKENHEAD

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EDITOR'S PREFACE

THE contents of Volume 2 have been selected from various parts of Physical Organic Chemistry in which important advances are currently being made, although not all the topics are at comparable stages of development.

Thanks to the excellent cooperation of authors and publishers it has again been possible to keep the time between the receipt of manuscripts and the publication date down to a few months. Future volumes with a similar publication schedule are being planned to appear at yearly intervals.

I shall be grateful for suggestions of topics and other constructive ideas which may help to maintain and improve the value of the series as a guide to current and signpost to future advances of the subject.

V. GOLD

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October 1963

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ISOTOPES AND ORGANIC REACTION MECHANISMS

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In the past generation remarkable advances in separation procedures, in the invention of new analytical techniques, in physical measuring devices, and in chemical theory have combined to aid in the establishment of a new field of organic chemistry concerned with reaction mechanism. This field is an important part of "physical organic chemistry," for in its development many of the concepts of the physical chemist have been coupled with purely organic chemical operations. Thus a general classification of the methods for studying organic

[1] Operated for the Atomic Energy Commission by Union Carbide Corporation.

reaction mechanisms has emerged. Although most of these can be interrelated, and sometimes overlap, the following five categories commonly apply to studies of reaction mechanisms:

1. Product Identification and Stoichiometry
2. Identification of Intermediates by Physical Methods
3. Kinetic Studies
4. Stereochemical Studies
5. Isotopic Studies

Gould (1959), in particular, has discussed the methods of physical organic chemistry, and has outlined sub-groups of the foregoing general classification. The application of radioactive isotopic investigations to organic reaction mechanism studies has been reviewed by Hans Schmid (1960), who discussed the principles involved, some false conclusions which might be drawn in the use of radio-active isotopes, and some applications to specific organic reactions.

It is the purpose of this chapter to classify and discuss isotopic investigations in the field of physical organic chemistry, and to present sufficient examples of each type of experiment to acquaint the reader with the kind of information attainable through the use of the very powerful and penetrating scientific scrutiny offered by the isotopic method. Since the chapter is not intended to be a complete and exhaustive survey of the field, the author has selected material for discussion on a subjective basis, and with particular reference to the rôle of "classical" and "non-classical" carbonium ions in certain reaction mechanisms. The techniques of nuclear magnetic resonance as applied to isotopes might properly be discussed, but these techniques as well as the analytical procedures for determining both radioactive and stable isotopes, such as Geiger-Müller, proportional, and scintillation counting, ion-current measurements, infrared and mass spectrographic techniques, density measurements and others, have been excluded for the reason that these subjects have been very adequately discussed elsewhere (Pople *et al.*, 1959; Snell, 1962; Tolbert and Siri, 1960).

Inherent in the classification of isotopic investigation employed here is the disadvantage that it does not coincide with the usual classifications of organic chemistry—that is, by type of compound or by class of reaction. It has the advantage, however, that it allows the isotopic method to be presented in an orderly fashion without being forced into a pattern which, although useful in many textbooks and treatises, would unnecessarily encumber the present discussion. The classification is outlined in the table of contents at the head of the chapter.

It would be an injustice to the scientists who worked so diligently on reaction mechanisms before the general availability of carbon-13,

carbon-14, oxygen-18, deuterium and tritium to imply that the tracer technique is peculiar to experiments in which isotopic labels are employed. For example, Lauer and Filbert (1936) and Hurd and Schmerling (1937), respectively, both demonstrated the 1,3-shift during the Claisen rearrangement by using alkyl or aryl groups to identify the carbon atoms 1 and 3 of the allyl group. Similarly, from the esterification of ethyl mercaptan with benzoic acid, and of methanol with thiobenzoic acid, it was deduced that the oxygen atom of methanol must remain intact during esterification with benzoic acid, as was later confirmed (Roberts and Urey, 1938) with the help of oxygen-18. However, the general availability of deuterium and tritium and, in particular, of carbon-14 has made it relatively simple to gain information which was previously either impossible or very difficult to obtain. It has also opened up new avenues for scientific imagination which have rewarded the investigator by yielding much clearer concepts of the fundamental processes of organic chemistry.

I. Experiments With One Label

A. *The Isotopic Dilution Method*

The determination, with the aid of an isotope, of the yield or quantity of a given material usually depends upon the use of the "carrier" or "dilution" technique. To illustrate this principle, consider a mixture containing, among other things, an unknown quantity (x) of an organic compound. Suppose that it is possible, by the proper application of physical techniques such as fractional crystallization, extraction or distillation, to isolate a small portion of the compound in pure form. To determine its weight in the mixture, it is necessary only to (1) add a carefully weighed amount (D_0) of the compound which is labeled with carbon-14, tritium, or other radioactive isotope and whose specific radioactivity (A_0) is known; (2) homogenize by dissolving the original mixture plus the labeled addend; (3) isolate a small portion of pure compound from the solution and (4) determine the new specific radioactivity (A_1) of the sample. Knowing the weight of labeled compound added and the amount of dilution of the labeled sample with non-radioactive compound, we may calculate the weight (x) as follows:

$$x = \frac{A_0 D_0}{A_1} - D_0 \tag{1}$$

The foregoing example is one in which the product to be determined is non-radioactive, whereas the added material (the addend) is radioactive. One limiting factor is that the weight of radioactive addend

should not be very large in relation to the unknown weight, for if A_0 and A_1 approach each other in value there is a corresponding decrease in precision. It is possible to use the reverse of the above technique, in which the compound to be determined is radioactive and the addend is non-radioactive. In such a determination the specific radioactivity of the compound to be determined must be known. An aliquot of the reaction mixture is diluted with a known amount of the inactive product, and a sample of the diluted compound is isolated and assayed for radioactivity. The measured radioactivity A_1 is related to the yield x (in milligrams) by the equation

$$A_1(D_1 + x) = A_0x \tag{2}$$

in which A_0 is the radioactivity of the undiluted product, and D_1 is the weight of diluent (addend) added. If D_1 is very large with respect to x, then equation (1) becomes

$$A_1D_1 = A_0x \tag{3}$$

The radioactivities A_0 and A_1 may be expressed per unit of weight or per mole of compound.

In the foregoing examples the yields of the product or products have been determined when (1) the molar radioactivity of the product or of the addend and (2) the weight of addend have been known. In many experiments involving radioactive products the exact molar radioactivities (A_0, equation 2) of the materials produced may not be known. In such cases the double-dilution method may be useful, and both yield (x) and radioactivity (A_0) may be determined by means of the following relation:

$$A_2(D_1 + D_2 + x) = A_1(D_1 + x) = A_0x \tag{4}$$

in which x is the unknown weight of radioactive product, and A_0 is the unknown specific or molar radioactivity of the product. The quantities A_1 and A_2 are the radioactivities, appropriately expressed, of the reisolated products after the successive additions of D_1 and D_2 weights, respectively, of non-radioactive diluent. The application of this method to the simultaneous determination of both yield and radioactivity of labeled chrysene has been discussed by Mayor and Collins (1951).

The application of the radioactivity dilution technique to the determination of yield or radioactivity of a product is not without its drawbacks. The most serious of these may be illustrated as follows. Suppose a given reaction product consists of two compounds, A and B, both of which possess equal molar radioactivities. It is desired to determine the yield of A through the dilution method by the addition of a weighed

amount of non-radioactive A. Compound B, not being diluted, will now be correspondingly more radioactive than A, and will thus be present in the diluted mixture as a highly radioactive contaminant. If A has been diluted 100 times, then contaminant B need be present only to the extent of 0·1 mole percent to cause an error of 10% in the observed molar radioactivity of A; that is, the observed radioactivity of A will be greater than the true value by nearly 10%. To remove the contaminating B, it is then necessary to add some non-radioactive B to the mixture, repurify A and redetermine its radioactivity. The process must be repeated until the repurified sample of A has a constant radioactivity content between two consecutive operations. It is essential to the proper use of this procedure for the investigator to have some prior knowledge of probable radioactive contaminants; it is known as the "hold-back" carrier technique, and has been nicely discussed and illustrated by DeWitt *et al.* (1956).

A special and very useful application of the isotope-dilution method is in the determination of optical purity of resolved or partially racemic optical enantiomers. Berson and Ben-Efraim (1959) derived the following equations:

$$C_+ = \frac{xC_0}{2}\left[\frac{1}{E + \dfrac{x+R}{2}}\right] \tag{5}$$

$$C_- = \frac{xC_0}{2}\left[\frac{2}{x+R}\right] \tag{6}$$

$$C_\pm = 1/2\left[\frac{xC_0}{2} \cdot \frac{1}{E + \dfrac{x+R}{2}}\right] + 1/2\,\frac{xC_0}{2}\left[\frac{2}{x+R}\right] \tag{7}$$

$$B = R + E \tag{8}$$

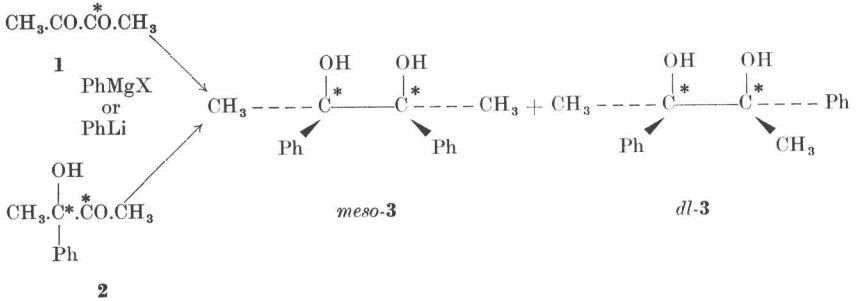
in which

B = weight of a solid substance B of unknown optical purity
C_0 = specific radioactivity (or atom percent excess) of racemic B used as addend in isotopic-dilution analysis
x = weight of racemic addend B
C_+ = specific radioactivity (or atom percent excess) of (+)-enantiomer after homogenization of B and the addend
C_- = specific radioactivity (or atom percent excess of) (−)-enantiomer after homogenization of B and the addend

$C_{\pm}$ = specific radioactivity of racemate after homogenization of B and the addend
R = weight of racemate in B
E = excess weight of one enantiomer (+) or (−) in B.

Berson and Ben-Efraim (1959) point out that the racemic modification of weight x and specific activity (or atom-percent excess) C_0, when added to the partially resolved mixture of weight B, followed by homogenization of the whole, can be described exactly by equations (5)–(8), in which the symbols have the significance defined in the preceding paragraph. After homogenization, the racemic material—which can be isolated from the mixture by crystallization or other means—consists of enantiomers which do not possess equal isotopic contents or specific activities. Therefore, $C_{\pm}$, the specific activity of the racemate, can be obtained by a weighted average (equation 7) of C_+ (equation 5) and C_- (equation 6). If the rotation of optically pure B is known, the enantiomeric purity of B in the mixture can be calculated from the specific activity of reisolated, optically pure B, or from the isotopic compositions and rotations of two suitable fractions isolated from the mixture, provided the differences in the determinations are large enough. The most useful aspect of the method, however, arises when the rotation of optically pure substance is unknown. By isolation of racemate followed by a determination of its specific activity, the optical purity of the original mixture B can be calculated from equations (7) and (8). From the optical rotation of the original, partially racemic B, and from equation (8), the rotation of optically pure enantiomer can then be calculated.

An interesting example of the use of the isotope-dilution method to gain mechanistic information was provided by Stocker *et al.* (1960), who demonstrated that in the addition of phenyl-lithium and a series of Grignard reagents to biacetyl (**1**) and phenylacetoin (**2**), the *meso:dl* ratio changed in the order 0·1 (PhLi); 0·5 (PhMgI); 2·3



(PhMgBr) and 3·4 (PhMgCl). Compounds **1** and **2** were labeled with carbon-14 as shown with the asterisk (*), and the yields of *meso*-**3** and *dl*-**3** 2,3-diphenylbutanediol-2,3 were determined through the isotopic-dilution method just discussed. Cram and Kopecky (1959) had indicated that the addition of phenylmagnesium bromide to biacetyl follows the "rule of steric control of asymmetric induction" (Cram and Abd Elhafez, 1952) if one assumes only that a methyl group possesses a smaller effective bulk than phenyl, and thus implied that *dl*-**3** should always be formed in greater yield than *meso*-**3** in the reactions of **1** and **2** with phenyl magnesium halides. The results of Stocker *et al.* show that the situation is considerably more complicated than indicated by the previous investigators, since the *meso*-**3**:*dl*-**3** ratio is actually dependent upon the *halide* in the halobenzene used to prepare the Grignard reagent.

B. *Simple Tracer Studies*

1. *The determination of radioactivity distributions and migratory aptitudes*

Before it is possible to consider the intimate mechanism of a reaction, it is important to know the identities and the yields of the products. When these products are different chemical compounds, the isotope-dilution method, just discussed, is very useful for this purpose. There are many chemical reactions, however, which proceed by *two or more different paths* to the same chemical entity. By proper choice of an isotopic label, coupled with unequivocal degradative methods, the relative contributions of these different paths can often be evaluated.

a. *Fused ring hydrocarbons.* Collins and his co-workers (Collins, 1948; Collins and Benjamin, 1953; Collins *et al.*, 1951; Collins *et al.*, 1953a, b) incorporated carbon-14 into phenanthrene and several of its derivatives, as well as into benz[a]anthracene and chrysene by means of the dehydration-rearrangement [Wagner rearrangement] of the appropriately substituted 9-fluorenyl (methanol-^{14}C) compounds. In Charts I and II are given two examples—the syntheses and degradative procedures for benz[a]anthracene-5,6-$^{14}C_1$ and chrysene-5,6-$^{14}C_1$, respectively. The number under each formula represents the relative molar radioactivity of the particular compound. From Chart I it is apparent that the fraction of radioactivity (0·48) remaining in benz[a]fluorenone-9-^{14}C (**12**) represents the fraction of total carbon-14 which was incorporated into the 5-position of labeled benz[a]anthracene [**8**]. The 6-position thus contains 0·52 times the molar radioactivity of **8**. In the calculation of the distribution of carbon-14 between the 5- and 6-carbons of the labeled chrysene [**16**, Chart II], it must be remembered

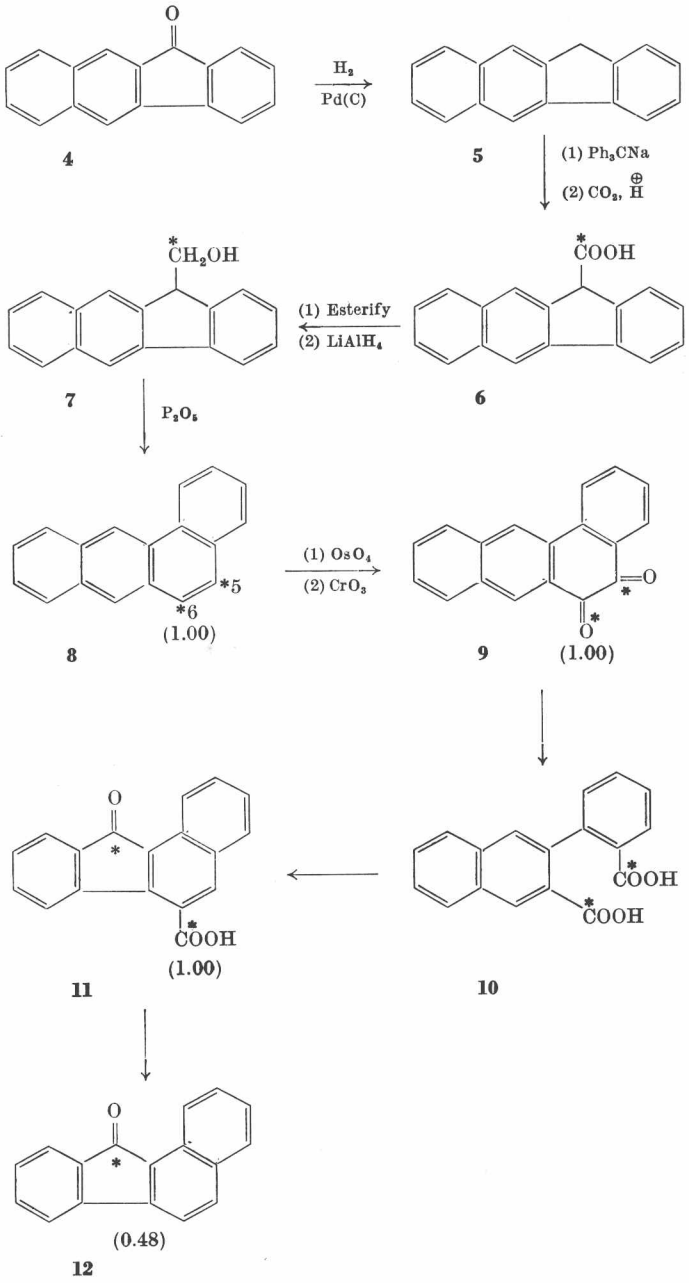

O
H_2
Pd(C)
4
5
(1) Ph_3CNa
(2) CO_2, $\overset{\oplus}{H}$
*CH_2OH
*COOH
(1) Esterify
(2) $LiAlH_4$
7
6
P_2O_5
(1) OsO_4
(2) CrO_3
*5
*6
(1.00)
8
9
(1.00)
O
*COOH
*COOH
(1.00)
11
10
(0.48)
12

CHART I

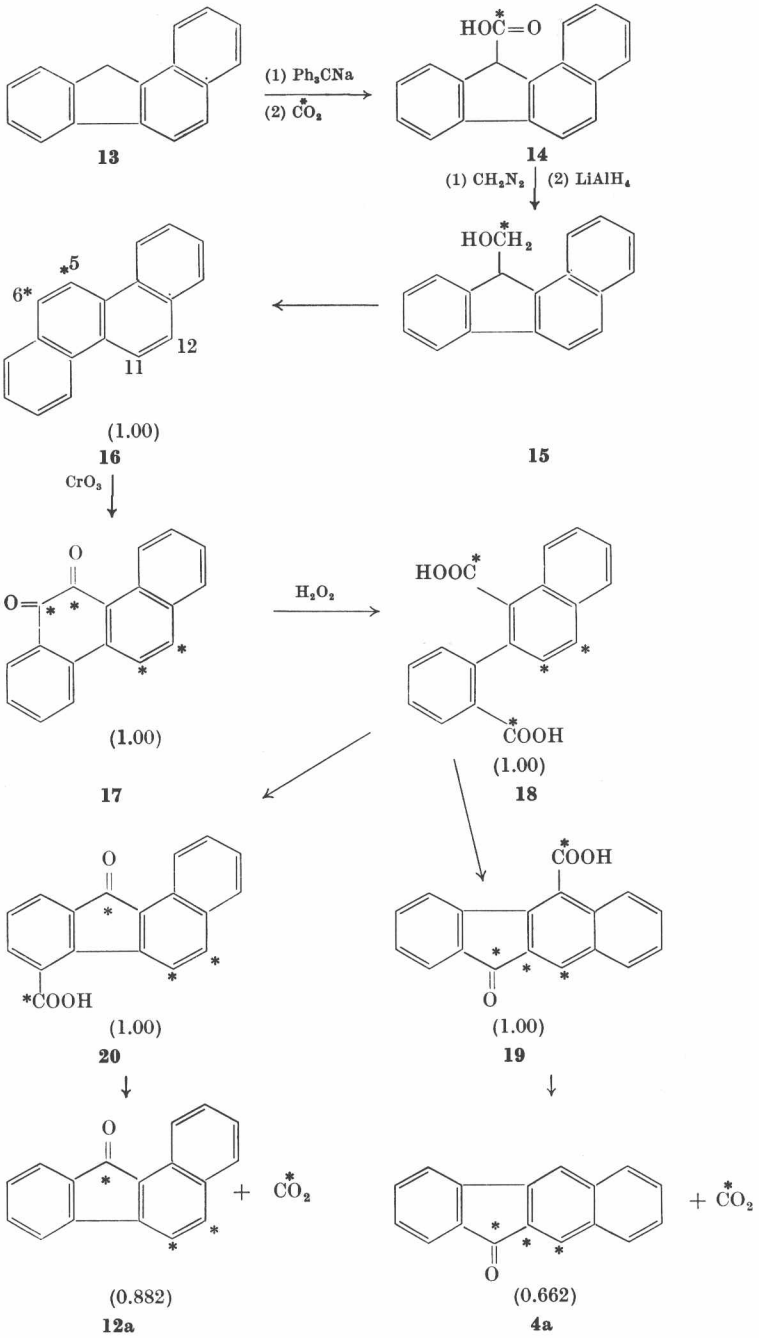


CHART II