TABLE IV

YIELDS OF PRODUCTS FROM THE DEAMINATION OF VII AS DETERMINED BY THE ISOTOPIC DILUTION METHOD

Experiment	3	4	5
Weight of hydrochloride of VII (grams)	1.5196	1.5061	1.4379
Radioactivity of VII (mc./mole)	5.725 ± 0.029	5.725 ± 0.029	5.725 ± 0.029
Experimental conditions	0.36 g. $NaNO_2$	0.37 g. $NaNO_2$	0.36 g. $NaNO_2$
	115 ml. H_2O	130 ml. H_2O	130 ml. H_2O
	3 hr. at 83–85°	1 hr. at 99°	6.5 hr. at 58°
Aliquot used to determine yields IX	2/5	2/5	2/5
Aliquot used to determine yields VIII	2/5	2/5	2/5
Weight of dead carbinol added to aliquot (grams) IX	2.2281	2.2136	1.6350
Weight of dead carbinol added to aliquot (grams) VIII	1.7108	2.0514	1.6012
Radioactivity of diluted carbinol (mc./mole) IX	0.5902	0.3585 ± 0.0014	0.4539 ± 0.0029
Radioactivity of diluted carbinol (mc./mole) VIII	.4450	.2269 ± .0012	.2682 ± .0004
Aliquot used to determine yield of VIII + X			1/5
Wt. of dead VIII added to aliquot (grams)			1.0020
Radioactivity of bromide: Derivative of VIII and X (mc./mole)			0.5104 ± 0.0048

VIII. The entire mixture was then treated in exactly the same way as described for the preparation of 1,1-diphenyl-2-*p*-tolyl-2-bromoethylene (XII), above. The bromoölefin was then purified by four crystallizations from ethanol and assayed for radioactivity. It was then calculated from the data of Table IV, experiment 5, that the combined yield of VIII and 1,1-diphenyl-2-*p*-tolyl ethylene (X) is 38.3%. The combined yield of IX and XI, obtained by difference, is 61.7%. This gives a *p*-tolyl/phenyl migration ratio of 1.24 for the rearrangement of VII to produce *both* carbinols (VIII and IX) and olefins (X and XI).

Oxidations.—The residue of mixed carbinols V and VI from the rearrangement of a sample of IV was divided into two portions. One portion was oxidized with potassium permanganate as described by Ciereszko and Burr.[13] The second portion was dehydrated with phosphorus pentoxide and the 4-methylstilbene was also oxidized as described. The benzoic and terephthalic acid fractions from the oxidations were isolated. Benzoic acid was purified by sublimation, m.p. 121.2°. Terephthalic acid was taken up in sodium carbonate solution. The solution was decolorized with Norite while hot and then acidified. The precipitated terephthalic acid was removed from the still hot solution by filtration. It was washed with hot water followed by alcohol and dried. The acid was treated with diazomethane, and the dimethyl ester was purified by crystallization from methanol, m.p. 141°, and assayed for radioactivity. The data are recorded in Table II.

Radiochemical Structure Determination of Compounds V, VII, VIII and IX.—The purified phenylurethan of carbinol V, 1.5 g., which was recovered from the carbon-14 dilution experiment 2, was treated with 5 g. of chromic oxide in acetic acid containing a small quantity of sulfuric acid. After heating the mixture on the steam-bath for 15 minutes, oxidation was complete. The oxidation mixture yielded 116 mg. of terephthalic acid and a small quantity of dark material. The terephthalic acid, after precipitation from sodium carbonate solution, had a radioactivity assay of 0.678 mc./mole. The phenylurethan of carbinol VI from experiment 2 was treated similarly and a very small quantity of terephthalic acid was obtained. This had a radioactivity assay of 0.0095 mc./mole. Carbinol VIII from experiment 3 was oxidized with chromic acid in acetic acid. Benzophenone was recovered and converted to the 2,4-dinitrophenylhydrazone derivative for purification and radioactivity assay. The derivative was non-radioactive. Likewise the 2,4-dinitrophenylhydrazone of 4-methylbenzophenone, obtained by chromic acid oxidation of carbinol IX in experiment 2, was non-radioactive. The rearrangements of compounds IV and VII, therefore, take place essentially without scrambling of the chain carbon atoms.

Analytical Determinations.—Carbon and hydrogen analyses were performed by the Huffman Microanalytical Laboratories, Wheatridge, Colorado. Carbon-14 determinations were carried out as described previously.[6-11]

OAK RIDGE, TENNESSEE

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, MERCK & CO., INC.]

The Reaction of Epoxides with Anhydrous Hydrogen Fluoride in the Presence of Organic Bases. The Preparation of 9α-Fluoro-4-pregnene-11β,17α,21-Triol 3,20-Dione 21-Acetate and Its 1-Dehydro Analog

BY RALPH F. HIRSCHMANN, RICHARD MILLER, JAMES WOOD AND R. E. JONES

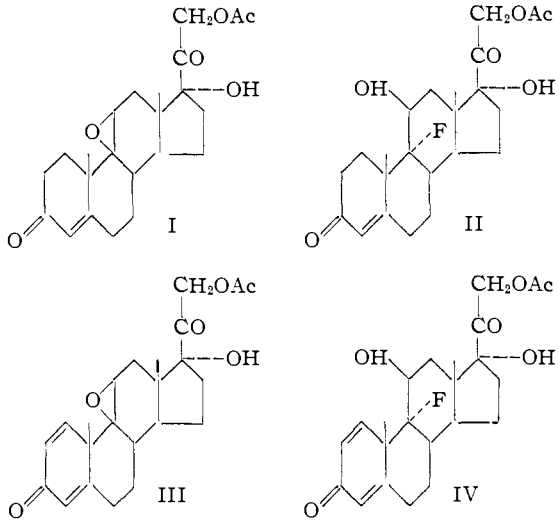
RECEIVED MAY 4, 1956

It has been possible to effect the conversion of 9β,11β-epoxy-4-pregnene-17α,21-diol-3,20-dione 21-acetate (I) to 9α-fluoro-4-pregnene-11β,17α,21-triol 21-acetate (II) in 75% yield through the use of anhydrous hydrogen fluoride in organic bases. In this manner the formation of the by-product described by Fried and Sabo is minimized. The analogous 1-dehydro-compound IV was likewise prepared in 75% yield from the corresponding epoxide III. The use of solutions of anhydrous hydrogen fluoride in organic bases, such as tetrahydrofuran, is suggested whenever a source of fluoride ions, soluble in organic media, is required.

In a recent communication[1] Fried and Sabo announced the conversion of 9β,11β-epoxy-4-pregnene-17α,21-diol-3,20-dione 21-acetate (I) to 9α-fluoro-4-pregnene-11β,17α,21-triol-3,20-dione 21-acetate (II) with anhydrous hydrogen fluoride in ethanol-free chloroform solution in about 50% yield. The product was found to be of great pharmacological importance since it possesses about ten times the glucocorticoid activity of hydrocortisone acetate.[1] In addition to II, Fried and Sabo isolated an unsaturated alcohol,[2] isomeric with I, from the hydrofluorination reaction.

(1) J. Fried and E. F. Sabo, THIS JOURNAL, **76**, 1455 (1954).

(2) R. P. Graber, C. S. Snoddy, Jr., and N. L. Wendler [*Chemistry and Industry*, 57 (1956)] have recently described the preparation of 17α-hydroxy-8(14)-dehydrocorticosterone acetate or its C_9-epimer by the reaction of I with 60% perchloric acid in chloroform solution at 0°. The characteristics of this unsaturated alcohol were found to be essentially the same as those of the by-product of Fried and Sabo.



In our hands the conversion of I to pure II proceeded in less than 50% yield when carried out in ethanol-free chloroform with anhydrous hydrogen fluoride. Paper strip chromatography revealed that the by-product was formed in very significant amounts. These data suggested that the yield of the hydrofluorination reaction might be improved by increasing the effective concentration of fluoride ions in the reaction mixture. Unfortunately the readily available inorganic fluorides were found to be insoluble in chloroform and in several other suitable solvents. This difficulty could be overcome, however, by carrying out the reaction in the presence of a mixture of anhydrous hydrogen fluoride and an organic proton acceptor. Indeed, the use of solutions of hydrogen fluoride in a variety of bases such as pyridine, tetrahydrofuran and aliphatic alcohols improved the yield of the desired fluorohydrin II relative to that of the by-product. In the experiments discussed below, tetrahydrofuran served as the Lewis base and chloroform was added merely to solubilize the epoxide acetate. The resulting reaction mixtures were homogeneous. The importance of the presence of a base was further demonstrated by the observation that anhydrous hydrogen fluoride alone is not an adequate source of fluoride ions. Treatment of the epoxide I with anhydrous hydrogen fluoride at −80° for 4.5 hours gave the by-product as the major crystalline product. In contrast, the desired fluorocompound could be obtained in fair yield from the addition of the epoxide to a solution of ammonium fluoride–hydrogen fluoride in anhydrous hydrogen fluoride at 0°, in spite of the fact that the lower temperatures favor the formation of II relative to that of the by-product as ascertained by us by paper strip techniques. In this system ammonia served as the base component.

Since the interaction of hydrogen fluoride with tetrahydrofuran reduces the acidity of the reaction medium, it was to be anticipated that the presence of very large amounts of base would prevent the acid-catalyzed opening of the 9(11)-epoxy-linkage. This proved to be the case. Thus, when the molar ratio of hydrogen fluoride to tetrahydrofuran was reduced to 0.4, only starting material was isolated, although the hydrogen fluoride was present in large excess relative to the steroid.[3]

This observation provided a simple method for a kinetic study of the reaction, since the reaction of aliquots could be stopped by the addition of an excess of tetrahydrofuran at desired time intervals. The rate of disappearance of the epoxide was determined polarimetrically,[4,5] because both II and the by-product are markedly more dextrorotatory than I.

Kinetic studies revealed that when hydrogen fluoride and tetrahydrofuran were employed in a molar ratio of about 1.65 or greater, the epoxide reacted at a rate suitable for preparative purposes even at the low temperatures desired (−30°).[6] Thus in a preparative experiment (acid–base ratio 1.94) the fluorohydrin was obtained in 65% yield. The rate studies led to a further refinement by focusing attention upon the importance of the order in which the reactants are combined. In the experiment just described (65% yield) a solution of the epoxide in a mixture of chloroform and tetrahydrofuran at about −65° was added to a solution of hydrogen fluoride in tetrahydrofuran likewise held at −65°. A surprisingly high initial rotation was observed. This can be attributed to the exothermic reaction produced when tetrahydrofuran is dissolved in hydrogen fluoride. It is preferable to add a chloroform solution of the epoxide free of tetrahydrofuran to the precooled mixture of tetrahydrofuran and hydrogen fluoride. This precaution, which was observed in the experiments presented in Fig. 1 and Table I resulted in a further improvement in yield. Thus a preparative run represented by curve 4, Fig. 1, afforded analytically pure 9α-fluorohydrocortisone acetate in 75% yield.

When the same procedure was applied to a Δ^1-unsaturated epoxide, 9β-11β-epoxy-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate (III), large amounts of unchanged starting material were recovered. It was found, however, that the reaction proceeded nicely at a higher temperature (0°) in the presence of a lesser amount[7] of tetrahydrofuran. In this manner the desired product

(3) As stated above, we observed that the hydrofluorination could be carried out in ethanol. On the other hand, Dr. R. P. Graber of these laboratories advised us that when chloroform is used as the solvent, no reaction occurs unless the chloroform is free of alcohol as specified by Fried and Sabo.[1] The leveling effect provides an explanation for this paradox. Since the solubility of hydrogen fluoride in chloroform is of a low order, the ethanol present in commercial chloroform prevents the acid-catalyzed opening of the epoxide. On the other hand, hydrogen fluoride is sufficiently soluble in ethanol to enable us to prepare an ethanol solution having a sufficiently high ratio of hydrogen fluoride to ethanol to allow the hydrofluorination reaction to occur.

(4) The lowest specific rotation for I obtained in the hydrogen fluoride–tetrahydrofuran–chloroform system was 14.4°, whereas the values for II and the by-product were +104 and +226°, respectively.

(5) The fluorohydrin 21-acetate was found to be stable in the reaction medium. The rotation of a solution of II in hydrogen fluoride–tetrahydrofuran–chloroform was unchanged after 26 hours at room temperature. The rotation of the by-product was unchanged after four hours at −32°, but on longer standing at room temperature the rotation gradually increased.

(6) No reaction occurred when a solution containing 0.33 mole of hydrogen fluoride, 0.23 mole of tetrahydrofuran and 0.010 mole of epoxide in chloroform (total volume *ca.* 51 ml.) was allowed to stand at −65°. Increasing the ratio of hydrogen fluoride to tetrahydrofuran will doubtless lower the minimum temperature at which the epoxide begins to react.

(7) Only 0.131 mole of tetrahydrofuran were employed per 0.333 mole of acid.

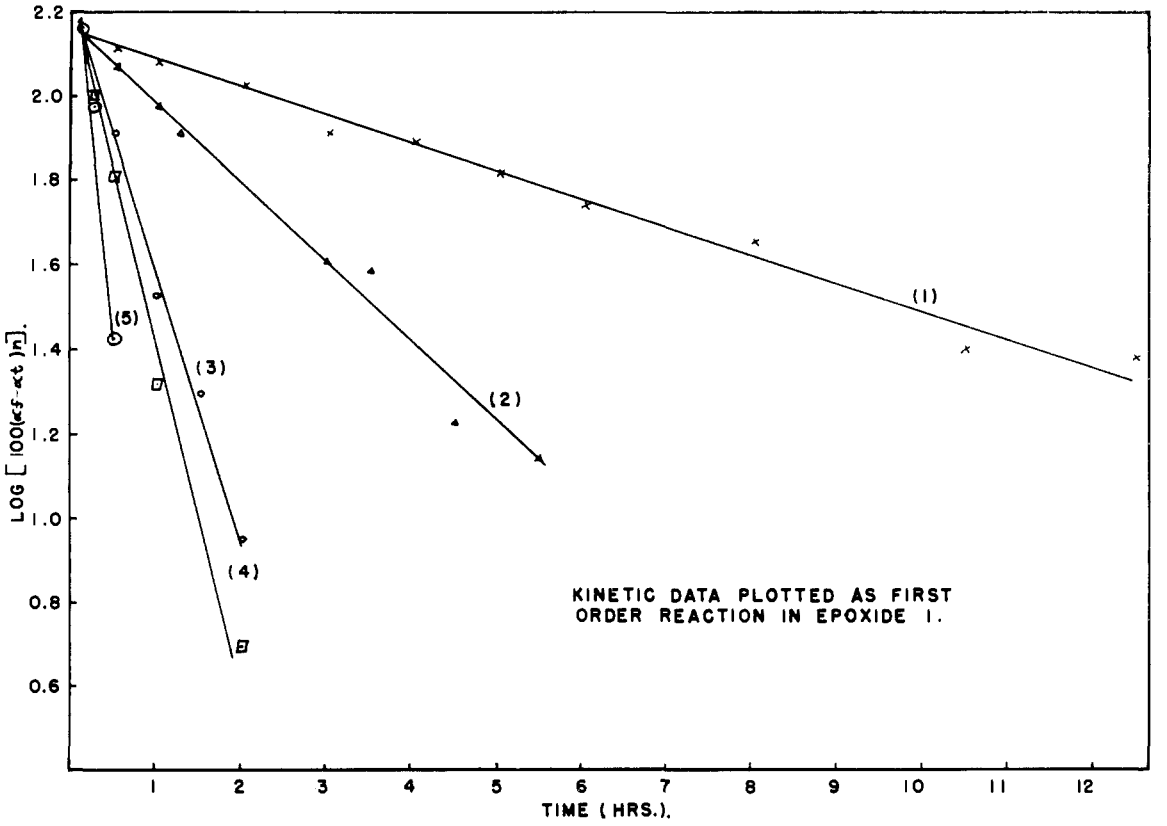


Fig. 1.

IV was isolated in 75% yield.[8] It is noteworthy that while the epoxide I is more reactive than the 1-dehydro-analog III, the latter apparently did not give a by-product analogous to the unsaturated alcohol derived from I.

It is felt that the procedures described above should prove useful not only in the formation of fluorohydrins from epoxides,[9] but should also be of value whenever a source of fluoride ions in organic solvents is required. The utility of the method is increased by the fact that the acidity of the medium can be varied easily.

Kinetics.—In order to evaluate the experimental results, the assumption was made that all products exhibiting rotation were produced at rates that bear a constant ratio to each other throughout the reaction. If this assumption is accurate, the expression $(\alpha_f - \alpha_t)$[10] is a measure of the concentration of the epoxide I. The molar excess of hydrogen fluoride over epoxide was large enough in the reactions described (at least 20 to 1) that the concentration of hydrogen fluoride may be considered to be essentially constant. A plot of log $(\alpha_f - \alpha_t)$ (Fig. 1) against time was found to be linear, and hence the reaction is first order in epoxide.

TABLE I

	Solution A		Solution B				
Curve	Epoxide I, mole	Chloroform, ml.	HF, mole	THF, mole	Chloroform, ml.	Molar ratio HF/THF	Half-life of I, hr.
1	0.0050	27	0.333	0.233	3	1.43	4.5
2	.0050	24	.367	.238	5	1.54	1.7
3	.0050	23	.400	.243	5	1.65	0.5
4	.0050	25	.333	.181	6	1.79	.4
5	.0050	21	.467	.252	5	1.86	.2

Experimental

All reactions were performed in screw-capped polyethylene bottles. In general, a solution of epoxide I in chloroform (solution A) was added gradually with stirring to a solution of anhydrous hydrogen fluoride in tetrahydrofuran and chloroform (solution B). Both solutions were precooled to −60 to −65° and the reaction mixture was kept in a Dry Ice-acetone-bath during the addition. The reaction mixture was then placed in a bath kept at −32 ± 2° during the reaction period.

At timed intervals aliquots were removed from the reaction bottle by means of polyethylene tubing which had previously been roughly calibrated. These aliquots were treated with weighed quantities of tetrahydrofuran in chilled polyethylene bottles to stop the reaction. An accurate measure of the aliquots was obtained by re-weighing the bottles. The aliquots and the tetrahydrofuran were selected to approximately 30 to 40% of aliquot by weight. The optical rotations of the resulting solutions were deter-

(8) The physical properties were identical with those described by us for the preparation of the fluorohydrin IV by a different route [R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, THIS JOURNAL, **77**, 3166 (1955)]. The preparation of IV from III has also been reported by J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer [*ibid.*, **77**, 4181 (1955)], also J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Ball and J. Korman [*ibid.*, **77**, 4438 (1955)] in unspecified and in 44% yield, respectively.

(9) I. L. Knunyants [*Compt. rend. acad. sci., U.S.S.R.*, **55**, [3] 227 (1947)] has described the opening of simple aliphatic oxides with hydrogen fluoride in ether. The role of the solvent in this reaction is not discussed. More recently, M. Kilpatrick and F. E. Liborsky [THIS JOURNAL, **75**, 577 (1953)] have studied the base strengths of aromatic hydrocarbons relative to anhydrous hydrofluoric acid.

(10) α_f is the rotation at the end of the reaction, *i.e.*, when no further change of rotation is observed, and α_t is the rotation at any time *t*.

mined after a period of adjustment to room temperature (20–25 minutes). The validity of this procedure for terminating the reaction was proven by the observation that after the addition of the tetrahydrofuran the rotation of solutions containing unchanged oxide as well as products failed to change in a 4-hour period. The normalized rotations (α_n)[11] were calculated from the resulting data.

The experimental details, given below, illustrate the application of these studies to the preparation of **9α-fluoro-4-pregnene-11β,17α,21-triol-3,20-dione 21-acetate (II)**. The conditions employed are essentially those represented by curve 4, Fig. 1, except that the concentration of the epoxide is about twice as great in the synthetic experiment as in the kinetic study.

To a solution of 6.96 g. of anhydrous hydrogen fluoride in 13.24 g. of tetrahydrofuran and 5 ml. of chloroform chilled to about −60° was added a solution of 4.018 g. of 9β,11β-epoxy-4-pregnene-17α,21-diol-3,20-dione 21-acetate in 25 ml. of chloroform likewise chilled to about −60°. The hydrogen fluoride–tetrahydrofuran reagent was immersed in an acetone–Dry Ice-bath while the steroid was being added. An additional 5 ml. of chloroform was used to aid in the transfer of the epoxide. The reaction mixture was removed from the acetone–Dry Ice-bath and subsequently maintained at −30° for four hours and then added at a suitable rate to a well agitated mixture of an aqueous solution of potassium carbonate, chloroform and ice. The weakly alkaline aqueous layer was separated and twice back-extracted with chloroform. The combined organic layers were washed with water. After removal of the solvent *in vacuo* the residue was heated with 5 ml. of pyridine and 3 ml. of acetic anhydride at 65° under nitrogen for 75 minutes to convert any by-product into a less polar diacyl derivative.[1,12] The bulk of the solvents was removed *in vacuo*, and the residue was distributed between chloroform and dilute hydrochloric acid. The aqueous layer was back-extracted twice with chloroform. The combined organic layers were washed with dilute acid, with water, with a solution of bicarbonate and finally with water. The filtered solution was concentrated *in vacuo* to a small volume and purified by passage through a column of neutral alumina (16 g.). The eluates, amounting to 85 ml. of chloroform, were concentrated and the fluorohydrin was obtained by the addition of benzene. One recrystallization from acetone–petroleum ether afforded a 74% yield of II, m.p. about 230° dec., $[\alpha]D$ +149° (dioxane), $\lambda_{max}^{CH_3OH}$ 239 mμ (*E* 17,000). Fried and Sabo reported a m.p. of 233–234°, $[\alpha]D$ +123° ($CHCl_3$), $\lambda_{max}^{CH_3OH}$ 238 mμ (*E* 16,800).

Anal. Calcd. for $C_{23}H_{31}O_6F$: C, 65.38; H, 7.38. Found: C, 65.35; H, 7.25.

In the preparation of **9α-fluoro-1,4-pregnadiene-11β,17α,-21-triol-3,20-dione 21-acetate** (IV), a solution of 3.00 g. of the corresponding 9β,11β-epoxide acetate (first described by Fried, *et al.*, and by Hogg, *et al.*[5]) in 18 ml. of chloroform was added to a mixture of 0.248 mole of hydrogen fluoride, 0.097 mole of tetrahydrofuran and 3.75 ml. of chloroform in the same manner as described above. An additional 3.75 ml. of cold chloroform was used to aid in the transfer of the epoxide solution. The solution was removed from the −60° cooling bath and then immersed in an ice-bath for 3.5 hours. The reaction mixture was again chilled in an acetone–Dry Ice-bath and then discharged into an aqueous solution of potassium carbonate. The work-up was carried out essentially as described above except that the acetylation step and the column treatment were omitted. The product obtained in 75% yield was identical with a specimen prepared by us by a different route.[8]

Acknowledgment.—We should like to acknowledge stimulating discussions with Mr. F. Bacher, Dr. J. Chemerda and Dr. K. Pfister III. We wish to thank again Dr. R. P. Graber and Mr. C. S. Snoddy, Jr., who made available to us their procedure for the purification of II.

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(11) In order to compare the rotations of various reaction samples, the term normalized rotation was utilized. In this paper the normalized rotation α_n is calculated as the rotation which would have been observed if the quenched solution contained 40% by weight of the reaction mixture.

(12) The acetylation step and the remainder of the work-up process as described herein were developed by R. P. Graber and C. S. Snoddy, Jr., to whom we are very much indebted.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Asymmetric Reductions. V. The Action of (+)-Di-(2-methylbutyl)-magnesium on Methyl *t*-Butyl Ketone

BY HARRY S. MOSHER AND PAULA KAUFMANN LOEFFLER

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(+)-Di-(2-methylbutyl)-magnesium has been prepared *via* the mercury dialkyl as well as by the dioxane precipitation procedure and its reaction with methyl *t*-butyl ketone studied. A comparison with the results obtained from the reaction of the corresponding Grignard reagent (prepared from (+)-2-methylbutyl chloride and magnesium) reveals that the amount of asymmetric reduction and the percentage yield of products are very similar. The bearing of this on the mechanism of the Grignard reduction reaction and the nature of the Grignard solution is discussed.

The reaction of the Grignard reagent prepared from (+)-2-methylbutyl chloride on methyl *t*-butyl ketone has been studied.[1] The formation of a partially active methyl-*t*-butylcarbinol as the reduction product has been interpreted in terms of the cyclic mechanism of Whitmore.[2] This interpretation was made assuming that the reducing species in the Grignard reagent was the ether complex of the alkylmagnesium chloride. It is recognized that the Grignard solution consists of an equilibrium of the alkylmagnesium chloride and the dialkylmagnesium in varying states of complexing with ether or magnesium halide.[3]

$$2RMgX \rightleftharpoons R_2Mg\cdot MgX_2 \rightleftharpoons R_2Mg + MgX_2 \quad (1)$$

The cyclic theory for the Grignard reduction reaction can be applied equally as well to the dialkylmagnesium compound as to the alkylmagnesium halide. The difference lies only in the replacement of the halogen in the latter with another alkyl group of the former. The reduction could still proceed by shift of the β-hydrogen[4] with its electron pair. If an unsymmetrical ketone is being reduced, optical isomers will be formed.[1] The following two formulas represent the two transition

(1) H. S. Mosher and E. La Combe, THIS JOURNAL, **72**, 3994 (1950).

(2) F. C. Whitmore, paper presented before the Atlantic City Meeting of the American Chemical Society, Sept., 1941.

(3) This has been reviewed completely by M. S. Kharasch and O. Reinmuth in "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp. 88–115.

(4) The final evidence that only the β-hydrogen is involved in this reduction reaction has been supplied by the deuterium tracer experiments of G. E. Dunn and J. Warkentin, *Can. J. Chem.*, **34**, 75 (1956).