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

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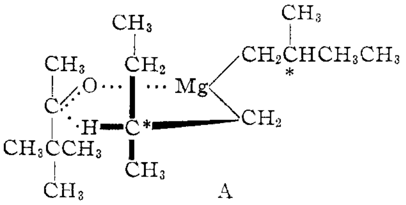
[1] H. S. Mosher and E. La Combe, This Journal, **72**, 3994 (1950).

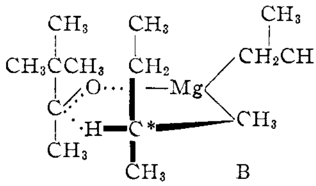
[2] F. C. Whitmore, paper presented before the Atlantic City Meeting of the American Chemical Society, Sept., 1941.

[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).

states resulting from the reaction of (+)-di-(2-methylbutyl)-magnesium with methyl *t*-butyl ketone. Hydrolysis of the resulting complex alcoholates would yield the enantiomorphic methyl-*t*-butylcarbinols.


A


B

The intracomplex "hydride ion" transfer could take place from the β-hydrogen of either of the two alkyl groups of the dialkylmagnesium. A study of models confirms the observation apparent from these two formulas that the transition state represented by A should be sterically favored since in the six-membered ring of the conformation of the transition state, the largest group of the ketone, in this case *t*-butyl, is adjacent to the smaller group of the dialkylmagnesium reagent, in this case methyl. In B, where the largest groups of the ketone and dialkylmagnesium, respectively, are on the same side of the transition state ring, it becomes more difficult for the β-hydrogen to approach the carbonyl carbon. Thus this interpretation predicts that the optically active alcohol resulting from A should predominate in the reduction product. It is apparent that this is the same conclusion arrived at regardless of which primary active amyl group the R comes from. It is also apparent that this is the same product predicted if the R group is replaced by halogen as in the usual representation of the Grignard reagent or by the OR group which would be present after one mole of R_2Mg had reacted. One might predict that the greater bulk of the (+)-2-methylbutyl group in the dialkylmagnesium over the chloro group in the alkylmagnesium chloride should give a greater steric requirement to the transition state of the R_2Mg reaction. Accordingly if the species responsible for reduction in the Grignard solution is the RMgCl, then it might be predicted that the amount of asymmetric synthesis would be greater in the reduction using the dialkylmagnesium reagent.

Since the exact species in the Grignard solution responsible for the reduction is not known, it became important to test this prediction by conducting the reaction of methyl *t*-butyl ketone with the dialkylmagnesium compound made from (+)-2-methylbutyl chloride as well as from the conventional Grignard reagent.[1] Any trace of chloride in the dialkylmagnesium solution would permit the establishment of the equilibrium[3] in equation 1. Even if it is assumed that the concentration of the chloride-containing species present at any one time is extremely small, if this equilibrium is attained at a rate faster than the rate of reaction of the dialkylmagnesium compound with the carbonyl compound, then it is possible that the major reaction path could proceed *via* the chloride-containing reagent in spite of its low concentration. It was therefore necessary to use a dialkylmagnesium compound obtained *via* the distilled dialkylmercury derivative which contained no trace of chlorine. Previous work on dialkylmagnesium solutions made by the dioxane precipitation method has shown that all of the halogen cannot be removed from the ether solution by this process.[5,6] (+)-Di-(2-methylbutyl)-mercury was prepared by treating the Grignard reagent from (+)-2-methylbutyl chloride with mercuric chloride. The distilled product gave a negative chloride test. It was converted to the (+)-di-(2-methylbutyl)-magnesium by heating in a sealed tube with excess magnesium powder at 130°. Titration of the ether extract of the reaction mixture indicated a 73% yield of dialkylmagnesium. This solution may have contained some unconverted dialkylmercury but it has been demonstrated that such compounds do not react with simple carbonyl derivatives under these conditions and could not therefore complicate the present reaction. This solution did not contain any chlorine.

Methyl *t*-butyl ketone was treated with the ether solution of (+)-di-(2-methylbutyl)-magnesium; the results are summarized in Table I. Another experiment, which is likewise summarized in Table I, was performed in which the (+)-di-(2-methylbutyl)-magnesium was prepared by the dioxane precipitation procedure.

TABLE I

REACTION OF THE (+)-DI-(2-METHYLBUTYL)-MAGNESIUM OR GRIGNARD REAGENT WITH METHYL *t*-BUTYL KETONE

Reagent	Reduction,[c] %	Enolization,[d] %	Addition,[e] %	Recovery, %	Excess dextro isomer,[f] %
R_2Mg (*via* R_2Hg)[a]	29	27	32	88	11.3
R_2Mg (*via* dioxane ppt.)	30	30	29	89	12.5
RMgCl (Grignard reagent)[b]	25	39	12	77	13.7

[a] R = $-CH_2C(CH_3)CH_2CH_3$ from (+)-2-methylbutyl chloride. [b] Taken from reference 1. Table I where other similar results are also described. [c] Yield of partially active methyl-*t*-butylcarbinol. [d] Yield of methyl *t*-butyl ketone. An excess of dialkylmagnesium or Grignard reagent was used in each case and this is therefore not recovered starting material. [e] This is based on the weight of residue boiling above 130°, calculated as normal addition product. Condensation or dehydration products may also be present. [f] See reference 8.

It is apparent that there was very little difference between these two runs made from the (+)-di-(2-methylbutyl)-magnesium prepared from the dialkylmercury compound or by the dioxane precipitation procedure in spite of the fact that the latter product contained about 1.5% of the chlorine of the original Grignard solution from which it was prepared. In each case about the same yields of products were obtained and, more important for the present purpose, about the same extent of

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(5) C. R. Noller and W. R. White, THIS JOURNAL, **59**, 1354 (1937).

(6) A. C. Cope, *ibid.*, **57**, 2238 (1935); **60**, 2215 (1938).

asymmetric reduction was observed. Furthermore the sign and extent of optical activity of the resulting methyl-*t*-butylcarbinol did not differ greatly from that obtained with the Grignard reagent. These results are therefore in full agreement with the cyclic mechanism for the Grignard reduction.

The similarities in the yields of addition, reduction and enolization products using the dialkylmagnesium or the conventional Grignard solution are striking. This correspondence in yields as well as the correlation of per cent. asymmetric reduction seems to be too great to dismiss as a coincidence. The obvious interpretation is that the same species in both the Grignard solution and the dialkylmagnesium solution is responsible for these reactions. The only possible reactant in the latter case is the R_2Mg, or its ether complex, radical or ionic dissociation product. Aston and Bernhard[7] came to the conclusion on the basis of rate studies of the reaction of methyl Grignard and dimethylmagnesium on acetone and ethyl acetate that the reactive species (for the addition reaction) in the Grignard solution is the R_2Mg. The above results are in accord with the interpretation that this is true for the reduction and enolization steps as well.

Experimental

(+)-2-Methylbutylmagnesium Chloride.—A Grignard solution was prepared from (+)-2-methylbutyl chloride,[1] 106.5 g. (1.0 mole), $\alpha^{25}\mathrm{D}$ +1.42° (1 dcm., neat), and sublimed magnesium, 25 g. (1.05 moles), in 900 ml. of anhydrous ether. The solution was allowed to settle and filtered into a storage flask through a glass wool plug. Titration indicated a 93.5% yield. This and similar Grignard and dialkylmagnesium solutions used in the following experiments were all transferred in an anhydrous nitrogen atmosphere in a dry-box.

(+)-Di-(2-methylbutyl)-magnesium by the Dioxane Precipitation Procedure.—A one molar Grignard solution, 625 ml., was treated with stirring with 72 ml. of purified dioxane in three equal portions at 12-hour intervals. After standing for 24 hours the precipitate was removed from the resulting slurry by centrifugation, stirred with ether and the ether solutions combined. Titration with acid indicated the presence of 0.25 gram atom of magnesium in the solution (80% yield of dialkylmagnesium). Rotation of the 0.25 molar di-(2-methylbutyl)-magnesium solution: $\alpha^{20}\mathrm{D}$ +0.12° (1 dcm.), $[\alpha]^{20}\mathrm{D}$ +2.9°. Volhard titration indicated the presence of 0.0094 equivalent of chloride ion (1.5% of that originally present in the Grignard solution).

(+)-Di-(2-methylbutyl)-magnesium *via* Dialkylmercury Intermediate.—An ether solution (1000 ml.) containing 0.87 mole at Grignard reagent from 2-methylbutyl chloride ($\alpha^{20}\mathrm{D}$ +1.42° neat) was refluxed for 12 hours under a Soxhlet extractor containing 85 g. (0.42 mole) of mercuric chloride. The reaction mixture was poured into an ice-cold ammonium chloride solution, and the organic layer and ether extracts of the aqueous layer combined and dried over calcium chloride. After the ether had been removed under a column, the residue was distilled through a 14 × 1 cm. Vigreux column to give 102 g. (69%) of (+)-di-(2-methylbutyl)-mercury, b.p. 78° (0.3 mm.), $\alpha^{20}\mathrm{D}$ +13.49° (*l* 1 dcm.), $[\alpha]^{20}\mathrm{D}$ +8.12°, d^{25}_4 1.636. Since this gave a negative chlorine[8] test, none of the alkylmercuric chloride was carried over in the distillation.

Duplicate Pyrex tubes each containing (+)-di-(2-methylbutyl)-mercury, 46 g. (0.134 mole), and sublimed magnesium powder, 6.6 g. (0.271 mole), were sealed and heated in a tube furnace for ten hours at 130°. The tubes were opened under a nitrogen atmosphere and the contents extracted with anhydrous ether. The ether solution was cleared by centrifugation (under nitrogen in stoppered centrifuge bottles) decanted into a calibrated flask and titrated (0.190 mole, 71% yield). This solution gave a negative chloride test with aqueous silver nitrate. Great care was taken to maintain an inert atmosphere since the dialkylmagnesium solutions appeared to be much more sensitive to air oxidation than the Grignard solution.

Reaction of (+)-Di-(2-methylbutyl)-magnesium with Methyl *t*-Butyl Ketone.—To an ether solution, 700 ml., containing 0.18 mole of (+)-di-(2-methylbutyl)-magnesium (prepared from the dialkylmercury compound) was added over a period of two hours methyl *t*-butyl ketone, 15 g. (0.15 mole), in an equal volume of ether. The reaction was carried out in a set up contained in a nitrogen atmosphere controlled dry-box. As each drop of ketone hit the solution, a yellow color developed and immediately disappeared. After stirring overnight, the reaction mixture was hydrolyzed by pouring onto a mixture of 300 g. of ice and 25 g. of ammonium chloride. The product was worked up in the usual manner with a final fractionation through a 12'' × 10 mm. column packed with $^1/_{16}$'' helices rated at 30 theoretical plates. Four components were separated: methyl-*t*-butylcarbinol, 4.5 g. (29% yield), b.p. 119°, $n^{20}\mathrm{D}$ 1.4150, $\alpha^{25}\mathrm{D}$ +0.26° (0.5 dcm., neat); methyl *t*-butyl ketone, 3.95 g. (26% yield), b.p. 106°, $n^{20}\mathrm{D}$ 1.3970; primary active amyl alcohol, 0.40 g., b.p. 129°; and 7.5 g. of residue boiling above 135° (29% yield calculated as addition product). The above yields were calculated by using the refractive index for determination of the composition of the intermediate cuts. A cut of the methyl-*t*-butylcarbinol, 0.70 g., $\alpha^{20}\mathrm{D}$ +0.26° (0.5 dcm., neat) was passed through a gas–liquid partition chromatography column packed with silicone oil-on-Celite and the center cut of the major peak collected. A small amount of methyl *t*-butyl ketone impurity was discarded in this way. This "purified" sample, $\alpha^{20}\mathrm{D}$ +0.28° (0.5 dcm., neat) was shown, however, to be contaminated with primary active amyl alcohol which has an identical retention time on this column. Since a small amount of primary active amyl alcohol ($\alpha^{20}\mathrm{D}$ −4.77°) would greatly affect the slight positive rotation of the reduction product, the acid phthalate derivative was prepared and purified. Primary active amyl alcohol forms a liquid acid phthalate and thus is readily removed during crystallization. It has been previously demonstrated[1] that no concentration of isomers occurs in the recrystallization of the acid phthalate of methyl-*t*-butylcarbinol. The acid phthalate which was crystallized from hexane three times had the properties, $[\alpha]^{20}\mathrm{D}$ +7.22° ($\alpha^{20}\mathrm{D}$ +0.26°, *c* 2.78, $CHCl_3$, *l* = 1), m.p. 84.5–85.5°. This corresponds to an excess of 11.3% of the dextro isomer.[9]

Using the same procedure the reaction mixture from 600 ml. of 0.25 *M* (+)-di-(2-methylbutyl)-magnesium solution, obtained by the dioxane precipitation method, was treated with 13 g. (0.13 mole) of methyl *t*-butyl ketone to give the results summarized in Table I.

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(7) J. G. Aston and S. A. Bernhard, *Nature*, **165**, 485 (1950).

(8) W. J. Jones, *et al.*, *J. Chem. Soc.*, 40 (1935), report for the compound they name "di-*dl*-amylmercury" a b.p. of 93° at 1 mm.

(9) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **105**, 1120 (1914), report a rotation of $[\alpha]^{20}\mathrm{D}$ +63.9° for the pure dextro isomer of the acid phthalate of methyl-*t*-butylcarbinol.