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

# Asymmetric Reductions. VI. The Action of the Grignard Reagent from (+)-1-Chloro-2-methylbutane on a Series of Alkyl *t*-Butyl Ketones[1]

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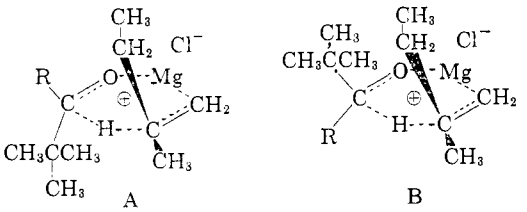
A series of six alkyl *t*-butyl ketones has been treated with the Grignard reagent from (+)-1-chloro-2-methylbutane (primary active amyl chloride) and the percentage asymmetric reduction determined by comparing the rotation of the resulting partially active secondary carbinol with that of the optically pure isomer as determined by resolution. The absolute configurations of the alkyl-*t*-butylcarbinols obtained in these asymmetric reductions have been deduced and in each case have been shown to be related. The absolute configurations found were those predicted on the basis of the previously postulated mechanism for the Grignard reduction reaction. This mechanism is based on a cyclic six-membered transition state for the hydrogen transfer process in which the stereospecificity is controlled by the steric interaction of the alkyl and *t*-butyl groups from the ketone with the methyl and ethyl groups of the Grignard reagent. The values for the per cent. asymmetric reductions in this series bear a *semi-quantitative* relationship to each other which is completely in accord with this postulate. In addition, the effect of using the Grignard reagent from primary active amyl chloride, bromide and iodide was compared.

The ability of an optically active reducing agent to accomplish an asymmetric reduction is now well established.[4-11] The reducing agents have been of two types, either alcoholates (aluminum[5,11] magnesium[4c,8] or "lithium-aluminum"[9]) of optically active, secondary alcohols, or optically active Grignard reagents.[4a,4b,4d,6,7] The stereospecificity of these reductions has been interpreted in terms of a six-membered ring transition state for the hydrogen transfer step.[5,7]

In the reduction of an unsymmetrical carbonyl compound by the Grignard reagent from (+)-1-chloro-2-methylbutane, two transition states of major importance may be postulated. In the case of the alkyl *t*-butyl ketones reported in this paper, these may be represented by A and B. The coördinated solvent molecules are omitted and the Grignard reagent is represented as RMgX.



A



B

If the transfer of the hydrogen takes place through the transition state represented by A, then one isomer will be formed; B leads to its enantiomorph. It was postulated[5] that the energy of activation for A would be lower than that for B, where R is a group smaller than *t*-butyl. This prediction was based on the assumption that there would be less steric interference when the larger group of the ketone, *t*-butyl in this case, was on the same side of the transition ring as the smaller group from the Grignard reagent, in this case methyl, as represented in A. If R in formulas A and B is varied, then as its bulk increases and approaches that of *t*-butyl, one would predict that the extent of asymmetric synthesis should decrease. The absolute configuration of primary active amyl chloride, and therefore the Grignard reagent prepared from it, is now known with considerable certainty[12] and is as represented in projection formulas A and B. Thus as long as R is smaller than *t*-butyl, the predominant isomer of the secondary alcohol should have the configuration predicted from transition state A.

Accordingly the series of alkyl *t*-butyl ketones where the alkyl groups were methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and isobutyl were treated with a slight excess of the optically active Grignard reagent from (+)-1-chloro-2-methylbutane. The products of the reaction were separated by fractionation as summarized in Table I. In connection with the specific yields of addition, reduction and enolization products, it is noteworthy that in the four runs on isopropyl *t*-butyl ketone which were conducted in approximately the same manner but at different times, the yield of reduction product varied from 29 to 44% and of enolization from 12 to 49%. This is a reflection on the difficulties of controlling the many variables in any Grignard reaction as normally conducted. In spite of these variations in yield, the rotation of the purified isopropyl-*t*-butylcarbinol was very nearly the same in each experiment. The purity of each of the reduction products was carefully checked by taking

(1) Presented in part at the 118th Meeting of the American Chemical Society, Sept. 8, 1950.

(2) Abstracted in part from the Ph.D. theses of W. M. F. (Sept., 1950), E. M. L. (July, 1952) and F. J. W. (Oct., 1954), Stanford University.

(3) Shell Fellowship holder, 1952–1953.

(4) (a) G. Vavon, C. Riviere and B. Angelo, *Compt. rend.*, **222**, 959 (1946); (b) G. Vavon and B. Angelo, *ibid.*, **224**, 1435 (1947); (c) G. Vavon and A. Antonini, *ibid.*, **232**, 1120 (1951); (d) G. Vavon and Y. Runavot, *Bull. soc. chim.*, [5] **22**, 357 (1955).

(5) W. E. Doering and F. W. Young, THIS JOURNAL, **71**, 631 (1948).

(6) E. F. Tatibauet, *Bull. soc. chim.*, [5] **18**, 867, 868, 871 (1951).

(7) (a) H. S. Mosher, E. M. La Combe, THIS JOURNAL, **72**, 3994, 4991 (1950); (b) H. S. Mosher and E. D. Parker, *ibid.*, **78**, 4081 (1956); (c) H. S. Mosher, J. E. Stevenot and D. O. Kimble, *ibid.*, **78**, 4374 (1956); (d) H. S. Mosher and P. K. Loeffler, *ibid.*, **78**, 5597 (1956).

(8) (a) A. Streitwieser and J. R. Wolfe, *ibid.*, **79**, 903 (1957); (b) A. Streitwieser, *ibid.*, **75**, 5014 (1953); (c) A. Streitwieser and W. D. Schoeffler, *ibid.*, **78**, 5597 (1956).

(9) A. Bothner-By, *ibid.*, **73**, 846 (1951).

(10) H. F. Fishcher, E. E. Conn, B. Vennesland and F. H. Westheimer, *J. Biol. Chem.*, **207**, 687 (1953), describe an example of an enzymatic, stereospecific hydrogen transfer reaction.

(11) K. Mislow and P. Newman, THIS JOURNAL, **79**, 1769 (1957).

(12) The essential information is to be found in the following references and is reviewed in detail in the Ph.D. Thesis of E. M. La Combe: Stanford University, 1952: (a) W. Marckwald, *Ber.*, **37**, 1045 (1904); (b) A. Fredga, "The Svedberg," Almquist and Winksells, Uppsala, 1945, p. 269; (c) S. Stallberg-Stenhagen and Stenhagen, *Arkiv. Kemi, Min. Geol.*, **24B**, 6 (1947); (d) P. A. Levene and A. Rothen, *J. Org. Chem.*, **1**, 100 (1936); (e) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **91**, 687 (1931); (f) R. L. Letsinger and J. G. Traynham, THIS JOURNAL, **72**, 850 (1950); (g) M. Winitz, S. M. Birnbaum and J. P. Greenstein, *ibid.*, **77**, 3106 (1955).

TABLE I

PARTIAL ASYMMETRIC REDUCTIONS

$$RCC(CH_3)_3 + C_2H_5CHCH_2MgX \xrightarrow[2,\ H_2O]{1,\ Et_2O} RCHOHC(CH_3)_3 + C_2H_5C{=}CH_2$$

| R | X | Moles ketone | Yield of products, % Reduct. | Olefin[a] | Enol.[b] | Residue[c] | Total recovery | $\alpha^{25}D$ (neat) of carbinol | M.p., °C., of carbinol deriv.[d] | Asymm. reduct.,[i] % |
|---|---|---|---|---|---|---|---|---|---|---|
| $-CH_3$ | Cl | [e] | 29[e] | 27[e] | 36[e] | 11[e] | 76[e] | +0.63[e] | 85.5–86.5 | 13.4[e] |
| $-CH_3$ | Br | 0.36 | 14 | 13 | 14 | 34 | 59 | .66 | 83.5–84.5 | 11.7[f] |
| | | .16 | 8 | 9 | 25 | 27 | 60 | .69 | 83.5–85.0 | 131.[g] |
| $-CH_3$ | I | .20 | 0.5 | 7 | 23 | 50 | 90 | ..... | ..... | ...[h] |
| | | .65 | 0.5 | 10 | 34 | 27 | 97 | ..... | ..... | ... |
| $-CH_2CH_3$ | Cl | .75 | 51 | 46 | 36 | 6 | 93 | −2.94[j] | 88–88.5 | 10.7 |
| $-CH_2CH_2CH_3$ | Cl | .82 | 52 | 36 | 35 | 2 | 89 | −3.87[j] | 92–93 | 11.3 |
| $-CH(CH_3)_2$ | Cl | .73 | 46 | 18 | 24 | 16 | 86 | −0.38[k] | 115–116 | 4.9 |
| | | .68 | 44 | .. | 12 | 22 | 78 | − .38[j] | | 4.2 |
| | | .41 | 30 | 27 | 43 | 11 | 84 | − .24[l] | | 5.1 |
| | | .15 | 33 | .. | 49[m] | 18[m] | . | − .37[m] | | 4.1 |
| $-CH_2CH_2CH_2CH_3$ | Cl | .67 | 39 | 37 | 42 | 1 | 82 | −3.78[j] | 98.5–100.5 | 11.0 |
| $-CH_2CH(CH_3)_2$ | Cl | .493 | 15 | 13 | 63 | 2 | 80 | −2.56[j] | 81–82 | 5.9 |

[a] Olefin determined by titration according to Johnson and Clark, *Ind. Eng. Chem., Anal. Ed.*, 19 869 (1947). [b] Enolization is amount of recovered ketone. Since there was a positive Gilman test for Grignard reagent at the completion of each run, this is not simply unreacted starting material. [c] This is a measure of the reaction products boiling above 180°. It is calculated on the basis of the normal addition product. This assumption is undoubtedly inaccurate since condensation and higher boiling dehydration products are also present in the residue. [d] Acid phthalate ester after several recrystallizations from hexane. [e] These values are the average of the three comparable runs, 1, 2 and 3, reported in Table I of ref. 7a. [f] This value for the percentage asymmetric reduction is calculated from the rotation of the crystallized acid phthalate $[\alpha]^{24}D$ +6.96° ($CHCl_3$) and using primary active amyl bromide with a rotation of 93% of that reported for the pure isomer. As was originally reported[7a] and as has been reconfirmed,[7d] there is no concentration of isomers during this recrystallization. [g] Same comment as *f* except bromide with 84% optical purity was used and gave acid phthalate, $[\alpha]^{22}D$ +7.01° ($CHCl_3$). [h] No isolable amount of the reduction products was obtained. [i] See Table II for maximum rotations of the pure carbinols upon which these figures are based. [j] Rotation of center cut from fractionation. Homogeneity checked by gas partition chromatography and infrared spectroscopy. [k] Cuts from this experiment were converted to the acid phthalate which was separated from neutral and steam-volatile material and the carbinol regenerated, $\alpha^{26}D$ −0.44°. [l] Same comment as *k*; regenerated carbinol, $[\alpha]^{25}D$ −0.46°. [m] This reaction mixture was analyzed and separated by stripping the ether under a column and subjecting the residue to gas partition chromatography.

the infrared spectrum[13] and by analysis using gas partition chromatography.[14] Therefore the rotation obtained for the reduction product could be used with confidence in calculating the percentage asymmetric reduction and it was not necessary to check the purity by quantitative conversion to the acid phthalate and regeneration as was done previously.[7a]

Of the alkyl-*t*-butylcarbinols reported in Table I, only methyl-*t*-butylcarbinol and *n*-propyl-*t*-butylcarbinol have been resolved previously. The four remaining examples now have been resolved by application of the classical methods.[15] Great care was exercised to ensure complete resolution; the details including criteria of complete resolution are given in the Experimental section. The rotation of the pure isomers and their derivatives are summarized in Table II. The percentage asymmetric reductions (defined as 100 × $\alpha$ observed/$\alpha$ maximum) are given in the last column of Table I.

(13) The major likely contaminant in the secondary carbinol was the corresponding ketone. A contamination of 1% of the carbinol by ketone could easily be detected by observing the carbonyl band at 5.85–5.88 $\mu$.

(14) The gas partition chromatography was done on a Carbowax column which, in almost every case, separated widely the secondary carbinol, ketone, primary active amyl chloride, primary active amyl alcohol and the hydrocarbon (+)-3,6-dimethyloctane which was a troublesome contaminant formed in some of the reaction mixtures. If there was any question concerning the separation of components, the purity was checked on a silicone oil gas partition column.

(15) A. W. Ingersoll, *Org. Reactions*, **2**, 376 (1944).

TABLE II

MAXIMUM MOLECULAR ROTATIONS OF ALKYL-*t*-BUTYLCARBINOLS AND THEIR ACETATES, BENZOATES AND PHTHALATES

| Carbinol | Carbinol (neat) | Acetate (neat) | Benzoate (neat) | Acid phthalate (in $CHCl_3$) |
|---|---|---|---|---|
| | [M]D 22–23° | | | |
| Methyl-*n*-butyl[a] | +12 | +17 | .. | +118 |
| Methyl-*i*-propyl[a] | + 4.3 | +25 | +80 | + 89 |
| Methyl-*t*-butyl[a] | + 7.8 | +26 | +93 | +160 |
| *i*-Propyl-*t*-butyl[b] | −14 | + 3.7[d] | − 0.5[d] | 0.0 |
| Ethyl-*t*-butyl[b] | −39 | −44 | −18[d] | + 3.3[g] |
| *n*-Propyl-*t*-butyl[c] | −55[e] | −59[c,e] | −20[e] | + 8.4[e] |
| *n*-Butyl-*t*-butyl[b] | −60 | −51[f] | −40 | − 13 |
| *i*-Butyl-*t*-butyl[b] | −78 | −66 | −43 | − 24 |

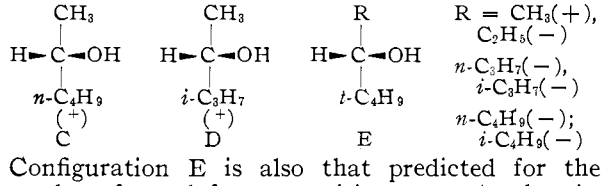
[a] P. G. Stevens, THIS JOURNAL, **55**, 4237 (1933). [b] See Experimental section. [c] P. G. Stevens, W. E. Higbee and R. T. Armstrong, THIS JOURNAL, **60**, 2658 (1938). [d] Calculated for the ester which was made from the carbinol that was 80% resolved. A density of 0.85 g./ml. was assumed for this acetate. [e] The carbinol was made by reduction of alkyl-*t*-butylcarbinol of 82% optical purity. These values assume no racemization during reduction. [f] Calculated from the acetate prepared from carbinol of 96% optical purity. [g] This value is influenced considerably by concentration; see Experimental.

That all of the alkyl-*t*-butylcarbinols produced in these asymmetric reduction reactions have the same configuration is strongly indicated by the application of Freudenberg's displacement rule[16] to

(16) K. Freudenberg, "Stereochemie," Franz Deuticke, Leipzig, 1933, p. 677.

the acetates, benzoates and acid phthalates of these carbinols as shown in Table II. In each case the molecular rotation increases algebraically in going from carbinol, to acetate, to benzoate, to acid phthalate. In addition the molecular rotations of the alkyl-*t*-butylcarbinols and each of the derivatives increases algebraically in going from the methyl derivative (line 3, Table II) to the isobutyl example (at the bottom of the table). Thus (+)-methyl-*t*-butylcarbinol must be configurationally related to the other alkyl-*t*-butylcarbinols of *opposite* sign. The only case which might be questioned is that of isopropyl-*t*-butylcarbinol in which the rotations of the derivatives, although greater than that of the parent carbinol, are so small that the significance of the trend is in doubt. Nevertheless, the only satisfactory vertical arrangement is as listed and the *l*-isomer will be considered configurationally related to the *l*-*n*-propyl-*t*-butylcarbinol. It is of passing interest that the acid phthalate of (−)-isopropyl-*t*-butylcarbinol showed negligible rotation with light of wave length from 4700 to 6900 Å. and in a wide variety of solvents yet was reconverted to the active carbinol, on saponification, with unchanged rotation.

The absolute configuration of all the carbinols in Table II can be deduced from (+)-methylisopropylcarbinol and (+)-methyl-*n*-butylcarbinol whose absolute configurations have already been established with certainty.[17] The absolute configurations of these two *d*-alcohols are represented by Fisher projection formulas C and D. In all probability, therefore, the other carbinols in Table II are represented by E. It therefore follows that the alkyl-*t*-butylcarbinols produced in the asymmetric reductions reported in Table I all have the same absolute configuration represented by E.[18,19]




Configuration E is also that predicted for the product formed from transition state A, that is, the transition state predicted to have the lower energy of activation on the basis of the known absolute configuration of the Grignard reagent and the steric interactions involved in the postulated cyclic mechanism for this reaction.

Not only are the configurations of the predominant alkyl-*t*-carbinol isomers correctly predicted in each case but *the extents of asymmetric reduction correlate in semi-quantitative fashion with that which would be predicted.* The alkyl groups involved may be arranged in the following order of increasing bulk: methyl < ethyl < *n*-propyl < *n*-butyl < isobutyl < isopropyl < *t*-butyl. Since in this and similar circumstances it is the branching on the α-carbon atom which is important[20] isopropyl is arranged after isobutyl. Thus there should be rather significant decrease in the percentage asymmetric reduction in going from methyl to ethyl to isopropyl but only minor decreases in going from ethyl to *n*-propyl to *n*-butyl. The percentage asymmetric reductions found (Table I, X is Cl) were: methyl, 13[7a]; ethyl, 11; *n*-propyl, 11; *n*-butyl, 11; isobutyl, 6; and isopropyl, 4-5. These results are in complete accord with the above mechanism.

As will be indicated in future papers the situation is much more complex in the alkyl phenyl ketone and alkyl cyclohexyl ketone series.

It was felt desirable to determine the effect on the asymmetric reduction of the particular halide, chloride, bromide or iodide, used in the preparation of the primary active amyl Grignard reagent. In addition the work of Shine[21] would indicate that the yield of reduction product would be higher with the iodide than the chloride. Accordingly the bromide and iodide were prepared, converted to the Grignard reagent which was then treated with methyl *t*-butyl ketone. The results of these reactions are summarized in Table I also. The percentage asymmetric reduction using the Grignard reagent from primary active amyl bromide was 13.1 and 11.7 in two separate experiments. This is a larger variation than we have observed in check runs with the chloride. The average of these two experiments (12.4% asymmetric reduction) is slightly less than that for the corresponding chloride (13.3% asymmetric reduction average of four comparable runs[7a]). The significance of this difference of approximately 1% is doubtful.

The corresponding iodide in two separate experiments gave no isolable amount of methyl-*t*-butylcarbinol. Since in a previous experiment it had been possible to separate as little as 0.001 mole of reduction product as the acid phthalate, it was concluded that the yield in this case was less than 0.5%. A titration for olefin indicated a 6% yield, calculated as 2-methyl-1-butene, in one case, and a 10% yield in the other. Since it was impossible to establish any trend in going from chloride to bromide to iodide, the spread in the two bromide experiments was not checked further.

The differences in yields of reduction in going from the chloride (27%) to bromide (8%) to iodide (less than 0.5%) is opposite to that reported by Shine[21] in a much more exhaustive study but corresponds to that reported by Kharasch and Weinhouse[22] in still another study. Shine's results were based entirely upon gas analysis for olefins. It is possible that in the case of the iodide there is some competing olefin-forming reaction.

**Acknowledgment.**—We wish to thank the Research Corporation for a grant and the Shell Oil Company for a fellowship which materially aided the progress of this investigation.

(17) (a) P. G. Stevens, THIS JOURNAL, **54**, 3732 (1932); (b) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **79**, 475 (1928); **69**, 165 (1926); **67**, 329 (1926); (c) P. G. Stevens, W. E. Higbee and R. T. Armstrong, THIS JOURNAL, **60**, 2658 (1938).

(18) Employing the nomenclature devised by R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1956), these alcohols, C, D and E, all have the S-configuration as does the naturally occurring (−)-primary active amyl alcohol.

(19) These conclusions concerning the relative configurations and sign of rotation of the alkyl-*t*-butylcarbinols agree with the predictions made on the basis of Marker's generalization, THIS JOURNAL, **58**, 976 (1936), using the value for the *t*-butyl group proposed in reference 17c.

(20) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 210.

(21) H. J. Shine, *J. Chem. Soc.*, 8 (1951).

(22) M. S. Kharasch and S. Weinhouse, *J. Org. Chem.*, **1**, 220 (1936).

TABLE III

ALKYL *t*-BUTYL KETONES

$$(CH_3)_3CMgCl + ClCR \xrightarrow[2,\ H_2O]{1,\ Et_2O} (CH_3)_3CCR + MgCl_2$$

| R | Equiv. of Grig. | Moles of acid chloride | Yield of ketone, %, based on Grig. | Yield of ketone, %, based on Acid chloride | Properties of ketones B.p., °C. | $n^{20}D$ |
|---|---|---|---|---|---|---|
| $CH_3$ | 1.30 | 1.50 | 33 | 29 | 105.2 | 1.3974 |
| $CH_2CH_3$[a] | 2.74 | 4.95 | 89 | 47 | 125.0–125.8 | 1.4049–1.4051 |
| $CH_2CH_2CH_3$[b] | 2.20 | 3.00 | 63 | 50 | 145.0–145.8 | 1.4109–1.4111 |
| $CH(CH_3)_2$[c] | 2.57 | 2.98 | 36 | 31 | 135.2–136.7 | 1.4049–1.4068 |
| $CH_2CH_2CH_2CH_3$[d] | 2.62 | 3.22 | 69 | 56 | 167.0–169.0 | 1.4149–1.4159 |
| $CH_2CH(CH_3)_2$[e] | 3.00 | 2.50 | 40 | 48 | 155.5–157.0 | 1.4135–1.4142 |
| | 2.28 | 2.85 | 61 | 49 | | |

[a] Cavalieri, Pattison and Carmack, THIS JOURNAL, **67**, 1784 (1945), prepared this ketone by the oxidation of the corresponding alcohol and report the following values, b.p. 124–126°, $n^{20}D$ 1.4049; Zook, McAlee and Horwin, *ibid.*, **68**, 2404 (1946), obtained ethyl *t*-butyl ketone by the action of *t*-butyl Grignard on ethyl propionate in 20% yield; reported properties, b.p. 44–45° (15 mm.), $n^{20}D$ 1.4215–1.4218; Petrov and Roslova *J. Gen. Chem. (USSR)* **10**, 973 (1940); *C. A.*, **35**, 2467 (1941), have a preliminary communication on the preparation of ethyl *t*-butyl ketone by the reaction of *t*-butylmagnesium chloride on propionyl chloride. [b] Prepared by Leroide, *Ann. chim.*, [9] **16**, 369 (1921), through oxidation of the corresponding carbinol, b.p. 145–148°, $n^{17}D$ 1.4148; also prepared by the action of *n*-propylzinc iodide on pivaloyl chloride, by Leers, *Bull. soc. chim.* [4] **39**, 434 (1926), b.p. 143.5°. [c] Haller and Bauer, *Ann. chim.*, [8] **29**, 316 (1913), report b.p. 133-135°, $n^{25}D$ 1.4051. [d] Prepared by Leers, *Bull. soc. chim.*, [4] **39** 652 (1926), by reaction of *n*-butylzinc iodide on pivaloyl chloride, b.p. 164°. [e] Made by Leers, ref. *d*, and also by Haller and Bauer, *Ann. chim.*, [8] **29**, 330 (1913), b.p. 157.5-158.5°.

## Experimental

**Ketones.**—The alkyl *t*-butyl ketones used in this study were made by the coupling of the appropriate acid chloride with the Grignard reagent from freshly distilled *t*-butyl chloride in the presence of cuprous chloride by the method of Cook and Percival.[23] With the exception of pinacolone, this was found to be the method of choice in the preparation of the ketones which are summarized in Table III.

**Asymmetric Reductions.**—The Grignard reactions were all conducted as indicated previously[7] with the results summarized in Table I. The filtered Grignard solutions, which had been prepared from primary active amyl chloride, $\alpha^{23}D$ +1.42 (neat), and sublimed magnesium[24] was added to the ketones in Mallinckrodt anhydrous ether. The reaction products were given a simple distillation and then carefully fractionated through a thirty-plate column. The homogeneity of the center cuts of the carbinol fractions was checked by gas partition chromatography on both a silicone-oil and Carbowax column and the infrared spectrum in each case demonstrated the identity of the carbinol and that it contained less than 1% ketone impurity.[25] Only in the case of the isopropyl-*t*-butylcarbinol experiments were special difficulties encountered. This carbinol boils at 149–150° and could not be separated by fractionation from small amounts of (+)-3,6-dimethyloctane, b.p. 160°, which occurred in some of the reaction mixtures. Since this hydrocarbon is strongly dextrorotatory, a small amount seriously affected the rotation of the carbinol fraction. This was originally separated by adsorption chromatography on alumina and more recently by gas partition chromatography. In addition the carbinol was converted to the acid phthalate and regenerated in two cases. Care was exercised not to cause any possible concentration of one isomer by fractional crystallization of the acid phthalate. Impure isopropyl-*t*-butylcarbinol fraction from the third experiment on this particular asymmetric reduction described in Table I, was converted to the acid phthalate, $\alpha^{25}D$ 0.00 ± 0.02° (*l dm.*, *c* = 2 to 20 chloroform, benzene, ethanol, dioxane), 56% yield, m.p. 112–113.5°, and regenerated to the original carbinol, $\alpha^{28}D$ −0.46 ± 0.02° (*l dm.*, neat), 71% yield, $n^{20}D$ 1.4298. This was also done on the first experiment described in Table I. An impure isopropyl-*t*-butylcarbinol fraction, $\alpha^{25}D$ −0.10 ± 0.01° (neat, *l* 0.5) was converted to the acid phthalate and all neutral impurities removed by extraction of its basic solution. The acid phthalate itself was subjected to steam distillation to remove volatile impurities and the original carbinol was then regenerated (75%, overall yield), $\alpha^{20}D$ −0.44 ± 0.02° (*l* 1, neat), $n^{20}D$ 1.4298.

**Resolution of Ethyl-*t*-butylcarbinol.**—Ethyl-*t*-butylcarbinol,[26] b.p. 136°, $\alpha^{20}D$ 1.4235, was converted to the *dl*-acid phthalate in 80% yield by heating for 12 hours at 100 °with pyridine and phthalic anhydride in the usual manner,[15] m.p. 88.0–88.3°. A slurry of brucine, 172 g., in 1800 ml. of acetone was added to a boiling solution of the acid phthalate, 115 g., in 500 ml. of acetone. The first crop of crystals obtained on cooling the solution weighed 159 g., $[\alpha]^{20}D$ −31.8° (*c* 2, acetone). The acetone filtrate was evaporated to dryness and both the more soluble and less soluble brucine salts were reconverted to the acid phthalates by dissolving in 300 ml. of acetone and pouring into 500 ml. of 1 *N* HCl. It had been found in many previous experiments that the brucine salt did not lend itself to further purification by repeated recrystallization of either the more soluble or less soluble forms at this stage. The acid phthalate from the less soluble brucine salt was washed with hydrochloric acid and extracted with chloroform. The extract was dried and evaporated and the residue was crystallized from petroleum ether; 48 g. (80%) of a very hard crystalline cake, m.p. 75–78.5°, $[\alpha]^{20}D$ +1.4° (*c* 2, $CHCl_3$). This was recrystallized from 100 ml. of petroleum ether and 5 ml. of acetone; 31 g., $[\alpha]^{24}D$ +2.25° (*c* 20, $CHCl_3$), m.p. 78.5–80.5°. From many previous experiments it was known that repeated careful, slow crystallizations would raise this rotation only slightly and this represented the eutectic composition for the *dl*, *d* mixture. This 31 g. was dissolved in *n*-hexane, carefully supercooled, seeded with pure *dl*-crystals and the crystals, 9 g., harvested in ten minutes. From the mother liquor, after reheating and allowing to cool slowly, there was obtained 17 g., m.p. 91.0–91.5°, $[\alpha]^{26}D$ +3.65° (*c* 20, $CHCl_3$). Recrystallization raised the rotation to $[\alpha]^{26}D$ +3.75 ±0.08° (*c* 20, $CHCl_3$). This final seeding procedure was erratic and worked only very occasionally but it was the only method found for getting beyond the eutectic mixture. Once the pure *d*-form was obtained this could be used for seeding. However, the *d*-form was much more soluble than the *dl*-form and the procedure described here was preferable.

The acid phthalate which was regenerated from the more soluble form of the brucine salt was extracted with chloroform, washed with cold dilute hydrochloric acid, treated with Norit, evaporated and the chloroform replaced with petroleum ether which precipitated a small amount of insoluble brucine. From 175 ml. of solution kept at 0° was obtained 23.5 g. of dense crystals, m.p. 80–81.5°, $[\alpha]^{23}D$ −1.9° (*c* 20, $CHCl_3$). These crystals were dissolved in *n*-hexane seeded with *dl*-acid phthalate and stored at 0°; 10.2 g., m.p. 84–86°, of *dl*-crystals formed as a hard crust.

(23) N. C. Cook and W. C. Percival, THIS JOURNAL, **71**, 4141 (1949).

(24) We are very grateful to the Dow Chemical Co. for a generous gift of triple sublimed magnesium used in these investigations.

(25) These carbinols were prepared prior to 1950. Their purity was rechecked in 1957 and no change in rotation was observed.

(26) L. Cavalieri, D. B. Pattison and M. Carmack, THIS JOURNAL, **67**, 1784 (1945).

On handling, fine granular crystals, 10.2 g., separated from the supersaturated mother liquors. These were recrystallized from *n*-hexane in which the acid phthalate was more soluble the further the resolution progressed; 7.7 g., m.p. 89.5–90.5°, $[\alpha]^{26}D$ −3.65° (*c* 25.3, $CHCl_3$). Repeated crystallizations raised the rotation to $[\alpha]^{27}D$ −3.75° (*c* 20.5, $CHCl_3$), m.p. 91.0–91.5°. This is the pure *l*-isomer. It is of interest that the rotation in $CHCl_3$ is very dependent upon concentration, actually going from a positive to a negative value: $[\alpha]^{26}D$ −3.95 ± 0.08° (*c* 30), −3.75 ± 0.16° (*c* 2 ), −3.10 ± 0.25° (*c* 10), −2.15 ± 0.25° (*c* 5), 0.0 ± 0.3° (*c* 2.5), +2.2 ± 0.6° (*c* 1.5.). The melting point diagram which was constructed from the data obtained from a series of synthetic mixtures of pure *dl*-ethyl-*t*-butyl acid phthalate, m.p. 88.0 to 88.5°, and the levorotatory sample $[\alpha]^{27}D$ −3.75° (*c* 20.5, $CHCl_3$), m.p. 91.0–91.5°, showed a eutectic at approximately 80% *l*, 20% *dl*, m.p. 82–83°.

A sample of the acid phthalate $[\alpha]^{27}D$ −3.75° (*c* 20, $CHCl_3$) was converted to the brucine salt and recrystallized several times. This was regenerated to the acid phthalate with uncharged rotation, $[\alpha]^{25}D$ −3.74° (*c* 20, $CHCl_3$).

*Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.20; H, 7.58. Found: C, 68.29; H, 7.33.

Ethyl-*t*-butylcarbinol was regenerated from the acid phthalate, $[\alpha]^{25}D$ −3.75° (*c* 20, $CHCl_3$), by dissolving in 25% sodium hydroxide, steam distilling and recovering the carbinol from the distillate by ether extraction, drying over magnesium sulfate and distilling, $n^{20}D$ 1.4230, $\alpha^{23}D$ +27.40 ± 0.03° (neat, *l* 1). The ethyl-*t*-butylcarbinol, $\alpha^{23}D$ −2.94°, from the Grignard reaction corresponds to 10.7% asymmetric reduction.

An acetate was prepared from the carbinol, $\alpha^{22}D$ +26.4° (neat), b.p. 74° (38 mm.), $n^{20}D$ 1.4103, $d^{23}$ 0.856, $\alpha^{24}D$ +12.16 (neat, *l* 0.5).

*Anal.* Calcd. for $C_9H_{10}O_2$: C, 68.31; H, 11.47. Found: C, 68.59; H, 11.61.

A benzoate was prepared from the carbinol, $\alpha^{23}D$ −22.4°, b.p. 20° (0.8 mm.), $n^{20}D$ 1.4912, $d^{23}$ 0.957, $\alpha^{25}D$ −3.19° (neat, *l* 0.5).

*Anal.* Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 75.98; H, 8.84.

**Resolution of Isopropyl-*t*-butylcarbinol.**—Isopropyl-*t*-butylcarbinol, 81 g., b.p. 150.9–151.1°, $n^{20}D$ 1.4290–1.4299, which was made by lithium aluminum hydride reduction of the ketone, was converted to the acid phthalate in the presence of pyridine[15] by heating in an oil-bath at 120° (100° was inadequate) for 25 hours. The crude product was recrystallized from chloroform, 152 g., (88% yield), m.p. 114.5–116.0°. The brucine salt was prepared and repeatedly crystallized from acetone to give the less soluble form, m.p. 173–175°, $[\alpha]^{28}D$ −23°. On hydrolysis this gave an acid phthalate, m.p. 100.5–103.0°, $[\alpha]^{25}D$ 0.00 ± 0.03°, which in turn was hydrolyzed to isopropyl-*t*-butylcarbinol, $\alpha^{28}D$ −7.22° (neat, *l* 1). Hydrolysis of the more soluble form of the brucine salt, $[\alpha]^{28}D$ −16.1°, gave acid phthalate, $[\alpha]^{28}D$ ±0.00 ± 0.03°, which was hydrolyzed to the carbinol, $\alpha^{28}D$ +7.22° (neat, *l* 1). The strychnine salt of the acid phthalate from the less soluble brucine salt was prepared and recrystallized, $[\alpha]^{28}D$ −25.7. The acid phthalate was regenerated, recrystallized and hydrolyzed to the carbinol, $\alpha^{28}D$ −8.94 (neat, *l* 1) $n^{20}D$ 1.4300. The acid phthalate from the more soluble brucine salt was converted to the cinchonine salt, recrystallized, m.p. 144–147° dec., $[\alpha]^{28}D$ +106°. The acid phthalate was regenerated and recrystallized, m.p. 105.5–107.0°.

*Anal.* Calcd. for $C_{16}H_{24}O_4$: C, 68.99; H, 7.95. Found: C, 69.03; H, 8.03.

This was hydrolyzed to the carbinol, $\alpha^{28}D$ +9.06° (neat, *l* 1). This value is taken as the maximum rotation of (+)-isopropyl-*t*-butylcarbinol and satisfactorily matches the maximum value obtained for the *l*-isomer.

An acetate and benzoate were prepared from the carbinol, $\alpha^{28}D$ +7.22°; acetate, b.p. 130° (155 mm.), $n^{21}D$ 1.4166, $\alpha^{28}D$ −1.44 (neat, *l* 1). *Anal.* Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.93; H, 11.89. Benzoate, b.p. 195° (32 mm.), $n^{19}D$ 1.4969, $\alpha^{25}D$ −0.16° (neat. *l* 1). *Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.37; H, 9.21.

**Resolution of Isobutyl-*t*-butylcarbinol.**—Isobutyl-*t*-butylcarbinol, b.p. 115–116° (150 mm.), $n^{20}D$ 1.4309, m.p. 17°, was prepared by a Meerwein–Ponndorf reduction of the ketone after an attempt at reduction with Raney nickel at 150°, 250 p.s.i., was unsuccessful. It was refluxed with pyridine and phthalic anhydride for 20 hours and the resulting acid phthalate recrystallized from hexane, 80% yield, m.p. 83.5–84.5°. Crystalline brucine or cinchonine salts could not be made but the strychnine salt was crystal line and was subjected to a systematic eight-stage crystallization from acetone. The more insoluble fractions, $[\alpha]^{25}D$ −29 to −30°, were converted to the acid phthalate, m.p. 69–73°, $[\alpha]^{25}D$ +5.7°, which was recrystallized four times and reconverted to the strychnine salt. The latter was recrystallized several times and hydrolyzed to an acid phthalate which after several recrystallizations melted at 76.5–77.5°, $[\alpha]^{23}D$ +8.7° (*c* 1.5, $CHCl_3$).

*Anal.* Calcd. for $C_{17}H_{24}O_4$: C, 70.40; H, 8.26. Found: C, 70.11; H, 8.17.

A composition–melting point diagram, which was constructed from data taken on the melting points of various synthetic mixtures of the *d*- and *dl*-forms, revealed an eutectic, m.p. 69–72°, with an approximate composition of 20% *dl*, 80% *d*.

The acid phthalate, $[\alpha]^{23}D$ +8.1° (*c* 1.5, $CHCl_3$), 2.92 g., was hydrolyzed to the carbinol which was steam distilled, 1.07 g., m.p. 40–41°. Four crystallizations of this alcohol from its melt failed to change this melting point. The rotation of this carbinol, $[\alpha]^{26}D$ +57.5° (*c* 20.4, methanol), was dependent upon concentration in chloroform as indicated by the following: $[\alpha]^{23}D$ +58.8° (*c* 19), +57.9° (*c* 35), +56.3° (*c* 56). Based on the assumption that the solid resolved carbinol has the same density as the *dl*-carbinol, namely 0.789 g./ml. at 20°, extrapolation of the specific rotation–concentration diagram to the absence of solvent gives a theoretical value of $[\alpha]^{23}D$ +54.5° (neat) for the supercooled liquid. The specific rotation decreased slightly with increased temperature. Since the carbinol obtained from the asymmetric reduction of isobutyl-*t*-butyl ketone had a specific rotation of $[\alpha]^{25}D$ −3.25° (neat), asymmetric reduction would be 5.9%.

An acetate and benzoate of the crystalline *d*-isobutyl-*t*-butyl-carbinol were prepared using carbinol of $[\alpha]^{25}D$ 54.5°; acetate, b.p. 73° (17 mm.), $n^{20}D$ 1.4176, $d^{22}$ 0.852 g./ml., $\alpha^{22}D$ +15.15° (neat, *l* 0.5). *Anal.* Calcd. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.98; H, 11.90. Benzoate, b.p. 88° (0.5 mm.), $n^{20}D$ 1.4870, $d^{25}$ 0.955 g./ml., $\alpha^{25}D$ +8.24° (neat, *l* 0.5). *Anal.* Calcd. for $C_{18}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.14; H, 9.78.

**Resolution of *n*-Butyl-*t*-butylcarbinol.**—The *n*-butyl-*t*-butyl-carbinol, $n^{20}D$ 1.4320, obtained by lithium aluminum hydride reduction (92% yield) of the ketone, was converted to the *dl*-acid phthalate, m.p. 100.5–102.0°, and then to the strychnine salt as described for the isobutyl isomer. The strychnine salt was difficult to crystallize, but it ultimately was subjected to a systematic seven-stage crystallization from acetone–methanol to give a less soluble salt, $[\alpha]D^{24}$ −20°; recrystallization from ethanol and isopropyl alcohol did not change the rotation. The acid phthalate was regenerated, but could be obtained only as a glass, $[\alpha]^{23}D$ +4.5° (*c* 2.8, $CHCl_3$). It was therefore saponified to the *n*-butyl-*t*-butylcarbinol, $n^{20}D$ 1.4314, $\alpha^{24}D$ +17.10° (neat, *l* 0.5). The *l*-phthalate from the more soluble fractions from the strychnine salt gave carbinol with rotation $\alpha^{24}D$ −16.39° (neat, *l* 0.5). Since the *l*- or *d*-phthalate did not crystallize, the same procedure was employed using the *dl*-tetrachlorophthalate of *n*-butyl-*t*-butylcarbinol, m.p. 126–128°. After forming and recrystallizing the strychnine salt, the less soluble form, $[\alpha]^{25}D$ −12°, was hydrolyzed to the acid tetrachlorophthalate, $[\alpha]^{22}D$ −9.69° (as a non-crystalline glass) which was saponified to the carbinol, $\alpha^{23}D$ +13.70° (neat, *l* 0.5).

The 3,5-dinitrobenzoate of the (+)-*n*-butyl-*t*-butylcarbinol, $\alpha^{24}D$ +17.10° (neat, *l* 0.5), was prepared (89% yield) and recrystallized three times from methanol, m.p. 107.5°, $[\alpha]^{25}D$ +10.0° (*c* 2.4, $CHCl_3$).

*Anal.* Calcd. for $C_{16}H_{22}N_2O_6$: C, 56.79; H, 6.55. Found: C, 56.80; H, 6.67.

By the same procedure the 3,5-dinitrobenzoate was prepared from the dl-*n*-butyl-*t*-butylcarbinol, m.p. 84.0–84.5°. A melting point–composition diagram, constructed from data taken on the melting points of a series of mixtures of the dextro and racemic forms, revealed an eutectic at approximately 90% concentration of racemic form, m.p. 81–83.5°. The dextro 3,5-dinitrobenzoate, m.p. 107.5°,

$[\alpha]^{25}D$ 10.0° (*c* 2.4, $CHCl_3$) was saponified to regenerate (+)-*n*-butyl-*t*-butylcarbinol, b.p. 76° (23 mm.), $n^{20}D$ 1.4310, $\alpha^{25}D$ +17.12° (neat, *l* 0.5), $d^{26}$ 0.823. The value for the pure isomer of *n*-butyl-*t*-butylcarbinol is taken as $\alpha^{25}D$ +34.24° (neat, *l* 1). Since the carbinol isolated from the reduction of *n*-butyl *t*-butyl ketone had a rotation of $\alpha^{25}D$ −3.78° (neat, *l* 1) the asymmetric reduction is 11.0%. In addition, the acetate of the carbinol obtained by asymmetric reduction was prepared, $\alpha^{25}D$ −2.60° (neat, *l* 1). Compared to the acetate of the 95.9% resolved carbinol described below, this indicates an asymmetric reduction of 11.1%, in excellent agreement.

The acetate, benzoate, and *p*-nitrobenzoate were prepared from the *n*-butyl-*t*-butylcarbinol, $\alpha^{25}D$ −32.8° (neat, *l* 1); acetate, b.p. 87° (20 mm.), $n^{20}D$ 1.4191, $d^{26}$ 0.851 g./ml., $\alpha^{26}D$ −11.25° (neat, *l* 0.5). *Anal.* Calcd. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 71.26; H, 11.91. Benzoate, b.p. 98° (0.5 mm.), $n^{20}D$ 1.4887, $d^{25}$ 0.936 g./ml., $\alpha^{25}D$ −7.29° (neat, *l* 0.5). *Anal.* Calcd. for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.25; H, 9.77. *p*-Nitrobenzoate, b.p. 144–145° (0.5 mm.), $n^{25}D$ 1.5070, $\alpha^{29}D$ −12.50°. *Anal.* Calcd. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90. Found: C, 65.32; H, 7.78.

(+)-1-Bromo-2-methylbutane was prepared by the method of Brauns,[27] 50 g. (41% yield), b.p. 60.8° (100 mm.), $n^{20}D$ 1.4453, $\alpha^{24}D$ +4.22° (*l* 1, neat), 84% optical purity. A second preparation gave 104 g. (43% yield), b.p. 57–58° (100 mm.), $\alpha^{26.5}$ +4.66°, 93% optical purity.

(+)-1-Iodo-2-methylbutane was prepared by treating the Grignard reagent prepared from the chloride[7a] with iodine in 57% yield, $n^{20}D$ 1.4955–1.4969, $\alpha^{21}D$ +8.65° (*l* 1, neat), 98.5% optical purity.[27] A second preparation gave 182 g. (46% yield), b.p. 70° (53 mm.), $n^{20}D$ 1.4969–1.4972, $\alpha^{25}D$ +16.8 (*l* 2, neat), optical purity[27] 96.5%.

(27) D. H. Brauns, *J. Res. Nat. Bur. Standards*, **18**, 315 (1937).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

# The Elimination Reaction of Alpha and Beta Deuterated *n*-Octyl Bromides with Potassium Amide in Liquid Ammonia[1]

BY SETA MAHAKIAN LUCK, DOUGLAS G. HILL, A. THEODORE STEWART, JR., AND CHARLES R. HAUSER

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The olefin produced by the reaction of *n*-octyl bromide-1-$d_2$ with potassium amide in liquid ammonia is shown to be formed exclusively by the β-elimination of hydrogen bromide, not partly through α-elimination of deuterium bromide as reported earlier. The olefin formed by the reaction of *n*-octyl bromide-2$d_2$ with this reagent arises not only from the β-elimination of deuterium bromide, but apparently also through a little α-elimination of hydrogen bromide as observed previously. This might be ascribed to an isotope effect.

It has previously been shown[2] that the olefins produced by the reactions of 2-ethylbutyl bromide-1$d_2$ and 2-ethylbutyl bromide-2$d_1$ with potassium amide in liquid ammonia and ether were formed exclusively from the anticipated β-elimination of hydrogen bromide and deuterium bromide, respectively.

However, the olefins formed from *n*-octyl bromide-1$d_2$ and *n*-octyl bromide-2$d_2$ with this reagent[2] appeared to arise not only from β-elimination, but also through some α-elimination accompanied by a 1,2-shift of hydrogen or deuterium from the β- to the α-carbon atom.

Evidence has now been obtained invalidating[3] the small extent of α-elimination reported for *n*-octyl bromide-1$d_2$ but supporting that for *n*-octyl bromide-2$d_2$.

**Results with *n*-Octyl Bromide-1$d_2$ (I).**—This deuterio halide was prepared by a modification of the method described previously[2] (equation 1).

$$n\text{-}C_6H_{13}CH_2CO_2C_2H_5 \xrightarrow[CH_3CO_2D]{Na} n\text{-}C_6H_{13}CH_2CD_2OD \xrightarrow{HBr} n\text{-}C_6H_{13}CH_2CD_2Br \quad (1)$$

The yield of the deuterio alcohol in the first step of this method was improved over that obtained earlier by the use of a larger excess of the sodium and carefully prepared deuterioacetic acid.

The deuterio halide I was prepared three times, but only one of these preparations contained the desired two deuterium atoms per molecule corresponding to formula I. The other two preparations contained less than two deuterium atoms per molecule indicating the presence of not only compound I but also *n*-octyl bromide-1$d_1$ and perhaps a little undeuterated *n*-octyl bromide.

The pure halide I was allowed to react with potassium amide in a mixture of liquid ammonia and ether and in liquid ammonia alone. The reaction medium appeared to be homogeneous under the former condition and non-homogeneous under the latter condition. The olefinic product was separated from the amine product[4] and isolated by distillation. The two other halide preparations were treated similarly.

In Table I are summarized the physical constants and deuterium contents of the three preparations of the halide and of the corresponding olefinic products. It can be seen from the notes to this table that the refractive indexes of the deuterated halide and olefin are in close agreement with those of *n*-octyl bromide and octene-1, respectively.

It can be seen from Table I that the pure halide I having two deuterium atoms per molecule (prepn. 1) gave an olefin that likewise had two deuterium atoms per molecule both under the homogeneous and non-homogeneous conditions. Similarly each of the two other halide preparations having less than

(1) Supported in part by the National Science Foundation.

(2) D. G. Hill, W. A. Judge, P. S. Skell, S. W. Kantor and C. R. Hauser, THIS JOURNAL, **74**, 5599 (1952).

(3) Preliminary mention of this was made in note 13 of a paper by D. G. Hill, B. Stewart, S. W. Kantor, W. A. Judge and C. R. Hauser, *ibid.*, **76**, 5129 (1954).

(4) Whereas such branched halides as 2-ethylbutyl bromide yield predominantly the olefin with potassium amide in liquid ammonia, *n*-octyl bromide gives mainly the corresponding primary amine or derivative.