[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OHIO STATE UNIVERSITY]

ASYMMETRIC INDUCTION AND RACEMIZATION IN COMPOUNDS CONTAINING THE OPTICALLY ACTIVE 2-METHYLBUTYL (ACTIVE AMYL) RADICAL

GEORGE Y. BROKAW AND WALLACE R. BRODE

Received September 4, 1947

In a continuation of induction studies in this laboratory, an attempt has been made to extend and correlate information in this field to include compounds containing the primary active amyl radical. This study of inductive effects has been directed primarily towards the induction produced in the reaction between a ketone (A) and an aliphatic Grignard reagent (B) to form a tertiary alcohol (C). Compounds (A) and (B) were chosen in such a manner that one of the two contained the optically active 2-methylbutyl (primary active amyl) radical.

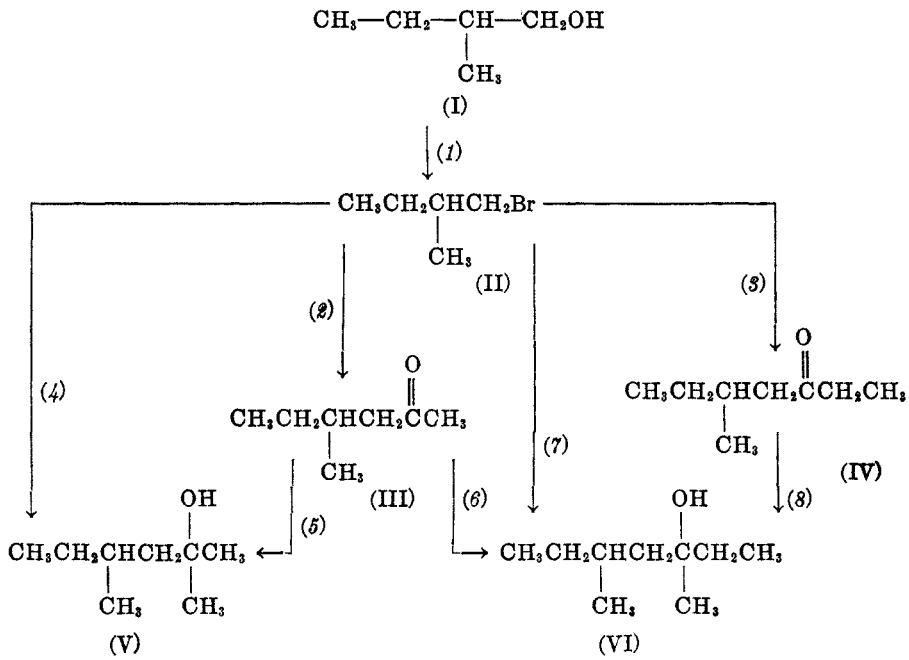


FIG. 1

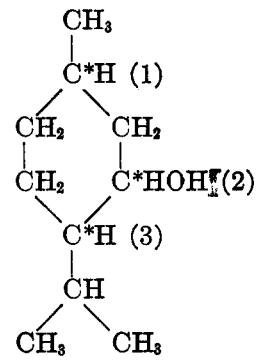
The other component was of such a nature that the resulting tertiary alcohol was 3,5-dimethyl-3-heptanol (VI), the compound for study, or 2,4-dimethyl-2-hexanol (V), the compound for reference. In certain of the procedures involved in the preparation of reagents (A) and (B) and in their interaction together, an unusual type of racemization was observed and studied.

The 2-methylbutyl radical was chosen as the optically active radical for use in this study partly because of its availability as "active amyl alcohol" (I) in

commercial fusel oil. Within this active amyl radical, the separation of the hydroxyl group and asymmetric center by the methylene structure permitted reaction upon the functional group without occurrence of Walden inversion or racemization by commonly accepted mechanisms.

By comparison of the above formulas and examination of the series of reactions in Fig. 1, it may be shown that carbon atom 2 in compound (I), carbon atom 4 in compound (V), and carbon atom 5 in compound (VI) are of identical configuration. The object of this study has been to determine the effect of the presence of this active center upon the configuration assumed by carbon atom 3 in compound (VI).

Recent investigations in the field of asymmetric induction have shown that the order of introduction of asymmetric centers may markedly influence the configuration produced. Hass and his co-workers (1) in attempting to synthesize *dl*-menthol (VII), partially reduced thymol to menthone, thus introducing asymmetric centers (1) and (3). Subsequent reduction of the menthone resulted in a considerable amount of the undesired diastereoisomer, *dl*-neomenthol. Brode and Van Dolah (2) in a recent study have shown that reversal of the order of creation of the asymmetric centers resulted in *dl*-menthol with only small amounts of *dl*-neomenthol present. No isomenthol or neoisomenthol was observed in the product. This reversal was effected by hydrogenation of thymol over copper-copper chromite, in which instance it is known that asymmetric centers (2) and (3) are the first to be introduced.



VII. Menthol

Among the reactions described in the chemical literature, involving optically active materials, that between a ketone and an aliphatic Grignard reagent to give a tertiary alcohol has been thoroughly investigated. Three approaches have been considered: (a) the reaction of an optically inactive ketone with an optically active solvent; (b) the reaction of an optically inactive ketone with an optically active Grignard reagent; and (c) the reaction of an optically active ketone with an optically inactive Grignard reagent. The first approach has met with negative results when applied to the type of reaction indicated above. The latter two approaches have previously met with some success, and both were considered in this study.

McKenzie and his co-workers (3) investigated some thirty reactions of α-ketonic esters of optically active alcohols with aliphatic and aromatic Grignard reagents. In each case the resulting α-hydroxy acid, after saponification, exhibited partial activity (usually in the order of 2–5%).

An important development was outlined by Roger (4) and further interpreted by Partridge (5) when they showed that in a reaction illustrative of approach (c), inverse order of introduction of substituents to the new center, when the inductive effect is sufficient, results in oppositely induced configuration. This result is a basis for one of the conclusions drawn from data obtained herein. Roger reacted optically active benzoin with ethylmagnesium bromide, and the optically active ethyl analog of benzoin (known to be of identical configuration) with phenylmagnesium bromide, obtaining diastereoisomeric ethylhydrobenzoins. Upon subsequent oxidation, the enantiomorphous forms of ethylbenzoin were produced.

TABLE I

3,5-DIMETHYL-3-HEPTANOL

	REACTION (6)		REACTION (7)		REACTION (8)	
	Trial (1)	Trial (2)	Trial (1)	Trial (2)	Trial (1)	Trial (2)
b.p.(35 mm.)	88.4–88.6	88.1–88.1	88.6–88.9	87.4–87.9	88.7–90.0	88.0–88.0
n_D	$1.4317^{24.2}$	1.4360^{15}	$1.4298^{24.2}$	1.4324^{28}	$1.4315^{24.2}$	1.4356^{15}
d	0.833^{24}	0.833^{28}	0.834^{24}	0.831^{28}	0.837^{24}	0.830^{28}
M_{470}*	—	+10.46	—	+9.91	+10.59	+10.28
M_{530}*	—	+8.04	—	+7.54	+8.10	+7.87
M_{589}*	6.49	+6.44	+5.99	+5.97	+.46	+6.34
M_{650}*	—	+5.29	—	+5.06	+5.37	+5.21
M_{470}/M_{650}	—	1.98	—	1.96	1.97	1.97

* The listed values for M_{589} are 48.0% (or less) of that which they would have been had bromide (II) been the optically pure dextrorotatory form.

EXPERIMENTAL

The series of reactions outlined in Fig. 1 were employed in this investigation, rotatory dispersions being obtained for each compound listed.

d(−)-2-Methyl-1-butanol (*I*), (b.p. 129°, n_D^{20} 1.4102, d^{25} 0.819, M_{470}^{20} −8.27, M_{530}^{20} −6.32, M_{589}^{20} −5.05, M_{650}^{20} −4.17): This optically active amyl alcohol was obtained by fractionation of fusel oils containing 10–22% of the desired alcohol. Columns with efficiencies near or in excess of 100 plates are essential to prevent this fractionation from being a long and very tedious process, since the isomeric isoamyl alcohol present boiled only 3° above the active component.

d(+)-2-Methyl-1-bromobutane (*II*), (b.p. 7104–71.7° at 150 mm., n_D^{20} 1.4455, d^{20} 1.225, M_{470}^{20} + 4.43, M_{530}^{20} +3.57, M_{589}^{20} +2.94, M_{650}^{20} +2.36): Bromination of (I) with PBr_3 resulted in compound (II). This bromide was observed to undergo racemization and rearrangement, resulting in *dl*-2-methyl-1-bromobutane and 2-methyl-2-bromobutane respectively, if the work-up procedure of Brauns (6) was not followed, and if the fractionation was not carried out at reduced pressure. The rotations listed above were obtained for partially racemized bromide which was employed in the induction study, and correspond to 48.0% of the values for the pure dextrorotatory isomer as obtained by Brauns and confirmed here.

The pure primary active bromide was relatively stable, both rearrangement and racemization being induced by heat and continuing thereafter at room temperature. Hydrobromic acid catalyzed racemization and inhibited rearrangement. Sodium acetate inhibited both rearrangement and racemization.

TABLE II

2,4-DIMETHYL-2-HEXANOL

	REACTION (4)		REACTION (5) Trial (1)	LITERATURE
	Trial (1)	Trial (2)		
b.p.(40 mm.)	77.0–77.4	76.4–77.0	76.9–77.0	64 @ 20 mm.
n_D	$1.4233^{24.2}$	$1.4250^{20.8}$	1.4250^{20}	—
d	0.827^{24}	0.818^{29}	0.820	—
M_{470}*	+9.84	+10.24	—	—
M_{530}*	+7.51	+7.89	—	—
M_{589}*	+6.07	+6.21	+6.71	—
M_{650}*	+4.93	+5.26	—	—
M_{470}/M_{650}	1.99	1.95	—	—

* The listed values for M_{589} are 48.0% (or less) of that which they would have been had bromide (II) been the optically pure dextrorotatory form.

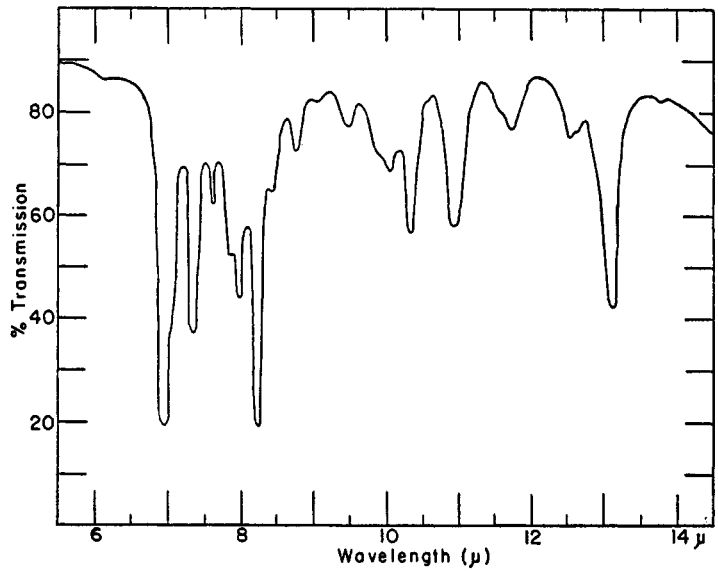


FIG. 2. INFRARED ABSORPTION SPECTRUM OF 1-BROMO-2-METHYLBUTANE

d-(+)-*4-Methyl-2-hexanone* (*III*), (b.p. 137.0–138.0°), and *d*(+)-*5-methyl-3-heptanone* (*IV*), (b.p. 157.0–158.0°): These ketones were prepared in excellent yield by the method of Newman and Booth (7), adding the Grignard reagent from (II) to the appropriate anhydride at −80°.

3, 5-Dimethyl-3-heptanol (*VI*), (see Table I): Nearly identical rotation was observed for this alcohol when prepared from either ketone (III) or ketone (IV). When prepared directly from bromide (II), the alcohol (VI) had a somewhat lower rotation.

2,4-Dimethyl-2-hexanol (*V*), (see Table II): As in the case of (VI), this alcohol also had a lower rotation when prepared directly from bromide (II) than when prepared from ketone (III).

An infrared investigation of certain C_6 compounds was undertaken to determine the extent of racemization and of rearrangement. *d*(+)-2-Methyl-1-bromobutane (Fig. 2) and 2-methyl-2-bromobutane (Fig. 3) were included among these compounds. The partially racemic primary bromide displays an absorption identical with that in Fig. 2. The tertiary bromide was found to have absorption maxima at 8.9 and 12.6 μ which were applicable for analysis. A measurement of the absorption of these peaks provided an estimation of the amount of tertiary bromide present. The rotatory power was an indication of the amount of *d*(+) primary bromide present. The remainder was *dl* primary bromide.

A mixture of known composition (by the method shown above) was refluxed with hydrobromic acid, sodium acetate, and by itself. The composition of each resultant mixture

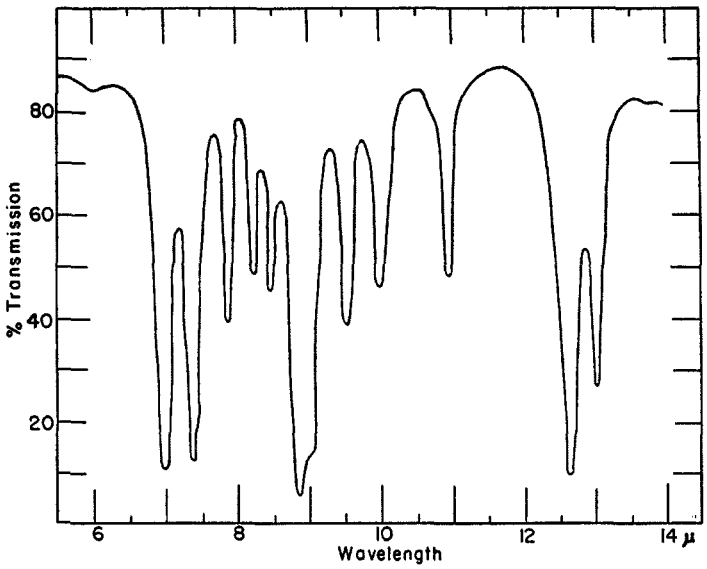


FIG. 3. INFRARED ABSORPTION SPECTRUM OF TERTIARY AMYL BROMIDE

was used to determine the relative amounts of racemization or rearrangement which had occurred.

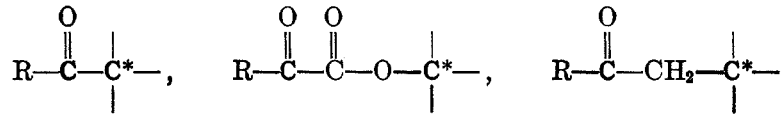
CONCLUSIONS

3,5-Dimethyl-3-heptanol was identical when prepared from either ketone (III or IV). This proved that inverse order of introduction of substituents to the new center resulted in identical configuration at that new center. In retrospect to the work of Roger and the interpretation of Partridge, it is reasonable to conclude that the ketones, in the reactions considered, exerted negligible influence toward preferential assumption of configuration at the new center.

When prepared directly from bromide (II), 3,5-dimethyl-3-heptanol (VI) showed a lower rotation than when prepared from ketones (III) and (IV). However, 2,4-dimethyl-2-hexanol (V), showed the same difference in rotation when prepared by the same two procedures. Since no second asymmetric center exists in (V), the difference must be ascribed to partial racemization of the op-

tically active center originally present. The difference noted for (VI), being analogous with respect to sign and order of magnitude, is therefore assumed to be due to the same effect.

The lack of inductive effect noted herein was correlated with results of Roger and of McKenzie to provide an interpretation of transmission or insulation of inductive power from directing center (C) to reaction center (C=O). The following structures are listed in decreasing ability to transmit this influence:



It is acknowledged that the compounds illustrating previous work possess structures permitting a coordination with the Grignard reagent. Since this might easily affect this last named conclusion, a projected program is planned to prove whether or not the methylene insulation is effective, such structures being present.

Both racemization and rearrangement of $d(+)$-1-bromo-2-methylbutane were initiated by heat but continued thereafter at room temperature. Variations in preparation of this bromide indicated that heat was the primary factor in initiating the deterioration of the optically active material.

The use of infrared absorption techniques was essential in determining the purity of the bromide (II) used for the induction study, as well as providing the only suitable method for investigation of the observed racemization and rearrangment. The absorption spectra for pure primary active amyl bromide ($M\ ^{D}_{589}+6.09$) (which is identical with that for the partially racemized bromide employed in the induction study) and for pure tertiary amyl bromide (the rearranged product) are presented in Figs. 2 and 3.

SUMMARY

The primary active amyl radical, when present as a part of the reagent molecules, has been shown to exert very little, if any, effect upon the configuration assumed by the new asymmetric center arising from the addition of a Grignard reagent to an unsymmetrical ketone.

The racemization (heretofore suspected, but never proved) and rearrangement of $d(+)$-2-methyl-1-bromobutane has been briefly studied. Two of the infrared curves used in this study are presented.

COLUMBUS, 10, OHIO

REFERENCES

(1) BARNEY AND HASS, *Ind. Eng. Chem.*, **36**, 85 (1944).
(2) BRODE AND VAN DOLAH, *Ind. Eng. Chem.*, **39**, 1157 (1947).
(3) MCKENZIE AND CO-WORKERS, *J. Chem. Soc.*, **85**, 1249 (1904); **95**, 544 (1909); *Biochem. Z.*, **237**, 1 (1931); **250**, 376 (1932); **231**, 412 (1931).
(4) ROGER, *J. Chem. Soc.*, 108 (1939).
(5) PARTRIDGE, *J. Chem. Soc.*, 1201 (1939).
(6) BRAUNS, *J. Research Nat. Bur. Standards*, **18**, 315 (1937).
(7) NEWMAN AND BOOTH, *J. Am. Chem. Soc.*, **67**, 154 (1945).