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THE ABSOLUTE CONFIGURATION OF *TRANS*-1,2-DIMETHYLCYCLOPROPANE

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Abstract—By application of the newly discovered fact that 1° alkyl chlorides with γ-hydrogen form cyclopropanes on treatment with sodium metal, ( )-*trans*-1,2-dimethylcyclopropane has been prepared from (+)-1-chloro-2-methylbutane. Rigorous assignment of configuration to the isomeric *cis*- and *trans*-dimethylcyclopropanes is thereby achieved. The absolute configuration, (1R : 2R) *trans*-1,2-dimethylcyclopropane, can be assigned to the ( ) enantiomer by several lines of argument and agrees with that calculated by Fitts.

1,2-DIMETHYLCYCLOPROPANES have been used so often as reference substances in studies of the mechanism of the addition of carbenes to olefins[1–3] that a firm establishment of *cis* and *trans* configuration is clearly desirable. With previous assignment having been based on the empirical Auwers–Skita rule,[1,4] a more rigorous and positive assignment can be based on the theoretical necessity that the *trans* isomer alone may exist in optically active form. In this paper, we report the preparation in optically active form of that isomer previously, and now correctly, considered to be *trans*.

The preparation is accomplished by an application of the cyclopropane synthesis reported in the preceding paper.[5] The dextrorotatory chloride obtained from laevorotatory 2-methyl-1-butanol[6] was treated with sodium to give a mixture of C_5 hydrocarbons in 63 per cent of theory. Analysis of this mixture by gas liquid partition chromatography (g.l.p.c.) showed it to consist of isopentane (55·6 per cent), 2-methylbutene-1 (23·4 per cent), ethylcyclopropane (9·3 per cent) and *trans*-1,2-dimethylcyclopropane (11·7 per cent). The two cyclopropane derivatives were identified by retention times and comparison of mass spectra with those of authentic samples. *cis*-1,2-Dimethylcyclopropane may be formed in very small amount, but in the absence of adequate identification cannot be considered to be an established product. The high degree of stereoselectivity is presumably a reflection in the transition state of the thermodynamically greater stability of the *trans* isomer.

The ratio of 1,2-dimethylcyclopropane to ethylcyclopropane is a measure of the ability of the intermediate carbene to discriminate between 2° and 1° hydrogen. Methylene generated photochemically from diazomethane shows no discrimination[7] in *solution*, but does discriminate in the *gas phase* at the higher total pressures.[8] This difference has been ascribed to the intervention of "hot" methylene molecules. In solution, formed with excess energy, these react on every collision with little or no discrimination; in the gas phase, they are cooled to thermal methylene molecules by

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[1] W. von E. Doering and P. M. LaFlamme, *J. Amer. Chem. Soc.* **78**, 5447 (1956).

[2] P. S. Skell and R. C. Woodworth, *J. Amer. Chem. Soc.* **78**, 4496 (1956).

[3] H. M. Frey, *J. Amer. Chem. Soc.* **80**, 5005 (1958); *Proc. Roy. Soc.* **251**, 575 (1959).

[4] J. Baudrenghien, *Bull. Soc. Chim. Belg.* **38**, 172 (1929).

[5] W. Kirmse and W. von E. Doering, *Tetrahedron* **11**, 266 (1960).

[6] H. C. Brown and C. Groot, *J. Amer. Chem. Soc.* **64**, 2563 (1942).

[7] W. von E. Doering, R. G. Buttery, R. G. Laughlin and N. Chaudhuri, *J. Amer. Chem. Soc.* **78**, 3224 (1956); D. B. Richardson, M. C. Simmons and I. Dvoretzky, *J. Amer. Chem. Soc.* **82**, 5001 (1960).

[8] H. M. Frey and G. B. Kistiakowsky, *J. Amer. Chem. Soc.* **79**, 6373 (1957).

prior collision with inert gas and then react with discrimination favoring 2° hydrogen over 1° by a factor of about 1·7. In the reaction of alkyl halide with sodium, the intermediate carbene is generated in a way[5] which is not expected to produce methylene with excess energy. In the present example reaction with 2° hydrogen is favored by a factor of 1·9 over reaction with 1° hydrogen. This observation can be considered to support the hypothesis that "hot" methylene is the reactive species in the photolysis of solutions of diazomethane.

MASS SPECTRA

	ethylcyclopropane		*trans*-1,2-dimethylcyclopropane	
m/e	obs.	lit[a]	obs.	auth.[b]
71	2·0	1·5	3·0	3·5
70	32	28	78	62
69	1·0	1·0	2·2	2·5
56	2·5	2·3	4·2	4·6
55	74	50·2	100	100
54	1·0	2·0	2·2	2·5
53	4·3	6·3	8·3	8·4
43	4·5	3·8	3·0	3·8
42	100	100	48	44
41	36	42	36	37
40	6·5	9·1	4·7	4·8
39	22	38	27	26
38	2·3	6·2	2·2	2·3

[a] American Petroleum Institute Research Project 44, Mass Spectrum 1652.
[b] From a sample prepared by D. L. MacDuffie.

The specific rotation of *trans*-1,2-dimethylcyclopropane was estimated by enriching a crude fraction of b.p. 28·0–28·5° to 26 per cent by separation on a preparative g.l.p.c. column. This material was then purified by passing many small batches through a small column of sufficient resolution to allow isolation of pure material, the specific rotation of which was 46·0°. Barring the unlikely possibility of partial racemization during the reaction of the active amyl chloride with sodium, this value may be taken as that of fully resolved material. Although the starting 2-methylbutanol-1 had a rotation (5·71°) somewhat below the most reliable value (−5·88°),[9] the discrepancy is due almost certainly to contamination by isomeric rather than enantiomeric alcohol.

The proof of structure of *trans*-1,2-dimethylcyclopropane is therefore complete, and, with it, the conclusion that methylene and dibromocarbene add to *cis*- and *trans*-butene by *cis*-addition[1] is given an unquestionably sound basis.

The absolute configuration of (-) *trans*-1,2-dimethylcyclopropane may now be deduced. Its configuration relative to ( ) 2-methylbutanol-1 is clear enough. Neither by analogy with known reactions nor by application of current mechanistic theory is there reason to suspect that the conversion to chloride and its subsequent closure to cyclopropane would jeopard the assymetric center in any way.

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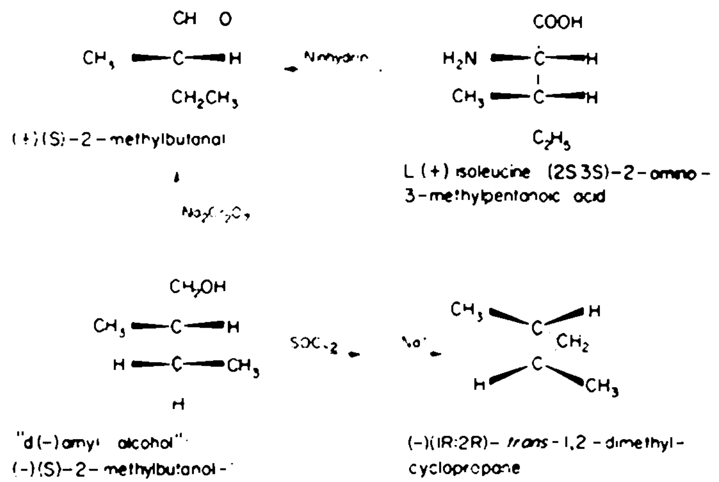
[9] F. v Falkenhausen and C. Neuberg, *Biochem. Z.* **242**, 482 (1931).



There are at least three arguments in the literature that relate 2-methylbutanol-1 to tartaric acid, the absolute configuration of which has been determined by X-ray crystallography.[10] One is by Freudenberg and Hohmann[11], another is by Crombie and Harper[12] and a third is by Mills and Klyne[13]. All agree in assigning the (S) configuration to (−)-2-methylbutanol-1.[14]

There is another more direct sequence relating d(−)amyl alcohol to L(+)isoleucine in which both are connected to (+)-2-methylbutanal, the former by oxidation with sodium dichromate,[15] the latter by reaction with ninhydrin.[16] Since the absolute configuration of the enantiomorphic isoleucines has been determined by Trommel and Bijvoet by X-ray crystallography[17] in the sense that D(−)isoleucine is (−)(2R:3R)-2-amino-3-methylpentanoic acid, d(−)amyl alcohol has the configuration (S)-2-methylbutanol-1. With complete consistency prevailing between the chemical interrelationships and the absolute configurational determinations by X-ray, the absolute configuration of (−)(S)-2-methylbutanol-1 is established. The absolute configuration of laevorotatory *trans*-1,2-dimethylcyclopropane is therefore (1R:2R).

Establishment of the absolute configuration of (−)(1R:2R)-*trans*-1,2-dimethylcyclopropane permits another comparison with the theory of optical activity.[18] The theoretical calculation of the specific rotation of the (1R:2R) enantiomer has been made quite recently by Fitts[19] on the basis of Kirkwood's theory. The calculated value (−16·0°) agrees in sign with that of the observed value (−46·0°). Better quantitative agreement might have been expected since a single conformation probably suffices to describe the molecule. The entire illustration consisting of the theoretical calculation,

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[10] J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, *Nature, Lond.* **168**, 271 (1951); A. J. van Bommel and J. M. Bijvoet, *Acta Cryst.* **11**, 61 (1958).

[11] K. Freudenberg and W. Hohmann, *Liebigs Ann.* **584**, 55 (1953).

[12] L. Crombie and S. H. Harper, *J. Chem. Soc.* 2685 (1950).

[13] J. A. Mills and W. Klyne, *Progress in Stereochemistry* Vol. I, p. 197. Academic Press, New York (1954).

[14] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956).

[15] E. J. Badin and E. Pacsu, *J. Amer. Chem. Soc.* **67**, 1352 (1945).

[16] W. S. Fones, *J. Amer. Chem. Soc.* **76**, 1377 (1954); F. Ehrlich, *Ber. Dtsch. Chem. Ges.* **40**, 2538 (1907).

[17] J. Trommel and J. M. Bijvoet, *Acta Cryst.* **7**, 703 (1954).

[18] For a review, see W. Kuhn, *Z. Electrochem.* **56**, 506 (1952).

[19] D. D. Fitts in A. Weissberger, *Technique of Organic Chemistry, Physical Methods of Organic Chemistry* (3rd Ed.) Vol. I, Part III, Interscience, New York (1960).

the absolute X-ray configuration and the present chemical interrelationship is a strikingly simple addition to the subject of absolute configuration.

EXPERIMENTAL

(+)(1R:2R)-trans-1,2-*Dimethylcyclopropane*. The starting material, (−)(S)-2-methylbutanol-1, was obtained by the fractional distillation of enriched d(−)amyl alcohol and had $[\alpha]_D^{20}$ −5·71° (neat). The most reliable value for pure alcohol is −5·88°.[•]

This alcohol was converted by thionyl chloride in pyridine according to Brown and Groot[•] to (+)(S)-1-chloro-2-methylbutane, $[\alpha]_D^{20}$ + 1·66° (neat).

The cyclization was carried out without solvent by adding 21·2 g (0·2 mole) (+)amyl chloride gradually to 4·6 g (0·2 mole) sodium in a flask equipped with a short Vigreux column, a condenser and a dry-ice trap. A slow stream of nitrogen was passed through the mixture. After all the chloride had been added, the temperature was raised to 150 for 1 hr. A total of 6·1 g (44 %) material boiling below 40° was collected.

For analysis, g.l.p.c. on a 6 m column of polyether was used. The products with their relative areas follow: isopentane (140); 2-methylbutene-1 (60); *trans*-1,2-dimethylcyclopropane (23·5); ethylcyclopropane (16·5); 3-methylbutene-1 (3); and a small, unidentified peak (1·5) having the retention time of 2-methylbutene-2 and *cis*-1,2-dimethylcyclopropane. Ethylcyclopropane and *trans*-1,2-dimethylcyclopropane were isolated and identified by their mass spectra. These were measured on a Consolidated Engineering Corp., Mass Spectrometer Model 21·401 at 70 volts.

When the cyclization was carried out in 50 ml cyclohexane, 42·4 g (0·4 mole) (+)-amyl chloride was added to 9·2 g (0·4 mole) sodium fast enough to maintain gentle reflux and the flask was modified by replacing the short column by a 50 cm one fitted with a distillation head. About 19 g material boiling below 40 was collected. Since it contained 7-8 % cyclohexane, the yield of C_4 hydrocarbons was 17·5 g (63 %). To determine the composition of this product four analyses on the 6 m polyether column were averaged; isopentane (125); 2-methylbutene-1 (52·6); *trans*-1,2-dimethylcyclopropane (26·2); and ethylcyclopropane (21·2).

The crude mixture was carefully fractionated in a 50 cm helix-packed column. A fraction, b.p. 28·0 28·5°, was analyzed four times by g.l.p.c. and found to contain 13·24 ± 0·31 % *trans*-1,2-dimethylcyclopropane. A solution of 2·935 g of this mixture (corresponding to 0·386 g *trans*-1,2-dimethylcyclopropane) made up to 10·00 ml with diethylene glycol dimethylether (diglyme) had an observed rotation of 1·67° (1dm tube). This corresponds to $[\alpha]_D^{20}$ 43 ± 2°.

The fraction, b.p. 28·0 28·5°, was then concentrated to 26 % by passing through a 2", 4 ft preparative silicone column (which failed to resolve the cyclopropane from its adjoining neighbors, isopentane and 2-methylbutene-1) and finally isolated pure by passing many 100 mg samples through the 1/4", 6 m polyether column (2-methylbutene-3-and 2-methylbutene-1 were fully resolved nearest neighbors). A solution of 54·3 mg pure *trans*-1,2-dimethylcyclopropane made up to 2·00 ml with 1·885 g diglyme had α^{20} - 1·25° (1 dm tube) corresponding to $[\alpha]_D^{20}$ - 46·0°.

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