by a Wood's metal bath. The temperature of decomposition was taken from the time carbon dioxide was evolved. Concomittantly the volatile products including xanthone distilled from the reaction mixture. In the experiments with silica gel or calcium oxide very little carbon dioxide or distillable products were produced. Xanthone could be isolated in 9% yield from the distillate. Although some charring occurred in the reaction vessel, acid could be recovered by dissolving the residue in water, filtering, and acidifying.

The products were analyzed by separating the xanthone from the distillate mixtures with petroleum ether (b.p. 30–60°) in which it is insoluble. The petroleum ether solution after concentration was chromatographed with alumina.

Reaction with anthracene. Anthracene (20 g.) was intimately ground together with 15 g. of lithium *o*-fluorobenzoate and heated in an evacuated heavy wall Pyrex bomb tube at 400° for 15 min. After cooling the contents of the tube was extracted continuously with benzene. Evaporation of the solvent yields a solid mixture of only anthracene and xanthone (1 g.).

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The Relative Stabilities of *cis* and *trans* Isomers. X. The 1,3-Cyclohexanedicarboxylate Esters[1,2]

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Since the pioneering work of von Auwers,[3] organic chemists have been interested in the relationships between the stereochemical structures of compounds and their bulk physical properties such as density and boiling point. The Conformational Rule appears to be the pertinent relationship of widest applicability.[4,5] Exceptions to the rule are known, but rare, and it is instructive to seek the reasons behind such exceptions. Among hydrocarbons, the only pair of isomers known to the authors which do not follow the rule are the bicyclo[3,3,0]octanes.[6] The reasons for failure in this case are now understood,[7] and the Conformational Rule therefore is a reliable and useful method for assignment of geometrical structure to hydrocarbons.

Compounds containing functional groups present potentially more difficult systems to understand. Eliel and Haber[8] have shown that isomeric pairs of the various methylcyclohexanols follow the conformational rule (in terms of molecular volume), but the isomer with an equatorial hydroxyl always boils higher than the axial epimer. They have made the reasonable suggestion that this fact may be due to hydrogen bonding. Clearly, application of the rule for structural determination of compounds other than hydrocarbons can give only tentative conclusions until such interactions have been better delineated.

Apparent exceptions to the rule are the isomeric esters of 1,3-cyclohexane dicarboxylic acid.[9] The heats of combustion indicate a lower enthalpy for the *trans* isomer, and this is opposite what conformational analysis predicts. The difference is only of the order of experimental error though, and is almost certainly incorrect *a priori.* The refractive index and density of the *cis*-dimethyl ester are lower than the corresponding values for the *trans* compound, but the boiling point (at reduced pressure) is higher. With the diethyl esters, the *cis* isomer is reported to have the higher boiling point and refractive index, together with the lower density.

The present work was undertaken with the intention of confirming or denying the various relationships in physical properties reported by Skita and Rössler, as very powerful analytical methods which were not available to the earlier investigators could be brought to bear on the problem.

The geometrical structures of the acids are known with certainty, as the *cis* isomer forms an anhydride and the *trans* has been resolved.[10] Samples of the diastereomerically pure methyl esters were prepared by treating the corresponding pure acids with diazomethane. Vapor phase chromatography of these compounds with a column of silicone on firebrick showed each was pure, and contained less than 1% of the other isomer. The densities (and refractive indices) of these compounds are in agreement with the rule (Table I) and agree well with those reported by Skait and Rössler. Because of the well known difficulty of obtaining accurate boiling points at reduced pressure, the boiling points were measured at atmospheric pressure (752 mm.). It was was found that the *cis* isomer boiled higher than did the *trans* as reported.[9]

The conformational rule qualitatively (quantitatively under certain conditions[11]) relates the dif-

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(1) Paper IX, N. L. Allinger and S. Greenberg, *J. Org. Chem.*, **25**, 1399 (1960).

(2) This work was supported by a Frederick Gardner Cottrell grant from the Research Corporation.

(3) K. von Auwers, *Ann.*, **420**, 84 (1920).

(4) N. L. Allinger, *J. Am. Chem. Soc.*, **79**, 3443 (1957).

(5) The rule states: "For stereoisomers in cyclic systems which do not differ in dipole moment, the isomer which has the smaller molecular volume is the isomer which has the higher heat content." It is usually true the isomer with the smaller molecular volume (higher density) is also the isomer of higher refractive index and higher boiling point, but the relationship is less dependable with these properties.

(6) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 436 (1935).

(7) Unpublished work by Dr. V. Zalkow.

(8) E. L. Eliel and R. G. Haber, *J. Org. Chem.*, **23**, 2041 (1958).

(9) A. Skita and R. Rössler, *Ber.*, **72**, 265 (1939).

(10) J. Boeseken and A. E. J. Peek, *Rec. Trav. Chim.*, **44**, 841 (1925).

TABLE I

Physical Constants of the Esters of 1,3-Cyclohexanedicarboxylic Acids

Ester	B.P. (752 mm.)	d_4^{20}	n_D^{21}
cis-Dimethyl	278	1.0997	1.4544
trans-Dimethyl	266	1.1098	1.4552
cis-Diethyl	294	1.0464	1.4496
trans-Diethyl	286	1.0483	1.4495

ference in enthalpy between the two isomers to the difference in molecular volume. As the difference in entropy between such a pair of isomers is expected to be quite small.[12] conformational analysis predicts the difference in free energy should favor the *cis* at equilibrium. The methyl esters were equilibrated by heating one isomer under reflux in a solution in methanol containing sodium methoxide. Analysis of the resulting mixture by vapor phase chromatography showed that it contained 30% of the *trans* isomer and 70% of the *cis*, which gives the latter a more negative free energy by 0.58 kcal./mole under these conditions (340° K). The energy (enthalpy) of a carbomethoxyl group in the axial position can be estimated by recognizing that the *trans* ester exists as a racemate and hence has its entropy increased by R ln 2 entropy units. At 340° K., assuming the contributions to the entropies of the two isomers are otherwise the same, $T\Delta S = 0.47$ kcal./mole favoring the *trans* isomer. Taking this into account, it is calculated for the reaction *trans* $\rightleftharpoons$ *cis*-1,3-dicarbomethoxycyclohexane that $\Delta H = -1.05$ kcal./mole, and this value is taken as a measure of the conformational energy of the carbomethoxyl group.[13,14] It is quite reasonable that the value is much smaller than the corresponding value for a methyl group (1.8 kcal./mole), as the ester group is flat, and when in the axial position it can turn in such a way as to largely avoid the axial hydrogens.[5] An axial carboxyl group is reported,[15,16] to have a somewhat larger energy (1.6–1.7 kcal./mole) than that found in the present work for the esters. The difference probably results because the carboxyl group can lower its energy by hydrogen bonding, and the group is more accessible for hydrogen bond formation when it is equatorial.

The diethyl esters were prepared from the acids using diazoethane, and they were equilibrated in absolute ethanol containing sodium ethoxide. The equilibrium composition was 71% *cis* and 29% *trans*, essentially the same as for the dimethyl esters. The physical constants for the two isomers were in good qualitative agreement with those reported by Skita and Rössler. The difference between the refractive indices of the *cis* and *trans* isomers is 0.0001 (Table I), and these numbers are regarded as experimentally indistinguishable. The densities vary by a significant amount, that of the *trans* being larger than that of the *cis* in agreement with the rule. The boiling point of the *cis* is higher than that of the *trans*.

The conclusion is drawn from the data that the Conformational Rule, which is based on densities as stated earlier, does apply correctly to these compounds. The fact that the constants of the diethyl esters are more similar than those of the dimethyl esters suggests that increasing molecular size would soon cause the properties of the *cis* and *trans* isomers to approach one another, and would presumably limit the usefulness of the rule to cases where the properties were significantly different.

The boiling points require comment. The dipole moments of either pair of isomers are quite similar,[9] that of the *cis* being some 0.2 D larger than that of the *trans* in each case. These differences are too small to be very meaningful, however, as clearly the Conformational Rule, and not the Dipole Rule, is being followed. The difference in boiling points appears too large to be ascribed to the difference in the total molecular dipole moments, and yet is in the reverse direction to that suggested by the Conformational Rule. Hence it appears that the boiling point difference in this case is determined principally by the intermolecular attraction of the separate dipoles in the molecules. The equatorial groups are more available and show larger attractive forces to other molecules, and hence the diequatorial *cis* isomers have the higher boiling points. With a series of cyclohexanols, the compounds with equatorial hydroxyl groups had higher boiling points than the corresponding axial epimers, and this fact was attributed to intermolecular hydrogen bonding.[8] As in the present case such hydrogen bonding is not possible and the same boiling point relationship still occurs, an economy of hypotheses suggests that in the cyclohexanol cases also, the dipolar attractions may be responsible for the observed results.

EXPERIMENTAL

cis- and trans-1,3-Cyclohexanedicarboxylic acids. These compounds were prepared by hydrogenation of dimethyl isophthalate with platinum oxide in acetic acid. The esters were hydrolyzed and the isomeric acids were separated and purified according to Skita and Rössler.[9] The *cis* acid had m.p. 168–169° (reported[9] m.p. 167.5°) and the *trans* isomer had m.p. 149–150° (reported[9] m.p. 150.5°).

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[11] N. L. Allinger, M. Nakazaki, and V. Zalkow, *J. Am. Chem. Soc.*, **81**, 4074 (1959).

[12] R. M. Gascoigne, *J. Chem. Soc.*, 876 (1958).

[13] This energy was independently determined in another way by E. L. Eliel, R. V. Acharya, and H. Haubenstock (private communication). Their tentative value is 1.2 ± 0.2 kcal./mole. See E. L. Eliel, *J. Chem. Ed.*, **37**, 126 (1960).

[14] The effectively small size of the carbomethoxyl group was noted earlier in the steroid series, N. L. Allinger R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, **25**, 922 (1960).

[15] R. D. Stolow, *J. Am. Chem. Soc.*, **81**, 5806 (1959).

[16] M. Tichy, J. Jonas, and J. Sicher, *Coll. Czech. Chem. Comm.*, **24**, 3434 (1959).

Esterifications. The esters were prepared from the pure acids with the appropriate diazolkane. The procedure below is representative.

A solution of diazoethane in methylene chloride was prepared from 20 g. of *N*-nitrosoethylurea in the usual way.[17] To this solution was added in small portions 2.0 g. of *cis*-1,3-cyclohexanedicarboxylic acid. The solvent was evaporated and the residue was distilled at 1.5 mm. The distillate was collected in three fractions, the last two of which were shown by vapor phase chromatography to be quite pure. Experiments with known mixtures showed that the *cis* and *trans* isomers were easily separable by vapor phase chromatography. A silicone on firebrick column was used for the separation with a column temperature of 200°. The retention times were on the order of 20 min., and no equilibration occurred on the column under these conditions. The physical constants of the esters are listed in Table I.

Equilibration. *cis*-Diethyl 1,3-cyclohexanedicarboxylate, 2.8 g., was dissolved in 100 ml. of absolute ethanol containing 2.0 g. of sodium. The resulting solution was heated under reflux for 2 hr., cooled, and poured onto a mixture of ice and 6*N* hydrochloric acid. The resulting cold acid solution was extracted with ether, and the combined ether solutions were washed with a dilute bicarbonate solution. After drying the ether solution with anhydrous magnesium sulfate, the solvent was evaporated and the residue was distilled at 1.5 mm. The distillate was analyzed by vapor phase chromatography, and was found to contain 71 ± 4% *cis* and 29 ± 4% *trans* ester. A sample of this material was again treated under equilibration conditions, and the product was isolated and analyzed as before. The composition was unchanged, indicating that equilibrium had been reached. The dimethyl esters were equilibrated in a similar manner, using methanol as the solvent and sodium methoxide as the base. The equilibrium mixture was found to contain 70 ± 4% *cis* and 30 ± 4% *trans* ester in this case.

Acknowledgment. The authors are indebted to Professor E. L. Eliel for helpful discussion concerning the present work.

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[17] W. E. Bachmann and W. S. Struve, *Org. Reactions*, **1**, 50 (1942).

Synthesis of Substituted Tetrahydrofurans. An Application of the Grignard Reagent from 3-Bromo-1-(1,1-dimethylpropoxy)propane[1]

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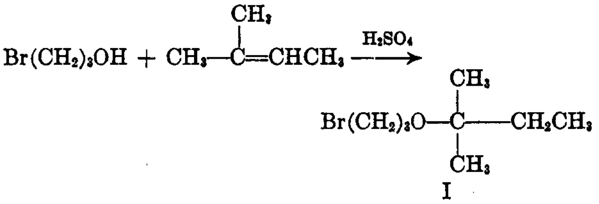
t-Butyl ester have been shown to be useful in certain syntheses involving malonic[2] and acetoacetic[3] esters because the ester groups can be cleaved by heating with a strong acid to produce a hydroxyl group and 2-methylpropene. Similarly, we have prepared the *t*-amyl ether of 3-bromo-1-propanol, converted the bromo ether to a Grignard reagent and examined some synthetic applications of this reagent resulting from cleavage of the ether grouping.

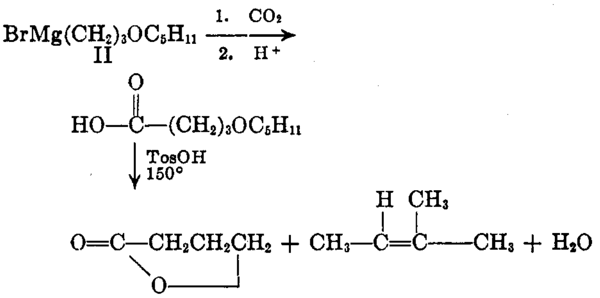
The method of Evans and Edlund[4] was adapted to the preparation of 3-bromo-1-(1,1-dimethylpropoxy)propane (I) from 3-bromopropanol and 2-methyl-2-butene.



$$Br(CH_2)_3OH + CH_3-\overset{\displaystyle CH_3}{\overset{|}{C}}=CHCH_3 \xrightarrow{H_2SO_4} Br(CH_2)_3O-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{C}}-CH_2CH_3$$

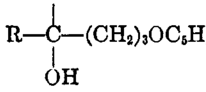
I

The bromo ether (I) formed a Grignard reagent (II) in about 80% yield as estimated by titration of an aliquot with standard acid. The structure of II was confirmed by carbonation. The resulting acid showed the expected analytical values and was converted to γ-butyrolactone by heating with a catalytic amount of *p*-toluenesulfonic acid.



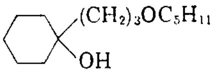
$$\underset{\text{II}}{BrMg(CH_2)_3OC_5H_{11}} \xrightarrow[2.\ H^+]{1.\ CO_2} HO-\overset{\displaystyle O}{\overset{\|}{C}}-(CH_2)_3OC_5H_{11} \xrightarrow{TosOH,\ 150^\circ} O=C-CH_2CH_2CH_2(-O-) + CH_3-\overset{H}{C}=\overset{CH_3}{C}-CH_3 + H_2O$$

The Grignard reagent (II) reacted normally with acetone, benzaldehyde and cyclohexanone to produce hydroxy ethers III, IV and V. These were converted to substituted tetrahydrofurans (VI, VII, VIII), water, and isoamylene by heating with *p*-toluenesulfonic acid.

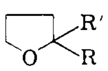


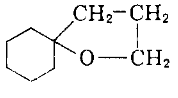
$$R-\underset{\displaystyle OH}{\overset{\displaystyle R'}{C}}-(CH_2)_3OC_5H_{11}$$

III. $R = R' = CH_3$
IV. $R = H, R' = C_6H_5$

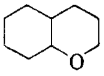


V





VIII



IX

VI. $R = R' = CH_3$
VII. $R = H, R' = C_6H_5$

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[1] Supported by a grant from Research Corporation.

[2] D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1286 (1944).

[3] W. B. Renfrow and G. B. Walker, *J. Am. Chem. Soc.*, **70**, 3957 (1948).

[4] T. W. Evans and K. R. Edlund, *Ind. and Eng. Chem.*, **28**, 1186 (1936).