

able glass rod (held in the neck of the flask by a neoprene stopper) which protruded into the flask and a 35-cm. length of glass tubing (6 mm.) which was connected to a 100-ml. gas buret (readable to 0.05 ml. and containing mercury) through a three-way stopcock. The tube connecting the reaction flask and three-way stopcock was equipped with a 20-cm. water jacket through which cool water could be circulated. During runs the bulb of the reaction flask was immersed completely in a rapidly stirred, insulated, mineral oil-bath the temperature of which could be maintained within 0.05° in the range of 90–120°. The reaction flask was attached by a 30-cm. length of light metal rod to a separate ringstand which was caused to vibrate by the movements of a small electric motor having a 30-g. metal weight attached to one side of the rotating shaft. The flask could be shaken by this arrangement through an arc of about 0.7 cm. at a constant rate (approximately 300 times per minute).

An accurately weighed sample of the acid to be decarboxylated (0.0029–0.0038 mole) sealed in a small, thin-

walled glass bulb and a measured portion of pyridine (or pyridine solution) (15–20 ml.) saturated with carbon dioxide were placed in the flask described above and the flask was immersed in the constant temperature bath, connected to the gas buret and shaken electrically. The system was allowed to attain equilibrium (about 20 minutes were usually necessary), the level of the mercury in the buret was set and the apparatus was closed to the atmosphere by manipulation of the three-way stopcock. If the buret reading remained constant for a period of 5 minutes, the reaction was started by breaking the sample bulb using the movable glass rod. Readings of the gas volume were taken every half-minute for the first 5–30 minutes of the reaction and subsequently at minute intervals. In every case studied, 95–98% yields of carbon dioxide were obtained. All runs were repeated at least once and values of α_i/t were always reproducible to within 3% for runs of the same initial acid concentration.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Stereospecificity in Rearrangements. IV. erythro- and threo-1-*p*-Chlorophenyl-1,2-diphenyl-2-bromoethanol¹

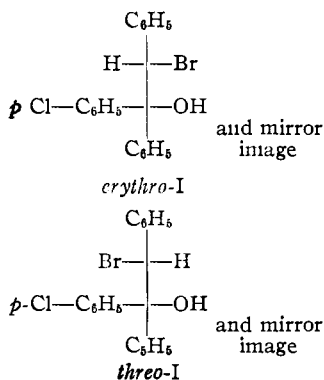
BY DAVID Y. CURTIN² AND ESTELLE K. MEISLICH

RECEIVED JUNE 27, 1952

dl-erythro- and *dl*-threo-1-*p*-chlorophenyl-1,2-diphenyl-2-bromoethanol have been prepared by the bromination of 1-*p*-chlorophenyl-1,2-diphenylethanol with N-bromosuccinimide. The erythro-racemate rearranges with ethanolic silver nitrate to benzhydryl *p*-chlorophenyl ketone, while with ethylmagnesium bromide in boiling benzene it gives *p*-chlorobenzhydryl phenyl ketone. Conversely, the threo-racemate with ethanolic silver nitrate gives *p*-chlorobenzhydryl phenyl ketone and with ethylmagnesium bromide gives benzhydryl *p*-chlorophenyl ketone. The corresponding epoxides are shown not to be intermediates in the Grignard rearrangements.

In the previous papers of this series³ it was shown that the course of the rearrangements of certain diastereoisomeric amino alcohols with nitrous acid was determined by the configuration of the reacting molecule. This paper reports a set of stereospecific rearrangements in a different system.

The two racemates of 1-*p*-chlorophenyl-1,2-diphenyl-2-bromoethanol (I) appeared to be ideally suited to the present purpose since a careful study had been made by Lane and Walters⁴ of the rearrangement and related reactions under a variety of conditions of the unsubstituted analog, 1,1,2-triphenyl-2-bromoethanol.



(1) Part of the Ph.D. Thesis submitted by Estelle K. Meislisch to Columbia University.

(2) Department of Chemistry, University of Illinois, Urbana, Illinois.

(3) (a) P. I. Pollak and D. Y. Curtin, *THIS JOURNAL*, **72**, 961 (1950); (b) D. Y. Curtin and P. I. Pollak, *ibid.*, **73**, 992 (1951); (c) D. Y. Curtin, E. E. Harris and P. I. Pollak, *ibid.*, **73**, 3453 (1951).

(4) J. F. Lane and D. R. Walters, *ibid.*, **73**, 4234 (1951).

It was found that a mixture of erythro- and threo-I was readily obtained by bromination of 1-*p*-chlorophenyl-1,2-diphenylethanol with N-bromosuccinimide. (This method of synthesis was first used by Lane and Walters for the preparation of 1,1,2-triphenyl-2-bromoethanol.)

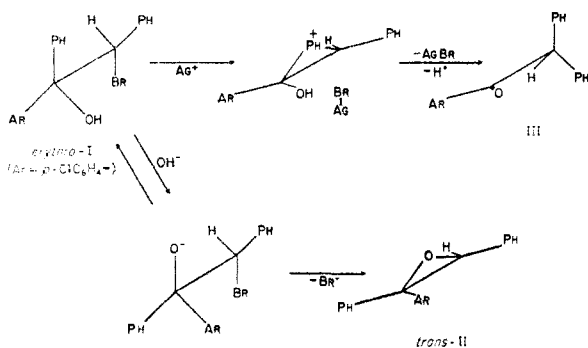
dl-erythro-I, m.p. 130°, and *dl*-threo-I, m.p. 109°, were separated from the crude bromination mixture by fractional crystallization.⁵ Their configurations were established by conversion to the corresponding epoxides (II) of known configuration.^{3c} Since this internal displacement reaction has been shown in other cases to occur with inversion of configuration,⁶ the isomer which was converted to *trans*-II was assigned the erythro-configuration while that which gave *cis*-II was concluded to be threo.

The two racemates of I were rearranged with silver nitrate in ethanol. *dl*-erythro-I gave a 78% yield of benzhydryl *p*-chlorophenyl ketone, III, identified by ultraviolet absorption spectrum and mixed m.p., while *dl*-threo-I gave a 65% yield of *p*-chlorobenzhydryl phenyl ketone, IV. Although the IV obtained melted over a 5° range the ultraviolet absorption spectrum indicated that it was contaminated by less than 10% and probably no appreciable amount of the isomeric ketone, III. These reactions are shown for one enantiomorph of the erythro-series.

The results are consistent with the expectation³ that each isomer should rearrange in such a way

(5) The terms "erythro" and "threo" will be used here as shown below.

(6) See S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. I, R. C. Elderfield, Editor, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 13.



that the two non-migrating aryl groups are *trans* to each other in the transition state.⁷

The rearrangement of each of the isomers of I was also carried out by treating the bromohydrin with ethylmagnesium bromide for 30 minutes in refluxing benzene. Again the rearrangement was stereospecific but with unexpected results. *dl*-erythro-I, which with silver nitrate had given III now gave only IV (in 60% yield) and *dl*-threo-I, which with silver nitrate had given IV, now gave III (in 55% yield). The ultraviolet spectra of the products indicated that there was no significant contamination of either ketone by the other.

Since epoxides have frequently been regarded as likely intermediates in such rearrangements of halo-hydrins with Grignard reagents,⁸ *cis*- and *trans*-II were subjected to treatment with anhydrous magnesium bromide in boiling benzene but each gave the same ketone, IV.

That the oxides (III and IV) were intermediates in the Grignard rearrangements was not yet rigorously excluded since the synthetic magnesium bromide (prepared from magnesium and bromine) might have contained hydrogen bromide or other impurities which made it a more active catalyst than the one present in the Grignard rearrangement mixture. The possibility existed, then, that *threo*-I reacted with ethylmagnesium bromide to give *cis*-II which rearranged to give III, stable in the environment, and that *cis*-II also rearranged in the presence of synthetic magnesium bromide to give III, which, however, in the presence of the more active catalyst rearranged to IV.⁹ Such rearrangements of one carbonyl compound to another have been reported to proceed under comparable conditions.¹⁰ This possibility was eliminated, however, since III could be recovered unchanged to the extent of 85% after treatment with anhydrous magnesium bromide and the ultraviolet spectrum of the crude product showed that little or none of the isomeric ketone was present. It has been con-

(7) There may be a three-membered cyclic intermediate ion in this rearrangement (compare D. J. Cram, *THIS JOURNAL*, **74**, 2129 (1952) and other papers). This possibility does not affect the argument here, however, since, when a molecule can rearrange to give either of two products, the relative amount of each of the products is determined by the relative free energy of the transition state leading to it whether or not an "intermediate" occurs after the transition state.

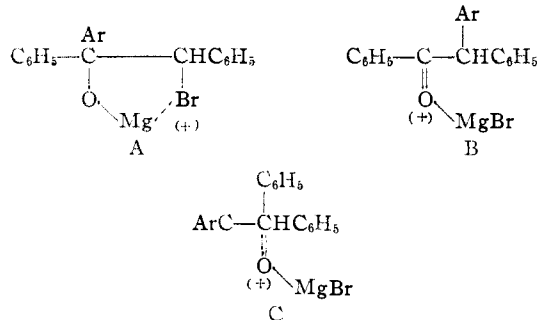
(8) See, for example, F. Runge, "Organometallverbindungen," Stuttgart Wissenschaftliche Verlagsgesellschaft M.B.H., Stuttgart, Germany, 1944, pp. 310, 331.

(9) Although the relative stabilities of III and IV have not been determined experimentally it is of interest to note that, statistically, IV would be favored by a factor of 2, i.e., that an equilibrium mixture would contain 67% of IV.

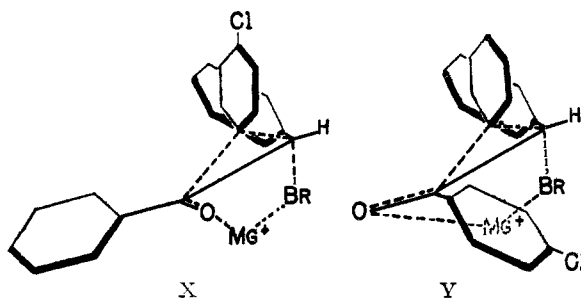
(10) See S. Danilov and E. Venus-Danilova, *Ber.*, **60**, 1050 (1927).

cluded, therefore, that the oxides, *cis*- and *trans*-II, are not intermediates in the rearrangement with ethylmagnesium bromide of *erythro*- or *threo*-I to ketones III and IV.

It seems likely that in the reaction of *erythro*- or *threo*-I the first step is the formation of a magnesium alcoholate (A) (which has additional solvation of the magnesium by ether and/or bromide ion). (A) can then rearrange directly to (B) or (C). The two transition states for the rearrangement of



erythro-I to (B) with migration of *p*-chlorophenyl and to (C) with migration of phenyl are shown below as (X) and (Y), respectively.¹¹



Since the relatively unstable *cis*-arrangement of phenyls in X favors reaction through Y, there must be an even more important factor in this case which favors X. It is proposed that this factor is the larger strain introduced by the solvation of Y compared with X. It can be seen from an examination of models of X and Y that X, with the two phenyls held out of the way, has more space available around the magnesium for solvation¹² by ether and bromide ion (or around the bromine and oxygen for solvation by additional magnesium atoms). It seems possible, therefore, that the more favorable solvation of X lowers its free energy sufficiently so that it is the preferred transition state for rearrangement. A study of another example of the importance of environment in determining the course of a reaction has been reported recently.¹³

The bromohydrins (*erythro*- and *threo*-I), when treated with butyllithium, did not rearrange but, instead, were converted to the same epoxides which had been obtained by treatment with potassium hydroxide (*trans*- and *cis*-II, respectively).

(11) For a more detailed discussion of this reaction and references to the previous literature, see T. A. Geissman and R. I. Akawie, *THIS JOURNAL*, **73**, 1993 (1951).

(12) The word "solvation" is used here to include partial covalent bond formation between magnesium and bromine or oxygen, as well as electrostatic interaction between atoms or molecules with charges or dipoles.

(13) C. L. Stevens and E. Farkas, *THIS JOURNAL*, **74**, 5352 (1952).

Experimental¹⁴

Bromination of *dl*-1-*p*-Chlorophenyl-1,2-diphenylethanol.—The alcohol (18.53 g., 0.06 mole) prepared by the method of Koelsch¹⁵ was brominated with freshly recrystallized *N*-bromosuccinimide (12.28 g., 0.07 mole) in 200 cc. of carbon tetrachloride in a Pyrex flask illuminated by an ordinary 60-watt bulb until reaction began. In 10 minutes a deep orange color appeared and the mixture refluxed vigorously. After 8 hours of refluxing the succinimide was removed by filtration and the residue was concentrated under a vacuum to give an orange oil. The oil was added to 600 cc. of hot petroleum ether and after filtration of the undissolved solid four fractions were obtained on cooling: 6.3 g., m.p. 110–116°; 0.93 g., m.p. 101–111°; 1.9 g., m.p. 90–97°; and 15.2 g., m.p. 85–96°. If these fractions are assumed to be bromohydrin they represent a total yield of 97%.

dl-erythro-1-*p*-Chlorophenyl-1,2-diphenyl-2-bromoethanol (*dl*-erythro-I) (2.26 g., 9.5%) was obtained by fractional crystallization of the two higher melting fractions above from petroleum ether. It melted at 130° in a preheated bath.

Anal. Calcd. for C₂₀H₁₆ClBrO: C, 62.0; H, 4.2; Cl, 9.2; Br, 20.6. Found: C, 62.1; H, 4.2; Cl, 8.8; Br, 20.7.

dl-threo-I (3.78 g., 16%) was obtained from the two lower melting fractions above by fractional recrystallization from petroleum ether. It melted at 109° in a preheated bath.

Anal. Calcd. for C₂₀H₁₆ClBrO: C, 62.0; H, 4.2; Cl, 9.2; Br, 20.6. Found: C, 62.0; H, 4.1; Cl, 8.9; Br, 20.6.

Conversion of erythro-I to *trans*-1-*p*-Chlorophenyl-1,2-diphenylethylene Oxide (*trans*-II).—erythro-I (0.30 g., 0.00077 mole) was treated with 0.41 g. (0.007 mole) of potassium hydroxide in 30 cc. of absolute ethanol. The mixture immediately became cloudy and after 2 hours in an ice-bath a white precipitate had formed. After addition of 50 cc. of water, extraction of the oxide with ether, drying evaporation of the ether and recrystallization of the residue from methanol there was obtained 0.19 g. (80%) of *trans*-II, m.p. 103.1–104.6°. Further recrystallization from methanol gave m.p. 104.2–105°. *trans*-II is reported to melt at 102–103°. ³⁰

Conversion of threo-I to (*cis*-II).—The procedure used for erythro-I, above, was employed. In this case, however, a 78% yield of *cis*-II, m.p. 87.7–89.2°, was obtained. The reported m.p. is 86.5–87.5°. ³⁰

Rearrangement of erythro-I with Silver Nitrate.—erythro-I (0.28 g., 0.00072 mole) was treated with 0.12 g. (0.00072 mole) of silver nitrate in 10 cc. of ethanol. There was an immediate precipitate of silver bromide and after shaking for 15 minutes the mixture was filtered. Concentration of the filtrate on a steam-bath gave 0.18 g. (78%) of benzhydryl *p*-chlorophenyl ketone (III) as flat needles, m.p. 108.8–110°. A mixed m.p. with authentic III, ^{3b} m.p. 108–109.5°, showed no depression. The ultraviolet spectra are compared in Fig. 1.

Rearrangement of threo-I with Silver Nitrate.—When the same procedure as above was carried out with threo-I (0.080 g.) an oil was obtained which crystallized after being taken up in ether, dried and concentrated to give 0.039 g. (65%) of IV, m.p. 97.0–102.4°. Further recrystallization did not raise the m.p. The ultraviolet spectra of the product and authentic IV^{3b} are shown in Fig. 2. When 50 mg. of the product was chromatographed on alumina activated at 400° for 4 hours (eluted with 10% benzene in ligroin and then 20%) the recovered ketone after recrystallization from ethanol still melted at 96.5–100.3°.

Rearrangement of erythro-I with Ethylmagnesium Bromide.—erythro-I (0.25 g., 0.00064 mole) dissolved in a small amount of benzene was added to a solution of ethylmagnesium bromide prepared from 0.04 g. (0.002 gram atom) of magnesium and 0.20 g. (0.0018 mole) of ethyl bromide. The mixture was refluxed for 15 minutes. After the addition of 25 cc. of benzene the ether was distilled off until the temperature reached 78°. The resulting solution was refluxed for 1/2 hour and then poured into 30 cc. of water. Extraction of the neutral fraction gave, after recrystallization from ethanol, 0.110 g. of IV, m.p. 98.7–101.5°. Concentration of the mother liquor afforded an additional 0.0120 g., m.p.

(14) All melting points are corrected. The microanalyses were carried out by the Schwarzkopf Microanalytical Laboratory, Middle Village, New York.

(15) C. F. Koelsch, THIS JOURNAL, 54, 2487 (1932).

Fig. 1 (upper curve).—Ultraviolet spectra of ethanol solutions (20 mg./l.) in a 1-cm. cell obtained with a Carey Recording Spectrophotometer: —, authentic III; -.-, product from erythro-I and silver nitrate; ---, product from threo-I and ethylmagnesium bromide.

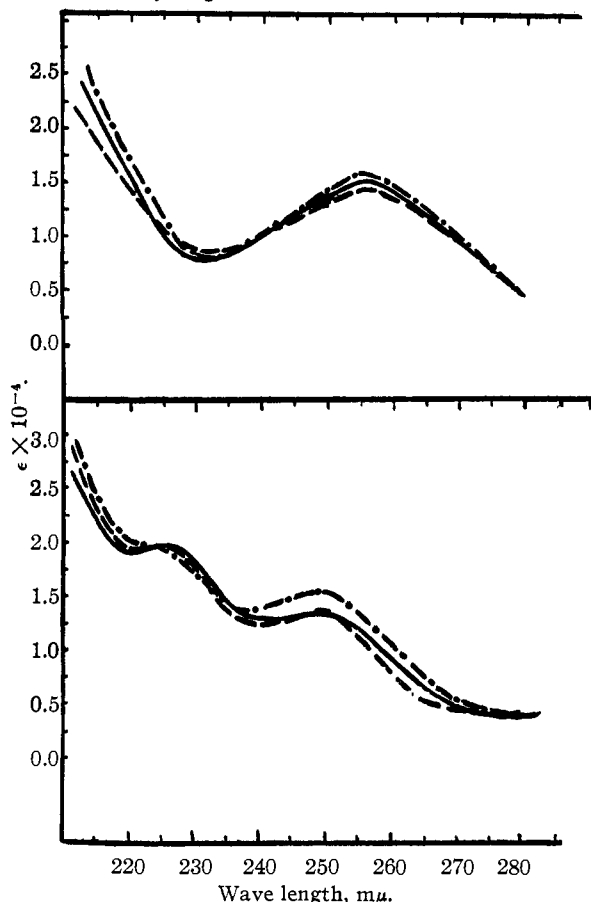


Fig. 2 (lower curve).—Ultraviolet spectra of ethanol solutions (20 mg./l.) in a 1-cm. cell obtained with a Carey recording spectrophotometer: —, authentic IV; -.-, product from threo-I and silver nitrate; ---, product from erythro-I and ethylmagnesium bromide.

98–101.0° or a total yield of 61%. A mixed m.p. with authentic IV showed no depression. The ultraviolet spectra are shown in Fig. 2.

Rearrangement of threo-I with Ethylmagnesium Bromide.—When threo-I was treated by the procedure above, a 55% yield of III, m.p. 107.2–108.6° (no depression when mixed with authentic III) was obtained. The ultraviolet spectra are shown in Fig. 1.

Reaction of *cis*-II with Magnesium Bromide.—Anhydrous magnesium bromide was prepared by the addition of several drops of bromine to 0.04 g. (excess) of magnesium turnings in 5 cc. of anhydrous ether.¹⁶ The flask was wrapped with aluminum foil to exclude light and the mixture was allowed to react for 3 hours. After the ether was distilled, a solution of 0.250 g. (0.00082 mole) of *cis*-II in benzene was added to the solid magnesium bromide and the mixture was heated for 15 minutes after which the ether was distilled and the benzene solution refluxed for 1/2 hour and poured into water. Extraction with ether gave 0.193 g. (77%) of pale yellow solid, m.p. 88–99°. Recrystallization from ethanol gave 0.132 g. (53%) of III, m.p. 100.5–103.8°. A mixed m.p. with authentic III showed no depression. The ultraviolet spectrum of the crude product, m.p. 88–99°, showed no evidence of contamination by IV.

Reaction of *trans*-II with Magnesium Bromide.—Under the above conditions *trans*-II (0.250 g.) gave a 78% yield

(16) H. H. Rowley, *ibid.*, 58, 1337 (1936).

of crude IV, m.p. 87–96°, which after crystallization from ethanol amounted to 0.140 g. (56%), m.p. 101.2–103.6°. A mixed m.p. showed no depression. The ultraviolet spectrum of crude IV showed no evidence of III.

Treatment of *p*-Chlorophenyl Benzhydryl Ketone (III) with Magnesium Bromide.—When a benzene solution of 0.110 g. of III was added to a suspension of magnesium bromide in ether and subjected to the conditions of the isomerization, 0.095 g. (86%) was recovered, m.p. 106–108°, of which the ultraviolet spectrum was identical with the original ketone. A mixed m.p. showed no depression.

Reaction of *erythro*-I with Butyllithium.—*erythro*-I (0.200 g., 0.00052 mole) was added to a solution of *n*-butyllithium in ether and the procedure used above for the Grignard re-

actions (excess) was followed. A 97% yield of *trans*-II, m.p. 93–99°, was obtained which after one recrystallization from methanol melted at 102.2–104.0° (mixed m.p. showed no depression).

Reaction of *threo*-I with Butyllithium.—*threo*-I treated as above afforded 0.156 g. (98%) of *cis*-oxide, m.p. 72–86°. After one recrystallization from methanol the m.p. was 87–88.4° and a mixed m.p. with *cis*-II prepared above showed no depression.

The ultraviolet spectra were obtained with a Carey recording spectrophotometer at concentration of 20 mg./l. in ethanol.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Synthesis of *cis*- and *trans*-3-Methylcyclohexanol. Reassignment of Configuration of the 3-Methylcyclohexanols

BY HARLAN L. GOERING AND CARL SERRES, JR.¹

RECEIVED JUNE 23, 1952

Authentic *cis*- and *trans*-3-methylcyclohexanol have been prepared from the diastereoisomeric 3-hydroxycyclohexane carboxylic acids by synthetic schemes designed to avoid ambiguities concerning configurations. Comparison of the solid derivatives of the authentic isomeric 3-methylcyclohexanols with the derivatives recorded in the literature clearly demonstrates the heretofore accepted assignment of configuration to be in error.

The diastereoisomeric 3-methylcyclohexanols have been reported several times in the literature and although discrepancies in the physical properties and melting points of solid derivatives suggest that the isomers were obtained in varying degrees of purity,² it appears that there is complete agreement in the assignment of configuration to the isomers. The 3-methylcyclohexanols were first prepared by Knoevenagel³ who designated the *trans* configuration to the predominating isomer obtained from the sodium and alcohol reduction of 3-methylcyclohexanone. Skita⁴ assumed that the isomer obtained from the catalytic (platinum) reduction of *m*-cresol in warm acid medium was the *cis* isomer and that the *trans* isomer was obtained when the reduction was carried out in cold neutral solution. Kenyon and co-workers⁵ assigned *cis* and *trans* configurations from a comparison of the relative viscosities of the alcohols with the relative viscosities of the diastereoisomeric 2- and 4-methylcyclohexanols. From a correlation of various physical constants Skita and Faust⁶ assigned configurations to the isomers in agreement with the earlier workers. More recently the Knoevenagel–Kenyon–Skita assignment has been taken for granted in several investigations.^{7–9}

In connection with another problem we were concerned with the structure of the 3-methylcyclohexanols. Since the assigned structures had not been unequivocally determined and as evidence was available which indicated that the previous assignment might be in error (see conclusion) we reinvestigated the structures of these isomers. In the present work authentic *cis*- and *trans*-3-methylcyclohexanol have been prepared and the assignment of configuration made by the earlier workers has indeed been found to be in error. Authentic *cis*- and *trans*-3-methylcyclohexanols were prepared from the isomeric 3-hydroxycyclohexanecarboxylic acids of the same configuration. The acids were selected as starting materials for an unequivocal synthesis of the isomeric 3-methylcyclohexanols because there can be no ambiguities concerning the configurations of the acids as the *cis*-3-hydroxycyclohexanecarboxylic acid (I) forms the lactone (II),^{10,11} whereas the geometry of the *trans* acid (IX) prohibits lactone formation.

A mixture of *cis*-(I) and *trans*-(IX) acids was prepared by the hydrolysis of ethyl 3-hydroxycyclohexanecarboxylate, which in turn was prepared from *m*-hydroxybenzoic acid by the method of Clarke and Owen.¹² This proved to be a more convenient method for preparing large amounts of the mixture of isomeric acids than the method of Perkins and Tattersall,¹¹ which involves the reduction of *m*-hydroxybenzoic acid with sodium and ethanol. The pure isomeric acids were obtained from the mixture as follows. The mixture was dissolved in ethyl acetate from which a crop of the *cis* acid separated. Evaporation of the mother liquor resulted in a mixture of the isomeric acids (as indicated by a neutral equivalent of 145 ± 2 as compared to the calculated value of 144), which

(1) Taken from the B.S. thesis of Carl Serres, Jr., University of Wisconsin, 1952.

(2) Some discrepancies in the melting points of the solid derivatives are possibly due to polymorphism which appears to be quite common among derivatives of 3-methylcyclohexanol.

(3) E. Knoevenagel, *Ann.*, **297**, 126 (1897).

(4) A. Skita, *ibid.*, **431**, 4 (1923).

(5) G. Gough, H. Hunter and J. Kenyon, *J. Chem. Soc.*, 2052 (1926).

(6) A. Skita and W. Faust, *Ber.*, **64**, 2878 (1931).

(7) (a) A. K. Macbeth and J. A. Mills, *J. Chem. Soc.*, 709 (1945);

(b) L. M. Jackman, A. K. Macbeth and J. A. Mills, *ibid.*, 2641 (1949).

(8) W. R. Brode and R. W. van Dolah, *Ind. Eng. Chem.*, **39**, 1157 (1947); Mousseron, Marszak and Bolle, *Bull. soc. chim.*, **9**, 260 (1942); M. Godehot and G. Cauquil, *Compt. rend.*, **198**, 663 (1934).

(9) D. S. Noyce and D. G. Demby, *This Journal*, **72**, 5743 (1950).

(10) E. J. Boorman and R. P. Linstead, *J. Chem. Soc.*, 258 (1935).

(11) W. Perkins and G. Tattersall, *ibid.*, 486 (1907).

(12) M. F. Clarke and L. N. Owen, *ibid.*, 2108 (1950).