prepared by a transesterification procedure.[24] Mono-testosterone succinate has been previously described[25] and the free carboxyl group was esterified by metathesis of the silver salt of the acid with methyl iodide.

EXPERIMENTAL[26]

The acid chlorides which were not commercially available were synthesized according to methods described in the literature: acrylyl chloride,[27] β-chlorocrotonyl chloride,[28] *tert*-butylacetyl chloride.[29] The acid chloride of α,α-dibenzylacetic acid was prepared using thionyl chloride (75%), b.p. 130–132° (1 mm.).

Testosterone β-chloropropionate. A solution of 24 g. of testosterone in 200 ml. of pyridine and 800 ml. of toluene was added dropwise with stirring and continued cooling at −10° to a solution of 70 ml. of β-chloropropionyl chloride in 600 ml. of toluene. After stirring at room temperature for 24 hours, 350 ml. of water was added. The toluene layer was separated and processed by successively washing with water, dilute hydrochloric acid, dilute bicarbonate, and water; it was dried with magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo.* The solid residue of the product was dried *in vacuo* at 80°.

Androstan-17-β-ol-3-one-β-iodopropionate. One gram of androstan-17-β-ol-3-one-β-bromopropionate was dissolved in 5 ml. of acetone and 50 ml. of a 15% acetone solution of sodium iodide was added. After 2 days the sodium bromide formed was filtered off, and 100 ml. of water was added. Upon standing, crystals of the product formed which were separated and dried *in vacuo.*

Testosterone acrylate. (By dehydrohalogenation of testosterone β-bromopropionate). A solution of 1 g. (2.36 mmoles) of testosterone β-bromopropionate and 0.42 g. (2.36 mmoles) of phenylbiguanide in 135 ml. of hot ethanol was concentrated on the steam-bath to the initiation of crystallization, and cooled. Filtration afforded 0.8 g. of a crystalline mixture which was extracted with two successive 40-ml. portions of boiling heptane. The cooled heptane extract yielded 0.39 g. (48%) of testosterone acrylate which melted at 158–160° and which did not depress the melting point of the product obtained from testosterone and acrylyl chloride. The residue from the heptane extraction was identified as phenylbiguanide hydrobromide.[23]

Testosterone acrylate polymer. A solution of 1 g. of testosterone acrylate in 5 ml. of boiling propanol was treated with three successive 1-ml. portions of 20% hydrogen peroxide at 0, 5, and 15 minutes and refluxed for 2 hours. After cooling, the oily insoluble mass of product separated and was solidified by trituration with ether. The product was insoluble in a wide variety of typical solvents except chloroform, but could not be purified.

We could not polymerize testosterone acrylate by ultraviolet light, nor through the use of benzoyl peroxide.[30]

Testosterone acetoacetate. A solution of 2 g. of testosterone and 6.12 g. of ethyl acetoacetate was maintained at 100° and 200 mm. for 10 hours. The excess of the reactant then was removed by distillation leaving a viscous residue which crystallized on treatment with methanol-water.

Methyl ester of monotestosterone succinate. The silver salt of monotestosterone succinate was prepared from an equivalent amount of the sodium salt of the acid and silver nitrate in water in 82.3% yield. The reaction mixture of 0.8 g. of the silver salt and 1 ml. of methyl iodide in 48 ml. of methanol after standing 48 hours in the dark, was separated from the formed silver iodide by filtration. Evaporation of the filtrate yielded an oil which crystallized on standing.

Testosterone β-(N-piperidino)propionate. A solution of 4 g. of testosterone β-chloropropionate in 100 ml. of xylene was treated with 5 ml. of piperidine and refluxed for 2 hours. On cooling, 1.15 g. (90%) of piperidine hydrochloride was separated and the filtrate was concentrated to a syrupy residue. Crystallization was induced by trituration with ether.

Acknowledgment. We are grateful to S. Kobrin for evaluation of the androgenic response of the compounds reported in this series, and to A. Lawrence for his technical assistance in the preparation of the compounds.

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[24] Bader, Cummings, and Vogel, *J. Am. Chem. Soc.*, **73**, 4195 (1951).

[25] Soc. pour l'ind. chem. a Bale, Swiss Patent 195,775 (May 16, 1938); *Chem. Abstr.*, **32**, 7217 (1938).

[26] Purification, yields, and melting points of the compounds described in this section are indicated in Table I.

[27] Stempel, Gross, and Mariella, *J. Am. Chem. Soc.*, **72**, 2299 (1950).

[28] Shriner and Keyser, *J. Am. Chem. Soc.*, **60**, 287 (1938).

[29] Homeyer, Whitmore, and Wallingford, *J. Am. Chem. Soc.*, **55**, 4211 (1933).

[30] Marvel, Weil, Wakefield, and Fairbanks, *J. Am. Chem. Soc.*, **75**, 2326 (1953).

Stereochemistry of Reduction of 2-Methylcyclopentanone

JEAN B. UMLAND AND BETTYE W. WILLIAMS[1]

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The reduction of unsymmetrical ketones to secondary alcohols produces an asymmetric carbon atom and when the ketone already contains an asymmetric center, the problem arises as to which epimer will be formed in larger amounts. Generalizations concerning the steric course followed in the reduction of ketones by the common methods have been made by Barton.[2] Unfortunately some of these generalizations appear to be based on experiments in which it was assumed that the more soluble epimer was obtained in pure form by fractional crystallization. The purpose of the present research was to compare in a quantitative manner the stereochemistry of the common methods of reduction using a single simple model compound. 2-Methylcyclopentanone, which is reduced to a mixture of *cis-* and *trans*-2-methylcyclopentanol, was selected as this model compound since the preparation and proof of configuration of these alcohols, as well as a quantitative procedure for analyzing the mixtures, have recently been described.[3] The results of these reductions are summarized in Table I.

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[1] Abstracted from a thesis submitted by Bettye W. Williams in partial fulfillment of the requirements for the degree of Master of Arts, 1956.

[2] Barton, *J. Chem. Soc.*, 1027 (1953).

[3] Umland and Jefraim, *J. Am. Chem. Soc.*, **78**, 2788 (1956).

TABLE I

ISOMERIC COMPOSITION OF MIXTURES OF *cis*- AND *trans*-2-METHYLCYCLOPENTANOL FROM REDUCTION OF 2-METHYLCYCLOPENTANONE

Reducing Agent	%, *trans*
$NaBH_4$[a]	73
$NaBH_4$[b]	74
Na and C_2H_5OH	87
Na and moist $(C_2H_5)_2O$	90
$Al[OCH(CH_3)_2]_3$[c]	24
H_2, PtO_2	72
$LiAlH_4$[d]	75

[a] Large excess of solid sodium borohydride added to solution of ketone in aqueous methanol. [b] Ketone added to water solution of small excess of sodium borohydride. [c] Reaction mixture worked up as soon as reduction was complete. [d] Ref. 3.

It has frequently been stated that reduction with sodium and alcohol affords a mixture of alcohols of the same composition as is obtained by direct equilibration and hence can be employed to measure the relative stability of epimers.[4] *cis*- and *trans*-2-Methylcyclopentanol were equilibrated with aluminum isopropoxide in refluxing isopropyl alcohol. Equilibrium was approached from both the *cis* and the *trans* sides; composition-time curves are shown in Fig. 1. From Fig. 1 the composition of the equilibrium mixture was estimated to be 58% *trans*-2-methylcyclopentanol. Therefore, in this case at least, reduction with sodium and alcohol does not afford a mixture of alcohols of the same composition as is obtained by direct equilibration and, indeed, gives a rather misleading idea of the relative stabilities of the two isomers.[5]

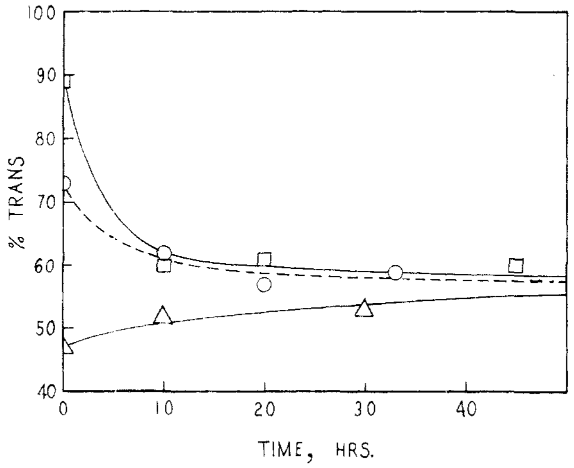

FIG. 1.—EQUILIBRATION OF *cis*- AND *trans*-2-METHYLCYCLOPENTANOL WITH ALUMINUM ISOPROPOXIDE IN REFLUXING ISOPROPYL ALCOHOL.

In agreement with Barton's generalizations sodium borohydride, sodium and alcohol, catalytic hydrogenation in neutral medium, and lithium aluminum hydride all give a preponderant amount of the more stable *trans* isomer whereas aluminum isopropoxide affords a larger amount of the less stable *cis* isomer. In this connection it is interesting to note that the preponderant product formed in the reduction of the acyclic ketones studied by Cram[6] can be predicted by Barton's generalizations, including the results of the reduction of 3-cyclohexyl-2-butanone with aluminum isopropoxide which are inconsistent with Cram's "Rule of Steric Control of Asymmetric Induction".[7]

The composition of the product obtained by sodium borohydride reduction was the same under two very different sets of experimental conditions and is similar to that obtained by lithium aluminum hydride reduction in accord with the observations of Cram and Greene[7] and Dauben, Micheli, and Eastham[8] on other systems. Reduction by means of sodium and moist ether gives almost the same steric result as is obtained by reduction with sodium and alcohol.

Since equilibration of *cis*- and *trans*-2-methyl cyclopentanol occurs under the conditions used for reduction with aluminum isopropoxide, material containing an even higher proportion of the *cis* isomer could probably be obtained by isolating the product prior to the completion of the reduction and this appears to be the most suitable method for the preparation of *cis*-2-methylcyclopentanol. Catalytic hydrogenation in acid medium, which is also said to afford a preponderant amount of the less stable epimer,[2] gave negligible yields of 2-methylcyclopentanol.

EXPERIMENTAL

2-Methylcyclopentanone. 2-Methylcyclopentanone was prepared as described by Umland and Jefraim.[3] It was purified immediately before reduction by fractionation with a Holzman column, b.p. 137.0° (752 mm.), n_D^{25} 1.4340 (lit.[3] b.p. 137.5° (761 mm.), n_D^{22} 1.4341).

Analysis of mixtures of cis- and trans-2-methylcyclopentanol. The isomeric composition of mixtures of *cis*- and *trans*-2-methylcyclopentanol obtained by reduction of 2-methylcyclopentanone was determined, as described by Umland and Jefraim,[3] from the melting point of the 3,5-dinitrobenzoate derivative by means of the binary melting point diagram using mixture melting points with *cis*- and *trans*-2-methylcyclopentyl 3,5-dinitrobenzoates to find out whether the sample was on the *cis* or *trans* side of the eutectic. This method of analysis has been shown, by analysis of synthetic mixtures of *cis*- and *trans*-2-methylcyclopentanol, to have an accuracy of ±2%.[3] To show that the samples contained only *cis*- and *trans*-2-methylcyclopentyl 3,5-dinitrobenzoates and were not contaminated with other substances, materials for the mixture melting point deter-

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[4] See, for example, Dauben and Jiu, *J. Am. Chem. Soc.*, **76**, 4426 (1954) and Ref. 2.

[5] A similar case has been reported by Huckel [Huckel, *Ann.*, **533**, 1 (1937)].

[6] See Cram, Elhafez, and Nyquist, *J. Am. Chem. Soc.*, **76**, 22 (1954) and previous papers in this series.

[7] Cram and Greene, *J. Am. Chem. Soc.*, **75**, 6005 (1953).

[8] Dauben, Micheli, and Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952).

minations were weighed with an accuracy of 1 p.p.h.; the isomeric composition of the mixture was calculated from the weight and isomeric composition of the sample as determined by analysis and the weight of pure *cis* or *trans* 3,5-dinitrobenzoate used and this calculated composition was compared with the composition determined from the melting point of the mixture. The calculated compositions agreed with the observed compositions within 1% which is well within experimental error. For example 8.83 mg. of 3,5-dinitrobenzoate containing 23.5% of the *trans* isomer by analysis was mixed with 1.00 mg. of pure *trans* 3,5-dinitrobenzoate to give a mixture calculated to contain 31% of the *trans* isomer. This mixture melted at 73.4° corresponding to 31% *trans*. The temperature reported is that at which the last solid disappeared.

Reduction of 2-methylcyclopentanone. A 2.0-g. sample (0.020 mole) of 2-methylcyclopentanone was reduced except where otherwise noted. All products were dried over potassium carbonate and distilled at *ca.* 35 mm. (b.p. <80°) to avoid the possibility of acid-catalyzed or thermal isomerization. Yields are included for comparison only and are not representative of those obtainable on a preparative scale.

A. Sodium borohydride. A large excess (eight fold) of solid sodium borohydride was added to a solution of the ketone in 25% aqueous methanol according to the procedure of Cram and Greene[7] for the reduction of L-(−)-3-cyclohexyl-2-butanone. From 1.28 g. (0.013 mole) of 2-methylcyclopentanone a 67% yield of 2-methylcyclopentanol was obtained which contained 73% of the *trans* isomer.

Reduction was also carried out by adding the ketone to a small (35%) excess of sodium borohydride in water. In this way a 75% yield of 2-methylcyclopentanol containing 74% of the *trans* isomer was obtained.

B. Sodium and alcohol. 2-Methylcyclopentanone was reduced with sodium and alcohol according to the procedure described by Dauben, Tweit, and Mannerskantz[9] for the reduction of *trans*-1-decalone except that the reaction mixture was cooled in an ice-salt bath during addition of the sodium and then was stirred overnight while cooling continually. A 56% yield of 2-methylcyclopentanol which contained 86% of the *trans* isomer was obtained. The product of a duplicate experiment contained 88% of the *trans* isomer. The low yield was probably due to base-catalyzed condensation of the original ketone; that it was not caused by selective destruction of one stereoisomer of the product was shown by subjecting mixtures of *cis*- and *trans*-2-methylcyclopentanol of known isomeric composition to the reaction conditions. The compositions were not changed.

C. Sodium and moist ether. Reduction with sodium and moist ether was carried out essentially according to the procedure of Vogel[10] for the preparation of methyl *n*-butyl carbinol. An 82% yield of 2-methylcyclopentanol containing 90% of the *trans* isomer was obtained. The product of a duplicate experiment contained 91% of the *trans* isomer.

D. Aluminum isopropoxide. The modified procedure of Macbeth and Mills[11] for ketones which condense readily was used for the reduction of 2-methylcyclopentanone with aluminum isopropoxide. When the reaction mixture was worked up as soon as reduction was complete, a 39% yield of 2-methylcyclopentanol which contained 24% *trans*-2-methylcyclopentanol was obtained from 3.0 g. (0.031 mole) of 2-methylcyclopentanone. A duplicate experiment gave identical results. In this case the low recovery of material was due to loss at some time in the isolation of the product, probably by evaporation during distillation of the relatively large amounts of isopropyl alcohol. This loss did not involve any fractionation of stereoisomers. When a 2.0-g. sample of 2-methylcyclopentanol of known isomeric composition was subjected to the isolation procedure, a 43% recovery of material of unchanged isomeric composition was obtained.

When the reaction mixture was refluxed for ten hours after reduction was complete the product contained 37% *trans*-2-methylcyclopentanol.

E. Catalytic hydrogenation. 2-Methylcyclopentanone (1.5 g., 0.015 mole) was hydrogenated without solvent at room temperature and 60 p.s.i. gage pressure with 0.08 g. of Adams platinum oxide catalyst in a Parr Series 3190 catalytic hydrogenation apparatus. Since the theoretical amount of hydrogen was too small to make an observable difference in pressure, shaking was continued for five days to insure complete reduction. After removal of the catalyst by filtration the product was distilled and a 70% yield of 2-methylcyclopentanol containing 71% *trans*-2-methylcyclopentanol was obtained. The product of a duplicate experiment contained 72% of the *trans* isomer.

Hydrogenation of 3.0 g. (0.031 mole) of 2-methylcyclopentanone in purified[12] glacial acetic acid for a period of three weeks did not result in complete reduction. The catalyst was removed by filtration and the reaction mixture was added to 570 ml. of 2.5 *N* sodium hydroxide. After refluxing for one hour to saponify any 2-methylcyclopentyl acetate formed, the alcohol was removed by azeótropic distillation with water. The distillate was saturated with potassium carbonate and extracted with ether. The almost negligible amount of 3,5-dinitrobenzoate derivative which was obtained from the product melted at 101.5–104.0° indicating that condensation had occurred.

Equilibration of cis- and trans-2-methylcyclopentanol. A solution of 3.0 g. (0.031 mole) of 2-methylcyclopentanol and 1 microdrop of 2-methylcyclopentanone[13] in 15 ml. of dry[14] isopropyl alcohol was refluxed with 44 ml. of 0.75 *M* aluminum isopropoxide in dry isopropyl alcohol. About 50% of the material was recovered regardless of time. Data are summarized in Fig. 1.

Attempted equilibration with sodium apparently led to condensation. Starting from the *trans* side the melting point of the 3,5-dinitrobenzoate derivative first decreased and then increased; individual results were not reproducible.

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(9) Dauben, Tweit and Mannerskantz, *J. Am. Chem. Soc.*, **76**, 4420 (1954).

(10) Vogel, *A Text-book of Practical Organic Chemistry*, 2nd ed., Longmans, Green and Co., London, 1951, p. 256.

(11) Macbeth and Mills, *J. Chem. Soc.*, 2646 (1949).

(12) Bruce and Ralls, *Org. Syntheses*, Coll. Vol. II, 191 (1943).

(13) The presence of a carbonyl compound is a necessary condition for effecting equilibration [Doering and Aschner, *J. Am. Chem. Soc.*, **71**, 838 (1949)].

(14) Isopropyl alcohol was dried by refluxing with and distilling from calcium oxide.

Dithiol Sebacic Esters

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This paper describes the synthesis and the properties of some dithiol sebacates. A literature search revealed that previous to this study only cyclohexyl and 2-methyl cyclohexyl dithiol sebacates were prepared.[1] These compounds were formed by the addition of dithiol sebacic acid to the appropriate olefin.

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(1) Cunnen, *Journal of Applied Chemistry (London)*, **2**, 353 (1952).