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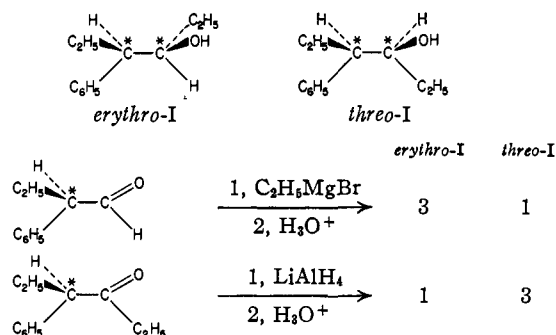
Studies in Stereochemistry. XVIII. The Preparation, Resolution and Assignment of Configuration to the 4-Phenyl-3-hexanol System<sup>1</sup>BY DONALD J. CRAM, FATHY AHMED ABD ELHAFAZ<sup>2</sup> AND HAROLD WEINGARTNER

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The four stereoisomers of 4-phenyl-3-hexanol have been prepared in an optically pure state, and their configurations relative to D-glyceraldehyde have been assigned. The reactions involved in the syntheses of these isomers provide two more illustrations of the operation of the "Rule of Steric Control of Asymmetric Induction."

The synthesis and resolution of the 4-phenyl-3-hexanol system and the determination of the relative configurations of the asymmetric carbon atoms of the four stereoisomers were undertaken for two reasons. The syntheses employed for this system provide further tests for the "Rule of Steric Control of Asymmetric Induction,"<sup>3</sup> and the results of solvolytic experiments in this system<sup>4</sup> provide further information regarding the constitution of phenonium tosylate ion-pairs.<sup>5</sup>

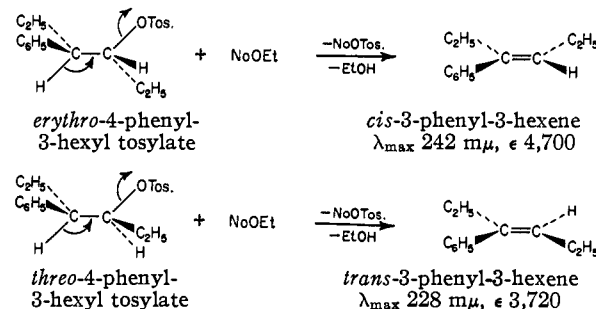
The "Rule of Steric Control of Asymmetric Induction" as Applied to the Preparation of 4-Phenyl-3-hexanol.—The formulations outline the two methods of preparation of 4-phenyl-3-hexanol<sup>6</sup> (I). Actual separation of the two diastereomers produced from the aldehyde indicates that the *erythro* predominated over *threo* material by a factor of at least 2.5/1, whereas infrared analysis of the diastereomeric mixture indicates that the ratio of *erythro* to *threo* isomer is about 3/1.<sup>7,8</sup> In the diastereo-



meric mixture of carbinols produced from the reduction of the ketone, the predominance of *threo* over *erythro* isomer was shown to be at least 2/1 by actual separation procedures, and infrared an-

alyses<sup>7</sup> indicated the ratio to be about 3/1. The *erythro*-carbinol was partially isolated as a crystalline solid from the products of the first reaction, and partially as the *p*-nitrobenzoate, whereas the *threo*-carbinol was isolated from the second reaction mixture as the acid phthalate derivative.

The structures of the *erythro*- and *threo*-4-phenyl-3-hexanols were established by the conversion of their tosylate derivatives with sodium ethylate to the *cis*- and *trans*-3-phenyl-3-hexenes, respectively. Although the olefins produced were undoubtedly contaminated with the unconjugated 4-phenyl-2-hexene, their ultraviolet absorption spectra (Fig. 1) serve to identify the two geometric isomers. Since the unconjugated olefin has negligible absorption



in the region from  $\lambda$  225  $\mu\mu$  to  $\lambda$  250  $\mu\mu$ ,<sup>9</sup> the observed spectra (Fig. 1) must be due to the conjugated olefins. The configurational assignments based on the spectral differences between the olefins from the two reactions are made on the same basis that has been used for similar assign-

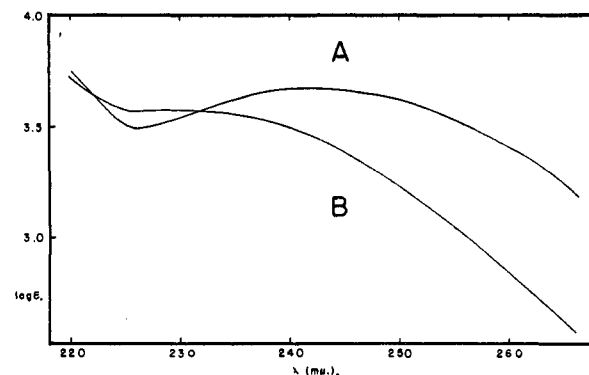


Fig. 1.—Ultraviolet absorption spectra in cyclohexane (Cary recording spectrophotometer, Model 11 PMS): curve A, *cis*-3-phenyl-3-hexene; curve B, *trans*-3-phenyl-3-hexene.

(9) The olefin, 3-phenyl-1-butene, serves as a model for this compound [D. J. Cram, *THIS JOURNAL*, **74**, 2137 (1952)].

(1) This work was supported by the Office of Ordnance Research, U. S. Army.

(2) Postdoctoral Fellow of the University of Ibrahim, Cairo, Egypt, at the University of California at Los Angeles.

(3) D. J. Cram and F. A. Abd Elhafez, *THIS JOURNAL*, **74**, 5828 (1952).

(4) D. J. Cram and F. A. Abd Elhafez, *ibid.*, **75**, in press.

(5) (a) D. J. Cram, *ibid.*, **71**, 3863, 3875 (1949); (b) **74**, 2129, 2159 (1952); (c) D. J. Cram and J. D. Knight, *ibid.*, **74**, 5839 (1952); (d) D. J. Cram, *ibid.*, **74**, 332 (1952); (e) F. A. Abd Elhafez and D. J. Cram, *ibid.*, **74**, 339 (1952).

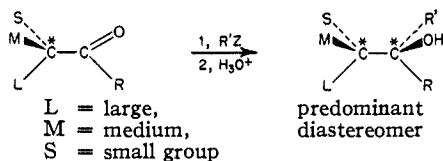
(6) F. Kayser and P. Jullien [*Bull. soc. chim. France*, **4**, 700 (1937)] had previously carried out the reaction of ethylmagnesium chloride with 2-phenylbutyraldehyde and had obtained the solid diastereomer in a pure state. An unseparated mixture of diastereomers was obtained by the reduction of 4-phenyl-3-hexanone with sodium and ethanol, but since the solid isomer could not be crystallized, it is likely that the liquid isomer predominated in this synthesis.

(7) See Table II in paper XIX of this series (ref. 4) for a description of the method employed.

(8) These configurational assignments are justified later in the paper.

ments in analogous systems.<sup>10</sup> Since the reactions used to produce the 3-phenyl-3-hexenes are clearly examples of *trans* elimination ( $E_2$ ) reactions,<sup>11</sup> the relative configurations of the two asymmetric carbons in the starting materials become defined.

Since phenyl is a bulkier group than ethyl, and ethyl is bulkier than hydrogen, the "Rule of Steric Control of Asymmetric Induction"<sup>3</sup> can be applied to the two syntheses of 4-phenyl-3-hexanol (I). In both of these syntheses that diastereomer predominates in the product which is predicted by the rule (see the formulation). Furthermore, the predominance of *threo*-I (liquid isomer) in the



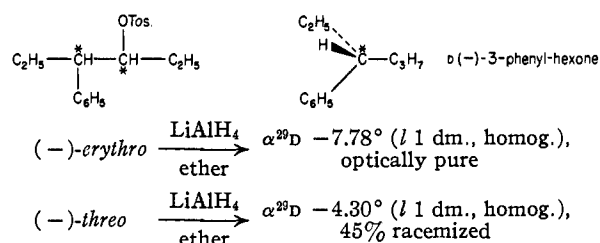
carbinols produced by the reduction of 4-phenyl-3-hexanone with sodium and ethanol<sup>6</sup> is also what would be predicted by the rule. Thus a total of fourteen syntheses where L, M and S are alkyl, aryl or hydrogen are now known which are consistent with the rule,<sup>3,5c,12</sup> and eighteen well authenticated syntheses<sup>13</sup> in which M is an amino, hydroxyl or methoxyl group have been found<sup>3,14</sup> to give predominantly that diastereomer predicted by the rule. The courses of twelve other syntheses which are somewhat more ambiguous also appear to be consistent with the rule.<sup>3</sup>

**The Resolution and Stereochemical Structures of the Isomers of 4-Phenyl-3-hexanol.**—The solid racemate (*erythro*) of I was partially resolved through the strychnine salt of its phthalic acid ester,<sup>15</sup> and the resulting fractions of the phthalic acid ester (both (+) and (-)) were converted to the 3,5-dinitrobenzoate derivatives. The favorable solubility characteristics of the enantiomeric esters (as compared to the racemic esters) permitted the isolation of both of the 3,5-dinitrobenzoates in an optically pure state. Optically pure (+)- and (-)-*erythro*-I were prepared by hydrolyses of these esters. The completely analogous procedure employed for the resolution of the *threo* racemate of I proved to be equally successful. The physical properties and analyses of the racemic and optically active 4-phenyl-3-hexanols (I) as well as of their 3,5-dinitrobenzoate, *p*-nitrobenzoate, tosylate and acid phthalate (only the two racemates) derivatives are recorded in Table I.

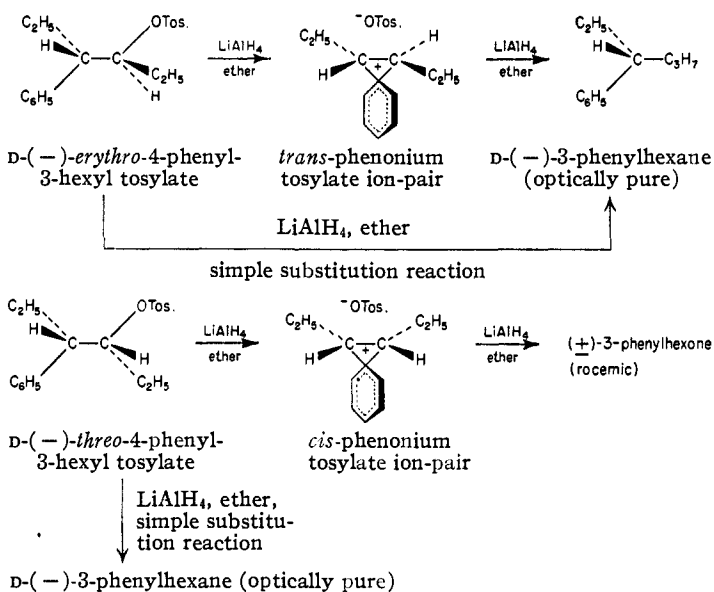
For purposes of determining the configurations of the asymmetric carbon atoms of the isomers of

- (10) D. J. Cram, *THIS JOURNAL*, **71**, 3883 (1949), and ref. 3.  
 (11) D. J. Cram, *ibid.*, **74**, 2149, 2152 (1952).  
 (12) D. J. Cram and J. D. Knight, *ibid.*, **74**, 5835 (1952).  
 (13) The configurations of the predominant product are well established, and the reactions are non-reversible (this excepts those reactions involving aluminum isopropoxide as a reducing agent for a ketone).  
 (14) D. Y. Curtin and E. K. Meislich, *THIS JOURNAL*, **74**, 2901 (1952).  
 (15) Attempts to form crystalline brucine, cinchonine and cinchonidine salts from this acid phthalate failed.

I relative to each other as well as relative to D-glyceraldehyde, the tosylates of (-)-*erythro*- and (-)-*threo*-I were treated with homogeneous ether solutions of lithium aluminum hydride. The 3-phenylhexane produced in each of these two reactions (the olefin was removed) was levorotatory, which fact indicates that the configuration of the carbon atom carrying the phenyl in each of the two starting compounds was the same. The configurations of 2-phenylbutane and 2-phenylpentane are known relative to D-glyceraldehyde,<sup>10,11</sup> the D-configuration<sup>11</sup> always being associated with the levorotatory isomer. The structural similarity between these two hydrocarbons and 3-phenylhexane



suggests that a similar relationship between sign of rotation and configuration exists in the latter compound. In the formulation the provisional con-



figuration, the name and sign of rotation are correlated. The convention used here is similar to that employed previously.<sup>11</sup>

As was expected from the results obtained in the 3-phenyl-2-butyl, the 2-phenyl-3-pentyl and the 3-phenyl-2-pentyl systems,<sup>11</sup> the (-)-*threo*-4-phenyl-3-hexyl tosylate produced hydrocarbon which was considerably racemized. The probable reason for this racemization process occurring is that symmetrical phenonium ions can be produced in the *threo* series, whereas in the *erythro* series the analogously constituted bridged ions (*trans*-phenonium ions) are asymmetric, and should go to optically pure 3-phenylhexane.<sup>16</sup> The formulations

- (16) It was previously demonstrated (ref. 11) that optically pure *erythro*-3-phenyl-2-butyl tosylate gave optically pure 2-phenylbutane when reduced with lithium aluminum hydride.

TABLE I  
 PHYSICAL PROPERTIES AND ANALYSES OF THE ISOMERIC 4-PHENYL-3-HEXANOLS AND THEIR DERIVATIVES

Compound	Proc. <sup>a</sup>	M.p., °C.	B.p.,		Yield, %	[α] <sub>D</sub> <sup>25</sup> - <sub>D</sub> <sup>20</sup> c 5% CHCl <sub>3</sub>	Mol. form.	Carbon, %		Hydrogen, %	
			°C.	mm.				Calcd.	Found	Calcd.	Found
Alcohols											
D,L-threo <sup>b</sup>	A		83	1	90		C <sub>12</sub> H <sub>18</sub> O	80.85	80.83	10.12	10.08
D,L-erythro <sup>c</sup>	A	44.5-45			92		C <sub>12</sub> H <sub>18</sub> O	80.85	80.95	10.12	10.21
D-threo <sup>d</sup>	A		83	1	95	-21.2 <sup>e</sup>	C <sub>12</sub> H <sub>18</sub> O	80.85	80.61	10.12	10.05
L-threo <sup>d</sup>	A		83	1	93	+20.9 <sup>f</sup>	C <sub>12</sub> H <sub>18</sub> O	80.85	80.91	10.12	10.42
D-erythro	A	41-42			92	-29.2	C <sub>12</sub> H <sub>18</sub> O	80.85	80.60	10.12	10.34
L-erythro	A	41-42			94	+28.7 <sup>g</sup>	C <sub>12</sub> H <sub>18</sub> O	80.85	80.67	10.12	10.31
<i>p</i> -Nitrobenzoates <sup>h</sup>											
D,L-threo	B	45-46			93		C <sub>19</sub> H <sub>21</sub> O <sub>4</sub> N	69.70	69.51	6.47	6.35
D,L-erythro	B	84-85			95		C <sub>19</sub> H <sub>21</sub> O <sub>4</sub> N	69.70	69.50	6.47	6.49
D-erythro	B	62-63			92	+32.4	C <sub>19</sub> H <sub>21</sub> O <sub>4</sub> N	69.70	69.55	6.47	6.21
L-erythro	B	62-63			87	-32.3	C <sub>19</sub> H <sub>21</sub> O <sub>4</sub> N	69.70	69.61	6.47	6.57
3,5-Dinitrobenzoates											
D,L-threo	B	40.5-41.5					C <sub>19</sub> H <sub>20</sub> O <sub>6</sub> N <sub>2</sub>	61.28	61.08	5.42	5.40
D,L-erythro	B	108-109					C <sub>19</sub> H <sub>20</sub> O <sub>6</sub> N <sub>2</sub>	61.28	61.18	5.42	5.40
D-threo	B	62-63				+9.2	C <sub>19</sub> H <sub>20</sub> O <sub>6</sub> N <sub>2</sub>	61.28	60.99	5.42	5.76
L-threo	B	62-63				-9.3	C <sub>19</sub> H <sub>20</sub> O <sub>6</sub> N <sub>2</sub>	61.28	61.18	5.42	5.31
D-erythro	B	132.5-133.5				-35.1	C <sub>19</sub> H <sub>20</sub> O <sub>6</sub> N <sub>2</sub>	61.28	61.07	5.42	5.28
L-erythro	B	132.5-133.5				+34.6	C <sub>19</sub> H <sub>20</sub> O <sub>6</sub> N <sub>2</sub>	61.29	61.09	5.42	5.48
<i>p</i> -Toluenesulfonates											
D,L-threo	C	73.5-74.5			77		C <sub>19</sub> H <sub>24</sub> O <sub>3</sub> S	68.65	68.50	7.28	7.15
D,L-erythro	C	Oil			70		C <sub>19</sub> H <sub>24</sub> O <sub>3</sub> S	68.65	69.00	7.28	7.57
D-threo	C	94-95			78	-22.1	C <sub>19</sub> H <sub>24</sub> O <sub>3</sub> S	68.65	68.65	7.28	7.20
L-threo	C	93.5-94.5			75	+21.6	C <sub>19</sub> H <sub>24</sub> O <sub>3</sub> S	68.65	68.47	7.28	7.18
D-erythro	C	42-43			79	-1.48	C <sub>19</sub> H <sub>24</sub> O <sub>3</sub> S	68.65	68.55	7.28	7.10
L-erythro	C	42-43			80	+1.56	C <sub>19</sub> H <sub>24</sub> O <sub>3</sub> S	68.65	68.42	7.28	7.45
Phthalic acid esters <sup>i</sup>											
D,L-threo		125.5-126.5					C <sub>20</sub> H <sub>22</sub> O <sub>4</sub>	73.56	73.45	6.79	6.99
D,L-erythro		99-101					C <sub>20</sub> H <sub>22</sub> O <sub>4</sub>	73.56	73.28	6.79	6.91

<sup>a</sup> See Experimental part. <sup>b</sup>  $n_D^{25}$  1.5072. <sup>c</sup>  $n_D^{25}$  1.5088. <sup>d</sup>  $n_D^{25}$  1.5071. <sup>e</sup>  $n_D^{25}$  -26.32°, (*l* 1 dm. homo.). <sup>f</sup>  $\alpha_D^{25}$  +26.30°. <sup>g</sup>  $\alpha_D^{25}$  +28.2°. <sup>h</sup> The D- and L-threo derivatives were never obtained in a crystalline condition. <sup>i</sup> The optically active derivatives have very poor crystallizing properties.

summarize the most probable reaction paths of these reactions.

The relatively greater degree of racemization (23% rearrangement) that occurred in the course of the reduction of the D-threo-tosylate of I is surprising in view of the lesser amounts of rearrangement that occurred during the similar reduction of L-threo-3-phenyl-2-butyl tosylate (5%), of D-threo-3-phenyl-2-pentyl tosylate (4%) and of D-threo-2-phenyl-3-pentyl tosylate (6%). One might expect that the strain of bringing two ethyl groups into an eclipsed configuration on the same side of a three-membered ring would be greater than that involved with two similarly oriented methyl groups, or with a methyl and an ethyl group. However, since simple reduction is a competing reaction whose rate probably varies from system to system, and since the concentration of lithium aluminum hydride (and possibly the composition) in ether was not the same in all of the above cases, the data are hardly comparable.

### Experimental Part

**Preparation of Racemic threo-4-Phenyl-3-hexanol.**—The ketone, 4-phenyl-3-hexanone<sup>17</sup> (b.p. 83-84° (2 mm.)), was

(17) M. Tiffeneau and J. Levy, *Bull. soc. chim. France*, **33**, 735 (1923).

prepared in 82% yield by the treatment of 2-phenylbutyramide with ethylmagnesium bromide. A solution of 308 g. of this ketone in 500 ml. of dry ether was added slowly to a mixture of 2.7 g. of lithium aluminum hydride and 1500 ml. of ether. After the addition was complete, the mixture was allowed to stand at room temperature for three hours, and was then decomposed with excess 2 N sulfuric acid solution. The organic layer was washed with water, with sodium carbonate solution, and it was then dried and evaporated to an oil. This oil was distilled (b.p. 83-85° (1-2 mm.)) to give 250 g. (80% yield) of a mixture of the two racemates of 4-phenyl-3-hexanol ( $n_D^{25}$  1.5080) which was submitted directly to infrared analysis.<sup>7</sup>

A mixture of 178 g. of this mixture of alcohols, 148 g. of phthalic anhydride and 500 ml. of dry pyridine was heated at 100° for 12 hours. The resulting solution was shaken with a mixture of ether and excess dilute sulfuric acid. The ether layer was washed with water and dried. When this solution was evaporated to a small volume and diluted with pentane (2-3 volumes), a solid separated which after recrystallization from an ether-pentane mixture amounted to 213 g. (65% yield), m.p. 125.5-126.5°. This material (acid phthalate of threo-4-phenyl-3-hexanol) was unchanged by further recrystallizations.

The filtrates were combined, the solvent was evaporated, and the oil was hydrolyzed to the free alcohol (see procedure A), which was converted to its *p*-nitrobenzoate (see procedure B). The resulting material when crystallized from an ether-pentane mixture gave a white solid which after recrystallization from ether-pentane amounted to 26 g. (8% yield), m.p. 84-85°. A sample of this material when hydrolyzed by procedure A gave erythro-4-phenyl-3-hexanol, m.p. 44-45°, m.m.p. with authentic material (see next section), 44-45°.

**Preparation of Racemic erythro-4-Phenyl-3-hexanol.**—Through the action of ethylmagnesium bromide on 2-phenylbutyraldehyde,<sup>18</sup> a 95% yield of a mixture of racemates of 4-phenyl-3-hexanol was obtained, b.p. 83–85° (1–2 mm.),  $n_D^{20}$  1.5090. This material was submitted directly to infrared analysis.<sup>7</sup>

A solution of 178 g. of this alcohol in four volumes of pentane was cooled to –78°. The solid that separated was recrystallized from pentane at 0° to give 71 g. (40% yield) of pure erythro isomer, m.p. 44–45°. The filtrates were combined, the solvent was evaporated, and the resulting alcohol was converted to the *p*-nitrobenzoate derivative (see procedure B). This ester was crystallized from an absolute ethanol solution at –78° to give material which after recrystallization from absolute ethanol amounted to 103 g. (32% yield), m.p. 84–85°. A small sample of erythro-I was converted to its *p*-nitrobenzoate, m.p. 84–85°, m.m.p. with above material 84–85°. The combined yields indicate that the original mixture of diastereomers must have contained at least 72% of the erythro isomer.

**Resolution of erythro-4-Phenyl-3-hexanol.**—The phthalic acid ester of erythro-4-phenyl-3-hexanol was prepared (procedure B) in 91% yield (crystallized from an ether-pentane mixture), m.p. 99–101°, m.m.p. with the phthalic acid ester of threo-4-phenyl-3-hexanol, 91–95°. A mixture of 165 g. (0.507 mole) of the erythro-acid ester and 167 g. (0.500 mole) of strychnine was dissolved in the smallest possible volume of boiling chloroform. To this solution was added six volumes of methanol, and the resulting solution was allowed to stand at room temperature. The material that separated (fraction a) and the filtrates (fraction b) were treated separately as follows.

**Fraction a.**—This material was recrystallized five times from a chloroform-methanol mixture, in each case the material in the filtrates being recycled in a systematic fractional crystallization procedure. In this manner 117 g. of strychnine salt ( $[\alpha]_D^{25}$  –28.5°, *c* 5% in CHCl<sub>3</sub>) was obtained whose rotation did not change with further recrystallization. This material was converted to the acid phthalate (57 g.) whose crystalline characteristics prevented any further purification. Hence the acid phthalate was hydrolyzed to the free alcohol, m.p. 34–39°, wt. 27 g. Recrystallization of this material did not improve the melting point or rotation. The crystalline characteristics of a sample of the *p*-nitrobenzoate of this alcohol also proved to be poor for purification purposes. However, the 3,5-dinitrobenzoate was prepared (procedure B) and recrystallized from boiling ethanol to give well defined crystals, wt. 34 g., m.p. 132–133°,  $[\alpha]_D^{25}$  –34.4° (*c* 3% in CHCl<sub>3</sub>). Further recrystallizations of this material did not change either the melting point or rotation. Hydrolysis of this ester (procedure A) gave 14 g. of optically pure erythro-I, m.p. 41–42°,  $[\alpha]_D^{25}$  –28.5° (*c* 6% in CHCl<sub>3</sub>).

**Fraction b.**—The filtrates from the original crystallization of the strychnine salt were combined with the final filtrates from the fractional recrystallization process, and the solution was evaporated to a low volume. When five volumes of acetone was added, salt separated (89 g.) which was converted by the usual method to the optically impure (+)-erythro-4-phenyl-3-hexanol, wt. 21 g., m.p. 34–39°. This material was converted to its 3,5-dinitrobenzoate (procedure B) which gave upon recrystallization from boiling absolute ethanol 28 g. of pure ester, m.p. 132.5–133.5°,  $[\alpha]_D^{25}$  +34.0° (*c* 5% in CHCl<sub>3</sub>). Hydrolysis of this material (procedure A) gave alcohol which when crystallized from pentane at 0° amounted to 12.5 g., m.p. 41–42°,  $[\alpha]_D^{25}$  +28.3° (*c* 6% in CHCl<sub>3</sub>).

**Resolution of threo-4-Phenyl-3-hexanol.**—A mixture of 142 g. (0.435 mole) of the phthalic acid ester of threo-4-phenyl-3-hexanol and 143 g. (0.430 mole) of strychnine was dissolved in a minimum amount of boiling chloroform to which was subsequently added four volumes of acetone. The solid that separated (fraction a) and the filtrates (fraction b) were treated separately.

**Fraction a.**—This salt was systematically fractionally recrystallized from a chloroform-acetone mixture until constant rotation was reached (six cycles),  $[\alpha]_D^{25}$  –54.9° (*c* 6% in CHCl<sub>3</sub>), wt. 120 g. This material was converted to the acid phthalate which could not be crystallized,<sup>19</sup> and

(18) D. J. Cram and R. Davis, *THIS JOURNAL*, **71**, 3871 (1949).

(19) Attempts to form crystalline brucine, cinchonine and cinchonidine salt of this material failed.

which was hydrolyzed (procedure A) to the optically impure threo-I, wt. 36 g.,  $\alpha_D^{25}$  –22.6° (*l* 1 dm., homog.). The *p*-nitrobenzoate ester of this alcohol was prepared but it could not be crystallized. The 3,5-dinitrobenzoate of the alcohol was prepared (procedure B), and was recrystallized from boiling absolute ethanol to give 30.5 g. of pure material, m.p. 61–62°,  $[\alpha]_D^{25}$  +9.2° (*c* 6% in CHCl<sub>3</sub>). This ester was hydrolyzed (procedure A) to give 16 g. of optically pure D-threo-4-phenyl-3-hexanol,  $\alpha_D^{25}$  –26.32° (*l* 1 dm., homog.).

**Fraction b.**—The original filtrates were combined with the final filtrates from the fractional recrystallization, and the salt present was converted to the acid phthalate ester which in turn was hydrolyzed to the free alcohol. This material was converted to the 3,5-dinitrobenzoate which after three crystallizations from boiling absolute ethanol amounted to 42 g., m.p. 61–61.8°. Hydrolysis of this material (procedure A) gave optically pure L-threo-4-phenyl-3-hexanol, wt. 18.2 g.,  $\alpha_D^{25}$  +26.30° (*l* 1 dm., homog.).

**Procedure A: The Hydrolysis of the Acid Phthalate Esters, the *p*-Nitrobenzoates and the 3,5-Dinitrobenzoates of the Isomers of 4-Phenyl-3-hexanol.**—A mixture of 0.1 mole of the ester in question, 0.5 mole of potassium hydroxide and 150 ml. of 50% aqueous methanol was refluxed for 14 hours. The mixture was then shaken with a mixture of pure pentane and water, and the pentane layer was washed with water and dried. The pentane was evaporated and the residual oil was flash distilled. In those cases where crystalline material was isolated, the oil was crystallized from pure pentane at 0°.

**Procedure B: The Preparation of the *p*-Nitrobenzoates, 3,5-Dinitrobenzoates and Phthalic Acid Esters of the Isomers of 4-Phenyl-3-hexanol.**—A solution of 0.1 mole of the alcohol and 0.11 mole of the freshly prepared acid chloride (in the case of the preparation of the acid phthalates, 0.1 mole of phthalic anhydride was employed) and 30 ml. of dry pyridine was heated at 100° for one hour. The resulting solution was poured onto a mixture of a large excess of 6 *N* sulfuric acid and ice. The resulting mixture was extracted twice with ether, and the ether layer was washed repeatedly with water, dried and concentrated to an oil. This oil was then crystallized from the solvent mentioned in each particular case.

**Procedure C: The Preparation of the Tosylate Esters of the Isomers of 4-Phenyl-3-hexanol.**—To a solution of the alcohol (0.01 mole) in 10 ml. of dry pyridine was added slowly 0.01 mole of pure *p*-toluenesulfonyl chloride. The solution was allowed to stand at room temperature for 48 hours, poured onto ice, and the resulting mixture was extracted twice with a 1 to 1 mixture of pure pentane and ether. The combined organic extracts were washed with cold dilute sulfuric acid, water, sodium carbonate solution and again with water. The solution was then dried, evaporated to an oil under reduced pressure, and this oil was crystallized from pure pentane. One recrystallization of the ester usually provided pure material.

In the case of the racemic tosylate of the erythro-alcohol, since the derivative did not crystallize, the oil was dissolved in pure pentane. This solution was cooled to –78° and the oil that separated was similarly precipitated three times from pure pentane. Finally a thin film of this oil was dried at 50° under high vacuum for one hour.

**Reaction of 4-Phenyl-3-hexyl Tosylates with Sodium Ethoxide.**—To a homogeneous solution of sodium ethylate (6 g. of sodium plus 40 ml. of absolute ethanol) was added 6.66 g. (0.02 mole) of threo-4-phenyl-3-hexyl tosylate, and the resulting solution was refluxed for 14 hours. The mixture was then cooled and shaken with ice-water and pure pentane. The pentane layer was evaporated through a short column, and the residual oil was passed through a short column of alumina (2.5 cm. by 15 cm.) with pure pentane as a developer. The column eluate was evaporated through a short column and the residual oil was flash distilled to give 2.7 g. of olefin (85% yield),  $n_D^{25}$  1.5033. This material was used directly for the ultraviolet spectrum.

The tosylate of erythro-4-phenyl-3-hexanol was similarly treated to give an 85% yield of olefin,  $n_D^{25}$  1.5089.

**Reaction of 4-Phenyl-3-hexyl Tosylates with Lithium Aluminum Hydride.**—A mixture of 800 ml. of anhydrous ether and 20 g. of lithium aluminum hydride was continuously shaken at room temperature for three hours and allowed to stand at room temperature for 12 hours. The clear solution was decanted and filtered through a thin pad of Celite.

To 310 ml. of this clear solution was added 4.6 g. of opti-

cally pure *D-erythro*-4-phenyl-3-hexyl tosylate, and the resulting solution was allowed to stand for fourteen hours. The mixture was then cautiously treated with ice-cold dilute sulfuric acid, the layers were separated, and the ether layer was washed with dilute acid, dilute base and again with water. The solution was dried, and the solvent was evaporated through a short column. The residual oil was mixed with 5 g. of 2,4-dinitrobenzenesulfonyl chloride and 30 ml. of glacial acetic acid and heated at 100° for one hour. The solution was then cooled, and shaken with pure pentane and water. The pentane solution was washed with water, with sodium carbonate solution, again with water and dried. The solvent was evaporated through a short column, and the residual oil was allowed to pass through a short column

of alumina (2.5 cm. by 15 cm.) with pure pentane as eluant. The column filtrate was evaporated through a short column, and the residue was flash distilled to give 1.15 g. of 3-phenylhexane (52% yield),  $n_D^{25}$  1.4850,  $\alpha_D^{25}$  -7.78° ( $l$  1 dm., homog.). This material is regarded as optically pure.

*Anal.* Calcd. for  $C_{12}H_{18}$ : C, 88.81; H, 11.19. Found: C, 88.54; H, 11.24.

Similar treatment of *D-threo*-4-phenyl-3-hexyl tosylate (5.7 g. of starting material plus 390 ml. of the same ether solution of lithium aluminum hydride) gave a 49% yield (1.33 g.) of 3-phenylhexane,  $n_D^{25}$  1.4849,  $\alpha_D^{25}$  -4.30° ( $l$  1 dm., homog.).

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

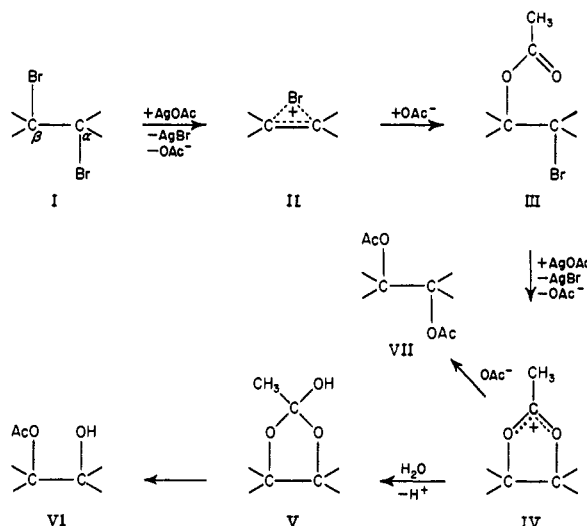
## The Role of Neighboring Groups in Replacement Reactions. XX. Some Conversions of Cyclopentane and Indan Derivatives<sup>1</sup>

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The control of the steric result and the nature of the product of replacement reactions by participation of neighboring bromine and acetoxy groups is further illustrated by reactions of several cyclopentane and indan derivatives. Cyclopentene dibromide, indene dibromide and *trans*-1-acetoxy-2-bromoindan all react with silver acetate in acetic acid to give the ester of *trans*-glycol in anhydrous solvent and the ester of *cis*-glycol in moist solvent. Participation by both neighboring bromine and acetoxy is indicated in the present cases. When acetoxy participates, the presence of water in the acetic acid gives rise to monoacetate, introduction of hydroxyl competing quite successfully with introduction of acetoxy. This furnishes a criterion for acetoxy participation and cases in the literature may be diagnosed in this way. Acetoxy participation may compete very successfully with bimolecular ( $S_N2$ ) displacement by acetate ion even at substantial concentrations of the latter. This is the case also with acetylation of 1-acetoxy-2-bromoindan.

Previous work has demonstrated the participation of the neighboring bromine atom and acetoxy group in replacement reactions of materials such as 2,3-substituted butanes<sup>3</sup> and 1,2-substituted cyclohexanes.<sup>4</sup> For example, treatment of 2,3-dibromobutane<sup>4a,b</sup> with silver acetate in acetic acid gives first acetoxy bromide III with an even number of Walden inversions by way of the ethylenebromonium ion II. The acetoxy bromide III reacts with acetoxy group participation to give the cyclic intermediate IV. The final fate of this intermediate depends on the medium in which it is produced. When the acetic acid solvent is dry, diacetate VII with over-all retention of configuration is the product. In glacial acetic acid containing more than an equivalent amount of water, orthomonoacetate V is derived from the cyclic intermediate IV and thus monoacetate VI with over-all inversion of configuration is the final product. In studying this type of neighboring group participation we investigated two five-membered ring systems, cyclopentane and indan, and the results are reported in the present paper. Also included are comments on still some other cases in the literature which add further evidence on the generality of the effect of the acyloxy group.



The materials studied in the present investigation were cyclopentene dibromide VIII, indene dibromide IX and 1-acetoxy-2-bromoindan X. The cyclopentene dibromide was obtained by addition of bromine to cyclopentene. The indene dibromide was the crystalline product from addition of bromine to indene and the 1-acetoxy-2-bromoindan was the acetate derived from acetylation of crystalline *trans* indene bromohydrin. On the basis of the usual considerations<sup>4</sup> the *trans* configuration is assigned to all three starting materials.

The treatment of cyclopentene dibromide VIII with silver acetate in dry glacial acetic acid gave rise to a diacetate which on saponification yielded a glycol XI, very nearly pure *trans* as demonstrated

(1) The material of this paper was presented in summary: (a) before the Organic Division of the American Chemical Society, St. Louis, Mo., Sept., 1948; (b) at the Eleventh National Organic Symposium, Madison, Wisconsin, June 21, 1949, page 65 of Abstracts; (c) at Montpellier, France, April 26, 1950 [*Bull. soc. chim.*, [5] **18**, 55C (1951)].

(2) Research Fellow, 1946-1947. Research supported by Research Corporation.

(3) S. Winstein and H. J. Lucas, *THIS JOURNAL*, **61**, 1576, 2845 (1939).

(4) S. Winstein, *et al.*, *ibid.*, **64**, (a) 2780, (b) 2787, (c) 2792, (d) 2798 (1942).