Studies in Stereochemistry. XXI. Steric Control of Asymmetric Induction in the Preparation of the 2,5-Dimethyl-4-phenyl-3-hexanol System[1]

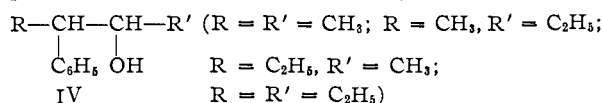By Donald J. Cram, Fathy Ahmed Abd Elhafez[2] and H. LeRoy Nyquist

All four of the stereoisomers of 2,5-dimethyl-4-phenyl-3-hexanol have been prepared in an optically pure state, and tentative assignments of configuration have been made. Application of the "Rule of Steric Control of Asymmetric Induction" to the reactions of 2,5-dimethyl-4-phenyl-3-hexanone with lithium aluminum hydride, and of 2-phenyl-3-methylbutanal with isopropyllithium, isopropylmagnesium bromide and diisopropylmagnesium indicates that the effective bulk of a phenyl group is greater than that of an isopropyl group in these types of reaction.

An investigation of the 2,5-dimethyl-4-phenyl-3-hexanol system (I) was undertaken for two reasons. (1) The balance of diastereomeric products
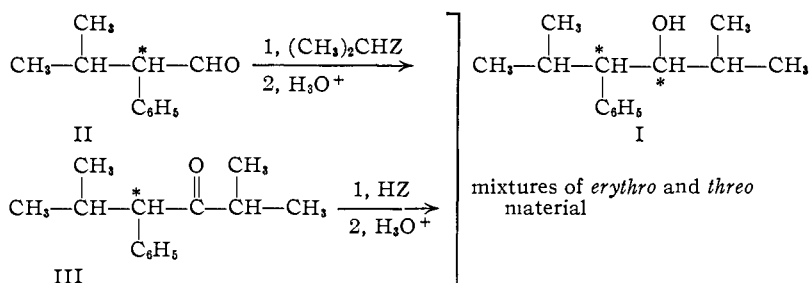
from the reactions formulated allows an estimate to be made of the relative bulks of a phenyl and isopropyl group in connection with the operation of the "Rule of Steric Control of Asymmetric Induction."[3] (2) Earlier investigations have pointed to marked differences in the course of the Wagner–Meerwein rearrangement and elimination reactions that characterize the solvolysis of systems in which different steric constraints are placed on the transition states involved.[4] System I is much more hindered than the four systems represented by the general formula IV which have been studied in the past, and the results of the solvolyses of sulfonates

$$R-CH-CH-R' \quad (R = R' = CH_3; \; R = CH_3, R' = C_2H_5;$$
$$\underset{C_6H_5}{|} \quad \underset{OH}{|}$$
$$IV \qquad R = C_2H_5, R' = CH_3;$$
$$R = R' = C_2H_5)$$

of I should cast new light on the constitution of phenonium sulfonate ion-pairs.[4b,4c] The current paper reports experiments directed toward the first of these objectives, and the results of the solvolytic experiments will be reported later.[5]

Results

The syntheses of 2-phenyl-3-methylbutanal (II) and 2,5-dimethyl-4-phenyl-3-hexanone (III) were carried out as shown in the formulations. The

imine V proved to be inordinately stable as has been found with certain other hindered imines,[6] and the over-all yield of ketone III was very poor. The reactions of aldehyde II with isopropyllithium in pentane, with isopropylmagnesium bromide both in the absence and presence of additional magnesium bromide (isopropylmagnesium bromide, 1 mole, and magnesium bromide, 6 moles) were studied, along with the reactions of ketone III with lithium aluminum hydride (both ordinary and inverse addition). The first reaction was carried out with large amounts of material, and the two racemates of alcohol I were separated as follows. The threo-isomer[7] crystallized from pentane solution at $-20°$ in a slightly impure form whereas the erythro-isomer was obtained from the filtrates by evaporating the pentane and crystallizing the oil from methanol–water at $-20°$. The filtrates were submitted
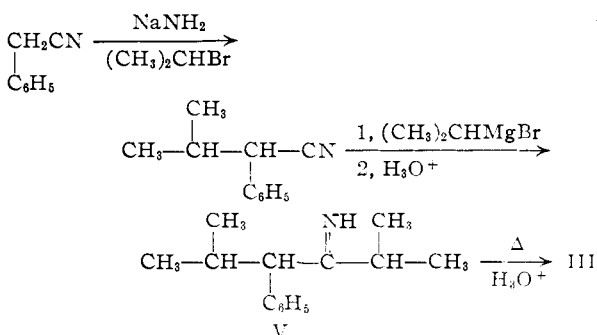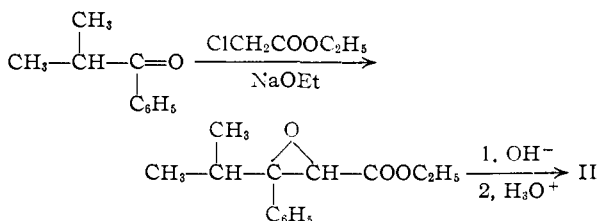
to two more complete cycles of selective crystallization similar to the first, and the combined crops of each isomer were recrystallized to give a total of 47% yield of threo-I (liquid at 25°) and a 43% yield of erythro-I (m.p. 65–66°).

(1) This work was sponsored 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) (a) D. J. Cram and F. A. Abd Elhafez, This Journal, 74, 5828 (1952); (b) D. J. Cram and J. G. Knight, ibid., 74, 5835 (1952); (c) D. J. Cram, F. A. Abd Elhafez and H. Weingarten, ibid., 75, 2295 (1953); (d) D. J. Cram and F. D. Greene, ibid., 75, 6005 (1953).

(4) (a) D. J. Cram, ibid., 71, 3863, 3875 (1949); (b) 74, 2129, 2137, 2152 (1952); (c) D. J. Cram and J. D. Knight, ibid., 74, 5839 (1952); (d) D. J. Cram, ibid., 75, 332 (1953); (e) D. J. Cram and F. A. Abd Elhafez, ibid., 75, 339, 3189 (1953).

(5) Paper XXIII of this series.

(6) P. L. Pickard and E. F. Engles, This Journal, 74, 4607 (1952).

(7) The configurational assignments will be justified in paper XXIII of this series which reports the results of the solvolysis of derivatives of these isomers.

TABLE I

PHYSICAL PROPERTIES AND ANALYSES OF THE ISOMERIC 2,5-DIMETHYL-4-PHENYL-3-HEXANOLS (I), THEIR DERIVATIVES AND PRECURSORS

Compound	Proc.[a]	Yield, %	M.p., °C.	$[\alpha]^{24-27}D$, c 5-7% (CHCl₃)	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Alcohols-I									
(±)-threo	..	43	....	....	$C_{14}H_{22}O$	81.49	81.71	10.74	10.44
(±)-erythro	..	47	65.5–66	....	$C_{14}H_{22}O$	81.49	81.20	10.74	10.60
(+)-threo	..	80	....	+14.56[b]	$C_{14}H_{22}O$	81.49	81.68	10.74	10.51
(−)-threo	..	82	....	−14.50[b]	$C_{14}H_{22}O$	81.49	81.57	10.74	10.80
(+)-erythro	A	94	69.5–70.2	+19.08	$C_{14}H_{22}O$	81.49	81.44	10.74	11.02
(−)-erythro	A	93	69.5–70.2	−19.11	$C_{14}H_{22}O$	81.49	81.43	10.74	10.82
I-p-Nitrobenzoates									
(±)-threo	B	90	118.5–119.5	....	$C_{21}H_{25}O_4N$	70.96	71.22	7.09	7.09
(±)-erythro	B	89	147–148	....	$C_{21}H_{25}O_4N$	70.96	70.66	7.09	7.24
Deriv. (+)-threo-I	..	23	144.6–145.5	+106.1	$C_{21}H_{25}O_4N$	70.96	71.26	7.09	6.90
Deriv. (−)-threo-I	..	21	144.6–145.6	−105.5	$C_{21}H_{25}O_4N$	70.96	70.67	7.09	7.28
Deriv. (+)-erythro-I	B	93	169–170	+46.76	$C_{21}H_{25}O_4N$	70.96	70.87	7.09	6.99
Deriv. (−)-erythro-I	B	90	169–170	−47.27	$C_{21}H_{25}O_4N$	70.96	71.07	7.09	7.52
I-Acid phthalates									
(±)-threo	C	80	147.5–148.5	....	$C_{22}H_{26}O_4$	74.54	74.26	7.39	7.52
(±)-erythro	C	92	166–167	....	$C_{22}H_{26}O_4$	74.54	74.66	7.39	7.19
Deriv. (+)-erythro	..	39	158–158.5	+67.13	$C_{22}H_{26}O_4$	74.54	74.29	7.39	7.10
Deriv. (−)-erythro	..	26	158–158.5	−66.96	$C_{22}H_{26}O_4$	74.54	79.49	7.39	7.31
I-3,5-Dinitrobenzoate									
(±)-threo	..	..	167.5–168.5	....	$C_{21}H_{24}N_2O_6$	62.98	62.99	6.04	5.49
(±)-erythro	..	..	167.5–168.5	....	$C_{21}H_{24}N_2O_6$	62.98	62.89	6.04	5.80
Deriv. (−)-erythro	B	85	167.5–168.5	....	$C_{21}H_{24}N_2O_6$	62.98	62.86	6.04	5.92
I-p-Bromobenzenesulfonates									
(±)-threo	D	64	78 63[c]	....	$C_{20}H_{25}O_3SBr$	56.46	56.37	5.90	5.77
(±)-erythro	D	68	65 73[c]	....	$C_{20}H_{25}O_3SBr$	56.46	56.19	5.90	6.04
2-Phenyl-3-methyl 1-Butanol (VI)	..	90	....	....	$C_{11}H_{16}O$	80.44	79.91	9.81	9.78
VI-Acid phthalate	..	92	98–100	....	$C_{19}H_{20}O_4$	73.05	73.18	6.45	6.42
VI-p-Nitrobenzoate	B	90	46–47	....	$C_{18}H_{19}O_4N$	68.96	68.98	6.11	5.80
VI-3-Nitro acid phthalate	B	85	159–160	....	$C_{19}H_{19}O_6N$	63.85	64.01	5.36	5.20

[a] See Experimental. [b] $\alpha^{25}D$, l = 1 dm., neat. [c] Decomposition. M.p. depends on rate of heating.

The two racemates were converted to their respective acid phthalates and resolved, the *threo*-isomer through the strychnine and the *erythro*-isomer through the brucine salt. In the latter resolution one antipode was obtained in optically pure state from the brucine salt after six crystallizations, whereas the enantiomer was obtained in an optically pure state by the separation of the partially racemic acid phthalates by fractional crystallization. The resolution of the *threo*-acid phthalate as the strychnine salt was only partially realized, and the final purification of each enantiomer was accomplished by conversion of the appropriate acid phthalate fractions to the respective *p*-nitrobenzoate derivatives, whose crystallizing properties were suitable for obtaining the two optically pure enantiomers. The (+)- and (−)-*erythro*-I were solids and the (+)- and (−)-*threo*-I were liquids at room temperature. The physical properties and analyses of the compounds used in these syntheses are reported in Table I. Evidence that virtual optical purity was realized is found in the near equivalence of the magnitudes of rotation of the enantiomerically related compounds.

When the product of the reaction of aldehyde II with isopropylmagnesium iodide was submitted to isolation experiments similar to those described above, racemic *erythro*-I was obtained in somewhat larger yields, but racemic *threo*-I could not be obtained. However, the reduction product, 2-phenyl-3-methyl-1-butanol (VI) was isolated in 3% yield through its *p*-nitrobenzoate, the identity of this derivative being demonstrated by its comparison with an authentic sample (prepared by the reduction of aldehyde II with lithium aluminum hydride followed by conversion of the resulting alcohol to its *p*-nitrobenzoate). Table I reports the physical properties and analyses of these substances.[8]

The mixtures of alcohols obtained in the different syntheses of I were analyzed making use of the marked differences in the infrared spectra of *threo*-I, *erythro*-I and primary alcohol, VI. The products of the reduction of ketone III and the reaction of

(8) After VI was isolated as its *p*-nitrobenzoate, the filtrates were hydrolyzed to impure I which was in turn converted to the acid phthalate derivative. From this mixture crystallized almost optically pure the acid phthalate of (−)-*erythro*-I, unaided by any asymmetric resolving agent (see Experimental for details). This sequence represents a *spontaneous resolution*, an occurrence that is even more remarkable in view of the fact that at the time it occurred, the resolution through the brucine salt had not yet been effected. A large number of other resolutions had been carried out in the same laboratory, and therefore the place was infested with seeds of optically active homologous compounds.

<div style="text-align:center">TABLE II</div>

Infrared Data Concerning Analyses of Mixtures of erythro- and threo-I, and Primary Alcohol VI

Run no.[b]	Sample	Slit (mm) = u =	1.38 λ = 9.00	1.52 λ = 9.40	1.04 λ = 12.45	0.655 λ = 10.70	1.46 λ = 13.47	1.89 λ = 14.00
..	Pure threo-I		0.235	0.397	0.182	0.139	0.123	1.29
..	Pure erythro-I[c]		.425	.222	.137	.337	.220	0.760
..	Pure alc.-VI		.210	.904	.109	.126	.495	.566
1	Ald. II + (CH₃)₂CHMgBr		.324	.443	.141	.244	.275	.817
..	24%-t-I, 50%-e-I, 26%-VI[d]		.329	.451	.140	.244	.253	.812
2	Ald. II + (CH₃)₂CHMgBr + MgBr₂		.326	.371	.151	.242	.219	.920
..	37%-t-I, 50%-e-I, 13%-VI[d]		.329	.384	.152	.242	.215	.920

Column headers under "Optical densities in the infrared[a]": "1st. Set equations" spans 1.38, 1.52, 1.04; "2nd. Set equations" spans 0.655, 1.46, 1.89.

[a] Beckman IR2T infrared spectrophotometer. All readings taken within four hours of one another in 0.03 mm. cell homogeneous liquid films, NaCl prism. [b] Same run numbers as Table III. [c] Since erythro-I is a solid, values were obtained by extrapolating linear plots. Highest known mixture, 80% erythro-I, 20% threo-I. [d] Values are in mole per cent. (t = threo, e = erythro).

<div style="text-align:center">TABLE III</div>

Results of Infrared Analyses of Mixtures of threo- and erythro-I and Primary Alcohol VI

Run[a] no.	Source of sample	1st. set of equations (mole %)[b] threo-I	erythro-I	VI	Sum	2nd. set of equations (mole %)[b] threo-I	erythro-I	VI	Sum
1	Ald. II + (CH₃)₂CHMgBr	27	48	24	99	23	47	31	101
2	Ald. II + (CH₃)₂CHMgBr + MgBr₂	38	49	12	99	37	50	12	99

| | | % compositions as read from plots | | | | | | | | |
		λ 8.98 μ threo	erythro	λ 9.51 μ threo	erythro	λ 10.69 μ threo	erythro	λ 13.02 μ threo	erythro	Average threo	erythro
3	Ald. II + (CH₃)₂CHLi (pentane)	52	48	55	45	51	49	52	48	52	48
4	Ket. II + LiAlH₄ (normal addit.)	91	9	88	12	90	10	89	11	90	10
5	Ket. III + LiAlH₄ (inverse addit.)	91	9	89	11	90	10	90	10	90	10

[a] Run nos. same as Table II. [b] See Table II for data.

isopropyllithium with aldehyde II lead only to mixtures of threo- and erythro-I, and therefore these mixtures were analyzed as two component systems. Known synthetic mixtures of erythro and threo-I were prepared, and plots of optical density vs. per cent. composition were made at the four wave lengths in the infrared most advantageous for analysis (0.03 mm. films at λ 8.98, λ 9.51, λ 10.68 and λ 13.02 μ). These plots were essentially linear, and since the pure erythro isomer cannot be handled as a liquid at 25°, the optical densities of this material as a liquid were obtained by extrapolation of the curves from 80% to 100% erythro isomer. The compositions of the unknown mixtures were then determined from their optical densities. In the two syntheses involving Grignard reagent, the products were analyzed as three component systems through the solution of two independent sets of three simultaneous equations. Corrections for deviations from Beer's law were then made by correcting the values obtained for the unknown mixtures with values obtained for known mixtures whose compositions approximated those of the unknowns. Table II records the relevant data, whereas Table III summarizes the results of the analyses.

An attempt was made to assign the relative configurations to each of the two racemates of I on the following basis. The p-bromobenzenesulfonates of threo- and erythro-I[7] were subjected to the action of sodium ethoxide in ethanol to give a mixture of olefin and ether (about 60 and 40%, respectively, for both isomers). The ultraviolet absorption spectra of these mixtures differed in only minor respects from that of toluene, indicating that the olefin produced was mainly unconjugated or, if conjugated, that the styrene type resonance was so damped sterically that it had little effect on the spectra.[9]
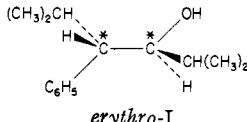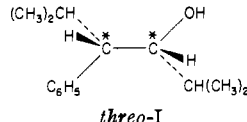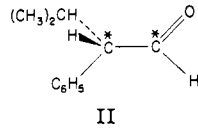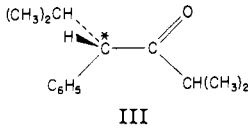
Discussion

Chart I summarizes the results concerning the distribution of alcohol I between the erythro and threo isomers in runs 1–5. It is clear from these results that the "Rule of Steric Control of Asymmetric Induction" holds in runs 1, 2, 4 and 5 if the phenyl is considered to possess an effectively larger bulk than the isopropyl group. Such a relationship is reasonable if the effective area occupied by the π-electrons is taken into account along with the fact that the two m-carbons and hydrogens of the phenyl make some contribution to the effective volume of that group. This relationship is also consistent with the observations that the reactions of 2-phenylpropanol and 3-phenyl-2-butanone leading to 3-phenyl-2-butanol[3a] were more stereospecific than analogous reactions leading to 3-cyclohexyl-2-butanol.[3d] A comparison of runs 1 and 2 on the one hand and run 3 on the other provides another illustration of the generalization that the Grignard reagent is more stereospecific than the corresponding alkyllithium reagent.[3b,3d]

A comparison of the results of runs 1 and 2 reveals that the addition of six moles of magnesium bromide (RMgBr = one mole) to the Grignard reagent not only results in cutting the amount of the

(9) In a number of analogous systems [D. J. Cram, This Journal, 71, 3883 (1949), and 74, 2149 (1952), ref. 3a and 3c] the configurations of the diastereomeric alcohols have been demonstrated through the use of the E₂ reaction to give substituted styrenes (one diastereomer giving cis- and the other trans-olefin) whose configurations were assigned on the basis of their ultraviolet absorption spectra.

Chart I

	erythro-I	threo-I
1, (CH₃)₂ CHMgBr → / + / 2, H₃O (run 1)	1.9	1
1, (CH₃)₂CHMgBr + 6 MgBr₂ → / + / 2, H₃O (run 2)	1.3	1
1, (CH₃)₂CHLi + pentane → / + / 2, H₃O (run 3)	1	1
1, LiAlH₄ (normal addit.) → / + / 2, H₃O (run 4)	1	10
1, LiAlH₄ (inverse addit.) → / + / 2, H₃O (run 5)	1	10

competing reduction reaction in half[10] (see Table III), but also provides a reagent that is markedly less stereochemically selective. A rationalization of these observations may be based on the equilibrium that exists in Grignard reagents between RMgX and $R_2Mg + MgX_2$.[11] It is reasonable to expect that $(CH_3)_2CHMgBr$ and $[(CH_3)_2CH]_2Mg$

$$2(CH_3)_2CH—Mg—Br \rightleftharpoons [(CH_3)_2CH]_2Mg + MgBr_2$$
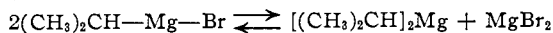
each have specific rates of reduction of and addition to carbonyl groups, as well as specific rates to give *threo vs. erythro* product. Since $[(CH_3)_2CH]_2$-Mg is much bulkier than $(CH_3)_2CHMgBr$, greater stereochemical selectivity should characterize the addition reactions of the former reagent.[3d] Since the addition of $MgBr_2$ shifts the equilibrium in favor of $(CH_3)_2CHMgBr$ (run 2), it is not surprising that less stereospecificity was experienced in run 2 than in run 1. Furthermore, of the two reduction reactions illustrated in VII and VIII, reaction VIII involving R_2Mg as the reducing reagent might be expected to go at the faster rate because of the reduced positive charge on the Mg.[12]

The previously made observation that the order of addition in the reaction of lithium aluminum hydride with ketones makes no difference in the

(10) C. G. Swain and H. G. Boyles [THIS JOURNAL, **73**, 870 (1951)] observed that the addition of magnesium bromide to diisopropyl ketone reduced the amount of reduction by *n*-propylmagnesium bromide by a factor of about 2.4 and increased the amount of addition by a similar factor.

(11) W. Schlenk, Jr., *Ber.*, **64**, 736 (1931); C. R. Noller and A. J. Castro, THIS JOURNAL, **64**, 2509 (1942); G. H. Coleman and J. W. Brooks, *ibid.*, **68**, 1620 (1946).

(12) Compare this explanation with that of Swain, *et al.* (ref. 10).

product distribution[3d] is confirmed by the identity of the results obtained in runs 4 and 5.

Experimental

Preparation of 2-Phenyl-3-methylbutanal (II).—A solution of sodium ethylate (74.5 g. of Na + 750 ml. of absolute ethanol) was mixed with 750 ml. of dry pure pentane (P_2O_5) and cooled to −10°. A mixture of 425 g. of isobutyrophenone and 354 g. of ethyl chloroacetate (both freshly distilled) precooled to 0° was added to the above well-stirred mixture at such a rate as to keep the reaction temperature between −10 and −5° (the reaction flask was cooled with an ice–salt-bath). After the addition was complete (two hours), the reaction mixture was held at 0° for 72 hours. The mixture was then held at reflux temperature for 8 hours, and the pentane was allowed to escape. The mixture was then cooled and mixed with 4 kg. of crushed ice and extracted with three successive 500-ml. portions of ether. The combined ether layers were washed five times with 1 *N* sodium hydroxide solution, three times with water and were dried. The solvent was evaporated, and the residual oil was distilled to give two fractions: first, b.p. 65–100° (1 mm.) (a mixture of isobutyrophenone and ethyl chloroacetate); second, b.p. 117–120° (1 mm.), wt. 287 g. (glycidic ester). This ester was added to a solution of sodium ethoxide (34.5 g. of sodium plus 580 ml. of 95% ethanol) and the homogeneous solution was allowed to stand at room temperature for 16 hours. The solid that separated was collected and washed first with absolute ethanol and then with dry ether. The solid was dried and added to 3 liters of ice cold 3 *N* hydrochloric acid solution. After four hours the mixture was submitted to steam distillation until no more volatile material came over. The distillate was extracted with ether, the ether layer was washed with water, dried and the ether was evaporated. The residual oil was distilled to give 162 g. of aldehyde II, b.p. 72–73° (1 mm.), $n^{25}D$ 1.5051. The semicarbazone melted at 144.4–145.2° (lit. m.p. 140°).[13]

Preparation of 2-Phenyl-3-methylbutyronitrile.—To 600 ml. of liquid ammonia (stirred) at −78° was added 0.5 g. of $FeCl_3$ that had been ignited to the oxide, followed by 26 g. of sodium in small pieces over a period of four hours. The deep blue color changed to black. The bath was then removed, and about two-thirds of the ammonia was allowed to escape. One liter of dry ether was then added and the reaction mixture was warmed to 25°. A solution of 117 g. of

(13) M. Tiffeneau, *Ann. chim. phys.*, [8] **10**, 355 (1907).

phenylacetonitrile in 250 ml. of ether was then added slowly while the stirred solution remained at 25°. The mixture was held at reflux for 8 hours with stirring and was then cooled to 0°. A solution of 205 g. of isopropyl iodide in 350 ml. of dry ether was now added to the stirred mixture at such a rate as to maintain vigorous reflux. The mixture was then held at reflux for an additional ten hours, cooled to 0° and 25 ml. of ethanol was added followed by 200 ml. of water. The ether layer was separated, the water layer was washed with ether, and the combined ether solutions were washed with 5% sodium bisulfite solution, 5% sodium bicarbonate solution and finally with water. The ether solution was dried, the solvent was evaporated, and the residual oil was distilled at 14 mm., the fraction b.p. 127–135° being collected (wt. 130 g.). This material was submitted to careful fractional distillation through a helix-packed column (three feet, 103 theoretical plates) at 49 mm. Two main fractions were collected: first, 246 g., b.p. 157–158°, n^{25}D 1.5032; second, 111 g., b.p. 174.4–174.5°, n^{25}D 1.5081.

The first fraction analyzed for 2-phenyl-3-methylbutyronitrile.[14]

Anal. Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.23. Found: C, 82.96; H, 7.96.

A small sample was hydrolyzed to the corresponding acid by the method of Stadel[15] to give product, m.p. 63.3–63.5° (lit.[5] m.p. 62–63°).

The second fraction analyzed for 2-isopropyl-2-phenyl-3-methylbutyronitrile.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.52; H, 9.51. Found: C, 83.99; H, 9.45.

Preparation of 2,5-Dimethyl-4-phenyl-3-hexanone (III).—To a solution of 3.95 moles of isopropylmagnesium bromide (106 g. of magnesium, 486 g. of isopropyl bromide in 700 ml. of ether) was added over a period of half an hour 250 g. of 2-phenyl-3-methylbutyronitrile in 450 ml. of dry ether. The resulting mixture was heated (with stirring) at reflux for seven days. The mixture was then cooled to 0° and 500 ml. of cold concd. hydrochloric acid was added at such a rate as to maintain a moderate reflux. The solid that separated was scraped away from the sides of the flask and the mixture was heated at reflux for two more hours. The mixture was cooled, and the ether layer was decanted. From this ether solution was obtained 7 g. of isobutylbenzene (b.p. 59–60° (14 mm.), n^{25}D 1.4834) and 35 g. of starting material (b.p. 122–124° (14 mm.), n^{25}D 1.5031).

To the water–solid mixture was added 250 ml. of concd. hydrochloric acid and 950 ml. of water, the remaining ether was evaporated and vigorous reflux was maintained for 40 hours. The mixture was then cooled, the water was decanted and the remaining solid was dissolved in chloroform. The aqueous layer was extracted with chloroform, the two chloroform solutions were combined, treated with decolorizing charcoal and filtered. Evaporation of the chloroform gave a gray amorphous solid which was collected and washed twice with ether. This solid (83.5 g.) gave a residue on ignition, and was shown by elementary analysis to contain nitrogen and chlorine. Attempts to decompose this complex failed. The ether solution used for washing the solid was evaporated to give the desired ketone, which was recrystallized from hot 95% ethanol, wt. 43.9 g., m.p. 48–49°.

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.35; H, 9.82.

Attempts to prepare carbonyl derivatives of this ketone failed, probably for steric reasons.

Reaction of 2-Phenyl-3-methylbutanal (II) with Isopropyl-lithium (Run 3).—To 7.0 g. of lithium ribbon in 500 ml. of dry pure pentane was added over a period of 48 hours 39.2 g. of isopropyl chloride dissolved in 500 ml. of pure pentane. After the addition was complete, the mixture was allowed to stand at room temperature for 12 hours, and the clear supernatant solution was decanted. To this solution was added (at such a rate as to maintain gentle reflux) 33 g. of 2-phenyl-3-methylbutanal. The excess reagent was decomposed by pouring the solution into ice-water and the pentane layer was separated, washed with water and dried. The solvent was evaporated, and the residual oil was flash distilled to give 37 g. of product, b.p. 89–94° (1 mm.),

n^{25}D 1.5069. This material was used directly in the separation of the pure diastereomeric racemates of 2,5-dimethyl-4-phenyl-3-hexanol (I). A 40-g. sample of the above material was distilled at 16 mm. pressure through a center-rod column (50 theoretical plates); the first 3 g. that distilled (b.p. 134°, n^{25}D 1.5057–1.5060) was discarded, and product was collected, b.p. 134–136°, n^{25}D 1.5057–1.5070, wt. 35 g. Only a very small pot residue remained. The above material was used directly for the infrared analysis.

Reaction of 2-Phenyl-3-methylbutanal (II) with Isopropyl-magnesium Bromide (Run 1).—To a solution of isopropyl-magnesium bromide (3.32 g. of magnesium, 15.24 g. of freshly distilled isopropyl bromide and 125 ml. of dry ether) was added dropwise 5.0 g. of aldehyde II in 100 ml. of ether. After the addition of aldehyde was complete, the mixture was decomposed with dilute sulfuric acid (propane was evolved), and the layers were separated. The ether layer was washed with sodium bicarbonate solution, with water and was dried. The ether was evaporated, and the residual oil was flash distilled twice to give 5.33 g. of product, n^{25}D 1.5077–1.5088. This material was used directly for the infrared analysis.

Reaction of 2-Phenyl-3-methylbutanal (II) with Isopropyl-magnesium Bromide in Presence of Large Excess of Magnesium Bromide (Run 2).—To 100 ml. of dry ether was added with stirring 41.3 g. of $MgBr_2 \cdot 2Et_2O$.[16] The solid went into solution (15 minutes) to form two liquid layers. Aldehyde II (5.0 g.) was added to this mixture, which was added dropwise to isopropylmagnesium bromide (3.32 g. of magnesium, 15.24 g. of freshly distilled isopropyl bromide and 125 ml. of dry ether). In this addition the lower layer that probably contained the magnesium bromide went in first followed by the upper layer that probably contained most of the aldehyde. The product was isolated as in the former reaction (see above) to give 4.51 g. of a mixture of alcohols, n^{25}D 1.5093–1.5085. This material was used directly in the infrared analysis.

Reaction of 2,5-Dimethyl-4-phenyl-3-hexanone (III) with Lithium Aluminum Hydride (Normal Addition) (Run 4).—To a stirred mixture of 2.81 g. (0.074 mole) of lithium aluminum hydride in 100 ml. of dry ether was added dropwise 15.0 g. (0.074 mole) of ketone III in 100 ml. of dry ether. The resulting mixture was stirred overnight, and the excess hydride was decomposed with ethyl acetate. The mixture was then shaken with dilute hydrochloric acid, and the ether layer was washed with sodium bicarbonate solution and finally with water. The ether solution was dried, the solvent was evaporated, and the residual oil was flash-distilled at 7 mm. (pot temperature of 133°). This material was distilled through a short center-rod column, b.p. 135° (16.4 mm.), n^{25}D 1.5030–1.5040. This material was used directly for the infrared analysis.

Reaction of 2,5-Dimethyl-4-phenyl-3-hexanone (III) with Lithium Aluminum Hydride (Inverse Addition) (Run 5).—A mixture of 2.90 g. of lithium aluminum hydride and 210 ml. of anhydrous ether was held at reflux for ten hours, and the solid was allowed to settle. The supernatant liquid was carefully decanted and a 5-ml. aliquot was titrated. The 180 ml. of remaining solution (containing 0.025 mole of lithium aluminum hydride) was added dropwise to a solution of 15.0 g. (0.074 mole) of ketone III in 50 ml. of dry ether. The reaction mixture was treated from this point on as in run 4, a total of 13.14 g. of product being obtained, b.p. 130°, n^{25}D 1.5030–1.5040. This material was used directly for the infrared analysis.

Separation of Two Racemates of 2,5-Dimethyl-4-phenyl-3-hexanol (I).—A mixture (255 g.) of the two racemates of I (obtained from the action of isopropyllithium on aldehyde II) was dissolved in 780 ml. of pure pentane and cooled to −20° for 12 hours. The supernatant mother liquor was decanted from the heavy cubic crystals of *threo*-racemate that had separated (this material is an oil at room temperature). The crystalline material was washed with 50 ml. of pure pentane (−78°) by decantation, and the combined pentane solutions were evaporated. The residual oil was taken up in 600 ml. of methanol, the solution was cooled to 0°, and water was added until the solution became slightly turbid. The *erythro*-racemate separated as white needles in eight hours at −20°, was collected and washed with 70% methanol–water that had been cooled to −20°. The filtrates were evaporated to a mixture of water and oil which

(14) S. V. Hintikka [*Ann. Acad. Sci. Fennical.*, **19A**, No. 1, 4 pp. (1923)] reported b.p. 128–130 (15 mm.) nD 1.5078.

(15) W. Stadel, *Ber.*, **19**, 1949 (1886).

(16) W. B. Plum, *J. Chem. Physics*, **5**, 172 (1937).

was shaken with pure pentane. The pentane layer was dried, and the carbinol mixture in the pentane was submitted to two more complete cycles of the above separation procedure. The combined samples of *threo*-I were recrystallized from pure pentane at −20° to give 112 g. of pure *threo*-racemate (oil at room temperature, $n^{25}D$ 1.5028). The combined samples of *erythro*-I were recrystallized from methanol-water to give 107 g. of pure product, m.p. 65–66°. The combined filtrates from the above separations were evaporated, and the residual oil was distilled, wt. 17 g. This material was converted to the 3,5-dinitrobenzoate derivative (procedure B[3c]) to give product that crystallized from chloroform, 7 g., m.p. 167–168°. When hydrolyzed back to alcohol (procedure A[3c]), this material provided 3.5 g. of additional *erythro*-I. The chloroform filtrates were evaporated, and the residue crystallized from ethanol at −20° to give 17 g. of ester, m.p. 59–62°. This material was hydrolyzed back to the alcohol (procedure A[3c]) which when crystallized from pentane provided an additional 7.0 g. of *threo*-I.

Preparation of Acid Phthalates of the Two Racemates of 2,5-Dimethyl-4-phenyl-3-hexanol (I). Procedure C.—A mixture of 24 g. of phthalic anhydride, 30 g. of *erythro*-I and 45 ml. of pure dry pyridine was held at reflux temperature for 48 hours, cooled and added to water. The mixture was shaken with ether, the ether layer was washed with dilute sulfuric acid, with water and was dried. The solvent was evaporated and the residual oil was crystallized from an ether-pentane mixture to give 50 g. of phthalic acid ester of *erythro*-I, m.p. 163–164°. When recrystallized from ethyl acetate this material appeared to change its crystalline form, m.p. 166–167°.

The acid phthalate of *threo*-I was prepared in a similar fashion. From 96 g. of alcohol was obtained 118 g. of acid phthalate, m.p. 147.5–148.5° (crystallized twice from an 80% methanol–20% water mixture). The filtrates from the crystallizations were hydrolyzed (procedure A[3c]) to give back 5.5 g. of pure *threo*-I, $n^{25}D$ 1.5028.

Resolution of Acid Phthalate Ester of *erythro*-2,5-Dimethyl-4-phenyl-3-hexanol (I).—A solution of 50 g. of the acid ester, 96 g. of brucine and 400 ml. of methanol was allowed to stand at −20° for 12 hours. The white needles that separated were collected and washed with methanol (−78°). This material was recrystallized from methanol four times and converted back to the acid phthalate by the usual method to give optically pure acid phthalate, 13.5 g., m.p. 158–158.5° (from ether-pentane), $[\alpha]^{27}D$ +67.13° (c 5%, CHCl₃). A small sample of this material was converted back to the brucine salt, which was recrystallized twice and reconverted to the acid phthalate. The material possessed virtually the same properties.

The filtrates from the initial brucine crystallization were converted back to acid phthalate, and this acid ester was submitted to systematic fractional crystallization from ethyl acetate. Racemic material accumulated in the head crop and (−)-material in the tail crop. An eight step series provided 8.0 g. of the pure enantiomer, m.p. 158–158.5°, $[\alpha]^{25}D$ −66.96° (c, 6% in CHCl₃), 21.0 g. of nearly racemic material, m.p. 164–167°, and 3.2 g. of intermediate fractions. The racemic material was recycled through the brucine salt to give an additional 6.2 g. of optically pure (+)-isomer. The filtrates were converted back to the acid phthalate which upon fractional crystallization gave 5.2 g. of optically pure (−)-isomer and 12.3 g. of racemic material rich in (−)-isomer.

The optically pure acid esters were hydrolyzed to their respective alcohols (procedure A[3c]), which were crystallized from pure pentane (see Table I).

Resolution of Acid Phthalate Ester of *threo*-2,5-Dimethyl-4-phenyl-3-hexanol (I).—A mixture of 108 g. of the acid phthalate of *threo*-I, 104 g. of strychnine and 1 liter of acetone was brought to boiling, the undissolved strychnine was collected, and the filtrates were cooled at −20° for 8 hours. The strychnine salt that separated was recrystallized five times from acetone and twice from methanol to give 35 g. of salt that was converted by the usual method to acid phthalate, 17.2 g., m.p. 66–78°, $[\alpha]^{25}D$ −65.8° (c 2.6 in CHCl₃). A small sample of this material was reconverted to the strychnine salt, but further recrystallizations of this salt were not only wasteful but did not improve the purity of the recovered acid phthalate.

The original strychnine filtrates were evaporated, and the residual material was converted to the acid phthalate which

was crystallized from ether-pentane to give 30 g. of near-racemic material, m.p. 144–147°. The filtrates were evaporated to an oil, which crystallized from pentane to give 18.0 g. of acid phthalate, m.p. 54–67°, $[\alpha]^{25}D$ +65.2 (c 3% in CHCl₃). All of the above fractions (except those on which rotations are reported) were put back at the appropriate places into a fresh cycle of operations similar to the first. A total of seven cycles of separation procedures gave the following balance: 30 g. of near-racemic acid phthalate, m.p. 146–148°; 35 g. of (+)-acid phthalate; 29 g. of (−)-acid phthalate. The active isomers were obviously not optically pure, and were therefore hydrolyzed to their respective alcohols (procedure A[3c]) which in turn were converted to the respective *p*-nitrobenzoates (procedure B[3c]). Each *p*-nitrobenzoate was crystallized and recrystallized from hot absolute ethanol to give 26 g. of the (+)-isomer and 23 g. of the (−)-isomer (see Table I for properties) in an essentially optically pure state. Each *p*-nitrobenzoate was hydrolyzed in an 80% ethanol-water solution containing two equivalents of potassium hydroxide (slightly modified procedure A[3c]). Each alcohol was flash distilled twice (see Table I for yields and physical properties).

Isolation of 2-Phenyl-3-methyl-1-butanol (VI) from Reaction of Isopropylmagnesium Bromide with 2-Phenyl-3-methyl-1-butanal and Spontaneous Resolution of *erythro*-2,5-Dimethyl-4-phenyl-3-hexanol (I) Derivative.—The reaction described under run 1 was carried out with 143 g. of aldehyde III to give 155 g. of distilled product, b.p. 83–88° (1 mm.). This material (140 g.) was crystallized from methanol-water by the method described in run 3 to give 40 g. (23% yield) of pure *erythro*-I, m.p. 65–66°. The remaining alcohol was recovered from the filtrates (96 g.), and converted to its *p*-nitrobenzoate (procedure B[3c]) which was fractionally crystallized from absolute ethanol to give three fractions: first, 60 g. of solid, m.p. 127–134°, whose m.p. did not improve with further crystallizations; second, 80 g. of solid, m.p. 47–60°; third, an oily residue from the filtrates of the above crystallizations. The third fraction was submitted to distillation at 1 mm. to give 6 g. of unreacted alcohol and a dark red pot residue that was discarded. The first fraction was hydrolyzed back to the alcohol (procedure A[3c]) which was crystallized from methanol-water to give 19 g. of racemic *erythro*-I, m.p. 65–66°, and filtrates. Alcohol was recovered from the filtrates and converted to the acid phthalate (procedure C). This material was crystallized three times from ether-pentane to give 3.5 g. of almost optically pure acid phthalate of (−)-*erythro*-I, m.p. 158–159°, $[\alpha]^{25}D$ −65.24° (c 25% in CHCl₃). A small sample of this material was converted back to the alcohol (procedure A[3c]), m.p. 69–70°, $[\alpha]^{25}D$ −18.95° (c 8% in CHCl₃), which in turn was converted to the *p*-nitrobenzoate, m.p. 169–170°, $[\alpha]^{25}D$ −45.6° (c 2.5% in CHCl₃).

The second fraction was crystallized eight times from ether-pentane to give 20 g. of the *p*-nitrobenzoate of 2-phenyl-3-methyl-1-butanol (VI), m.p. 46–47°, m.p. with an authentic sample (see next section) 46–47°. Hydrolysis of this sample to the alcohol (procedure A[3c]) and flash distillation of this product provided 9.8 g. of VI, $n^{25}D$ 1.5142. A small sample of this alcohol was converted to its acid phthalate and 3-nitrophthalic acid ester (see Table I for analyses and properties).

Preparation of 2-Phenyl-3-methyl-1-butanol (VI).—A solution of 2.0 g. of 2-phenyl-3-methyl-1-butanol (III) in 10 ml. of ether was added dropwise to 0.5 g. of lithium aluminum hydride and 25 ml. of ether. The mixture was decomposed with 5 ml. of ethyl acetate and shaken with dilute hydrochloric acid. The ether layer was washed with sodium carbonate solution, with water, and was dried. The solvent was evaporated, and the product was twice flash distilled to give 18 g. of alcohol (V), $n^{25}D$ 1.5142. A small sample was converted to its *p*-nitrobenzoate (procedure B[3c]), m.p. 46–47°.

Preparation of the *p*-Bromobenzenesulfonates of Racemic *erythro*- and *threo*-2,5-Dimethyl-4-phenyl-3-hexanol (I) (Procedure D).—The usual pyridine-*p*-bromobenzenesulfonyl chloride method gave poor yields, probably because of steric retardation of the reaction rate. Therefore, the following method was applied. To a solution of 10.3 g. of racemic *threo*-I in 150 ml. of dry benzene (distilled from potassium) was added 5.0 g. of potassium metal. The mixture was held at reflux temperature for 8 hours, cooled to 15° and filtered through a plug of glass wool into a solution of 13.0 g. of pure *p*-bromobenzenesulfonyl chloride in 50 ml.

of dry benzene at 15°. The resulting mixture was stirred at 15° for one hour and at room temperature for two additional hours. The benzene was evaporated under reduced pressure at 20°, and the residual oil was shaken with 0.1 N sodium hydroxide for 30 minutes. The oil was then extracted into pure pentane, the pentane layer was dried and passed through a column of 150 g. of basic alumina. The column was washed with additional pentane until no more ester appeared in the eluates. The column eluate was evaporated to about 60 ml., and the pentane solution was cooled to −20° for ten hours. The heavy crystals that separated were collected and recrystallized from pentane to give 13.5 g. of the sulfonate ester. These esters decomposed upon melting, and the decomposition points were completely unreproducible, even on the same sample. Examples are given in Table I.

Reaction of Sodium Ethylate with the _p_-Bromobenzenesulfonates of Racemic _erythro_- and _threo_-2,5-Dimethyl-4-phenyl-3-hexanol (I).—To a solution of sodium ethylate (2.0 g. of sodium and 16 ml. of absolute ethanol) was added 3.4 g. of the _p_-bromobenzenesulfonate of racemic _threo_-I. The resulting solution was heated at 95° for 18 hours, cooled, and shaken with a mixture of cold water and pure pentane.

The organic layer was washed with water, dried and treated with decolorizing carbon. The solvent was evaporated through a short column, and the residual oil was twice flash distilled at 18 mm. to give 1.50 g. of colorless oil, n^{25}D 1.4946.

Anal. Calcd. for $C_{14}H_{20}$: C, 89.29; H, 10.71. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 87.13; H, 10.44.

From the above analysis and the reagent it appears that the oil is about 60% olefin–40% ethyl ether (2,5-dimethyl-4-phenyl-3-ethoxyhexane).

A similar procedure was applied to the reaction of sodium ethylate with the _p_-bromobenzenesulfonate of _erythro_-I. From 4.25 g. of starting ester, 1.90 g. of product was obtained, n^{25}D 1.4993.

Anal. Calcd. for $C_{14}H_{20}$: C, 89.29; H, 10.71. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 87.14; H, 10.49.

This mixture would also appear to be about 60% olefin and 40% ethyl ether.

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Studies in Stereochemistry. XXII. Rearrangement of the 1,1-Diphenyl-2-propyl into the 1,2-Diphenyl-1-propyl System[1]

BY DONALD J. CRAM AND FATHY AHMED ABD ELHAFEZ[2]

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The preparation and resolution of 1,1-diphenyl-2-propanol and its derivatives are reported. Treatment of the optically pure (−)-alcohol with thionyl chloride produced a mixture from which optically pure D-_erythro_-1,2-diphenyl-1-propyl chloride was isolated. Attempts to prepare 1,1-diphenyl-2-propyl chloride from 1,1-diphenyl-2-propyl _p_-bromobenzenesulfonate with lithium chloride in acetone gave 1,1-diphenyl-1-propene. Solvolysis of optically pure 1,1-diphenyl-2-propyl _p_-bromobenzenesulfonate in acetic acid gave a mixture of partially racemic 1,1-diphenyl-2-propyl acetate, and of optically pure _threo_- and _erythro_-1,2-diphenyl-1-propyl acetates. The ratio of _threo_ to _erythro_ isomers was the same as that obtained from a solvolysis of _threo_-1,2-diphenyl-1-propyl _p_-bromobenzenesulfonate under the same conditions, a fact which suggests a common intermediate (a _trans_-phenonium ion) for the two processes. The mechanistic implications of these results are discussed.

This study constitutes a further inquiry into the mechanism of solvolytic reactions involving phenonium ion[3] intermediates,[4] particularly into the question of the relative ease of formation of diastereomerically related bridged ions. The 1,1-diphenyl-2-propyl (I) and 1,2-diphenyl-1-propyl (II) systems are capable of producing the same bridged ions A. Through the use of product analyses an attempt has been made to trace the stereochemical course of the various stages of these reactions.

## Preparation and Reactions of the 1,1-Diphenyl-2-propyl System

The alcohol, 1,1-diphenyl-2-propanol (III), was resolved through the brucine salt of its acid phthal-

(1) This work was sponsored 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) Although the term "ethylenephenonium ion" would be more appropriate, since only this one kind of phenyl bridged ion has been considered so far in this series of papers, the abbreviated expression has been used.

(4) (a) D. J. Cram, THIS JOURNAL, **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._, **75**, 332 (1953); (e) F. A. Abd Elhafez and D. J. Cram, _ibid._, **75**, 339 (1953); (f) D. J. Cram and F. A. Abd Elhafez, _ibid._, **75**, 3189 (1953); (g) S. Winstein, N. Brown, K. C. Schreiber and A. H. Schlesinger, _ibid._, **74**, 1140 (1952); (h) S. Winstein and K. C. Schreiber, _ibid._, **74**, 2165, 2171 (1953); (i) J. D. Roberts and C. M. Regan, _ibid._, **75**, 2069 (1953); (j) J. G. Burr, Jr., and L. S. Ciereszko, _ibid._, **74**, 5426, 5431 (1952); (k) P. S. Bailey and J. G. Burr, Jr., _ibid._, **75**, 2051 (1953).
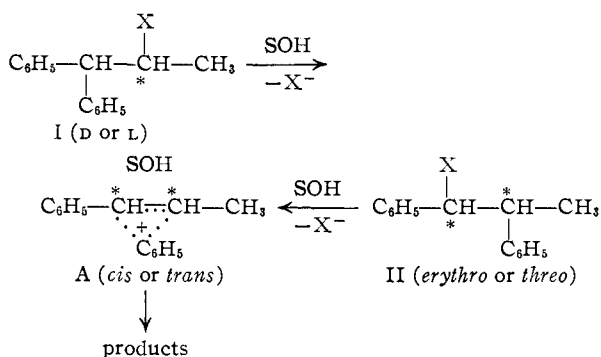
ate to give the (−)-acid phthalate, whereas the (+)-isomer was freed from racemic material by fractional crystallization. That virtual optical purity was reached is indicated by the rotations and melting points of the enantiomeric alcohols, acid phthalates, _p_-nitrobenzoates, acetates and _p_-bromobenzenesulfonates that are reported in Table I. The preparation of the optically pure isomers of 1,2-diphenyl-1-propanol (IV) and its derivatives has been reported previously.[5]

In an attempt to form 1,1-diphenyl-2-propyl chloride, the _p_-bromobenzenesulfonate of III was treated with lithium chloride in acetone as solvent

(5) (a) D. J. Cram and F. A. Abd Elhafez, _ibid._, **74**, 5828 (1952); (b) F. A. Abd Elhafez and D. J. Cram, _ibid._, **74**, 5846 (1952); (c) D. J. Cram and F. A. Abd Elhafez, _ibid._, **74**, 5851 (1952).