Reactions of Methyl-Substituted Cyclopentanones with Lithium Aluminum Hydride and Methyllithium. Structural Determinations and Proton Nuclear Magnetic Resonance Study of the Reaction Products

Min-Hon Rei[1]

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907, and National Science Council, Taipei, Taiwan, 107 ROC

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Four methyl-substituted cyclopentanones were reacted with lithium aluminum hydride in tetrahydrofuran and with methyllithium in ether at 0 °C. In general, secondary trans alcohols were formed preferentially with lithium aluminum hydride, while tertiary cis alcohols were obtained as the major product with methyllithium. In 2,5-dimethyl- and 2,2,5-trimethylcyclopentanones, the original preference of the cis alcohols was reversed when methyllithium was replaced with methylmagnesium iodide. The structures of the reaction products were determined by comparison with an authentic trans alcohol which was prepared from the hydroboration–oxidation of the corresponding olefin. ^{1}H NMR studies of the resultant alcohols are presented. The chemical shift of 1-H or 1-Me decreases as the number of methyl substituents increases; these chemical shifts are smaller in the trans alcohol series than those in the cis alcohols. An enormously large decrease in chemical shift, 1.25 ppm, was observed when 1-H was shielded by two *cis*-methyl groups at C-2 and C-5. The same phenomenon was observed for the 1-Me group. The vicinal coupling constants of 1-H were found to be 4.5 Hz for the cis alcohols and 8.0 Hz for the trans alcohols in the 2,5-dimethyl- and 2,2,5-trimethylcyclopentanol systems.

Enormous amounts of studies have been conducted on the stereochemical and conformational problems in the cyclohexyl[2] and norbornyl[3] systems. In the simple cyclopentyl system, only relatively few studies have been reported. Conformational analysis of cyclopentyl derivatives was reviewed in brief.[4] Solvolyses of secondary methyl-substituted cyclopentyl tosylates were reported.[5,6] Due to the similarity in bond strain in the cyclopentyl and norbornyl derivatives, Brown and co-workers have used the cyclopentyl derivatives as the model compounds for the norbornyl derivatives in the solvolyses reactions.[7] However, the basic informations of these cyclopentanols, such as the stereochemistry[8,9] of their formation from the corresponding ketones and the structural determination of these reaction products, were only studied briefly.[10] To bridge this gap, the stereochemical course of the addition of methyllithium and of lithium aluminum hydride to four methyl-substituted cyclopentanones and the structural determinations of the resultant alcohols are reported in this paper. The stereochemical courses of these reactions are analyzed and explained with an empirical equation and are to be reported later.[11] In that equation, the energy difference responsible for the stereochemical course of the lithium aluminum hydride reduction of a ketone is expressed in terms of steric strain and product stability controls. In the case of the methyllithium addition reaction, only the steric strain control is responsible for the stereochemistry.

Experimental Section

Materials. All the ketones used in this study were specially purchased from Chemical Sample Co. (Columbus, Ohio 43220) by Professor H. C. Brown and made available to the author (Table I). The purity of these ketones was better than 99%, and no further purification was attempted. Ethyl ether and tetrahydrofuran (THF) were reagent grade, dried with calcium hydride, and stored under positive nitrogen pressure before use. An ethereal solution of methyllithium (1.67 M) was obtained from Foote Mineral Co. (Exton, Pa. 19341).

General Procedure for the Addition of Methyllithium (MeLi). In a nitrogen-flushed and flame-dried flask, an ethereal MeLi solution (10 mmol) was cooled to 0 °C in an ice bath and was added to an ethereal solution of ketone (1 M, 10 mmol). After 3 h, the reaction was terminated by the addition of a saturated ammonium chloride solution (1 mL). The organic layer was decanted from the fine inorganic salt, dried over anhydrous magnesium sulfate or potassium bicarbonate, and analyzed directly by GLC[12] without further purification. For product isolation, a larger scale reaction (50 or 100 mmol) was conducted at room temperature and the products were isolated by preparative GLC.

1,2,4,4-Tetramethylcyclopentene. 1,2,4,4-Tetramethylcyclopentanols (79 g, 50 mmol) which were prepared from the reaction of 2,4,4-trimethylcyclopentanone with methylmagnesium iodide (MeMgI) were refluxed with iodine (20 mg) for 2 h. After separation by a preparative GLC, two olefins were obtained in a ratio of 18 to 82 with n^{20}D 1.4285 and 1.4354, respectively. Having a single vinyl proton in its ^{1}H NMR spectrum, the minor component was assigned to 1,3,3,5-tetramethylcyclopentene. The major one was 1,2,4,4-tetramethylcyclopentene according to its ^{1}H NMR spectrum (Table II). Anal. Calcd for C_9H_{16}: C, 87.02; H, 12.98. Found: C, 86.69; H, 12.98. Other olefins prepared by this method were 1,2,3-trimethylcyclopentene and 1,2,3,3-tetramethylcyclopentene. Anal. Calcd for C_8H_{14}: C, 87.19; H, 12.81. Found: C, 87.25; H, 12.77. Anal. Calcd for C_9H_{16}: C, 87.02; H, 12.98. Found: C, 87.02; H, 13.00.

Hydroboration–Oxidation of 1,2,3,3-Tetramethylcyclopentene. The olefin (2 mmol) was hydroborated and oxidized according to a literature method.[13] Two alcohols in a ratio of 16 to 84 were obtained after the reaction products were worked up. By comparing GLC retention times of the two alcohols which were obtained from the reaction of MeLi and the corresponding ketone, the minor alcohol from the hydroboration–oxidation of the olefin was found to be 1,2,2,*trans*-5-tetramethylcyclopentan-*r*-1-ol.[29] Other trans alcohols prepared by this method were *trans*-2-methylcyclopentan-1-ol, *trans,trans*-2,5-dimethylcyclopentan-*r*-1-ol, *cis,trans*-2,5-dimethylcyclopentan-*r*-1-ol, 1,*trans,trans*-2,5-trimethylcyclopentan-*r*-1-ol, 1,*cis,trans*-2,5-trimethylcyclopentan-*r*-1-ol, 2,2,*trans*-5-trimethylcyclopentan-*r*-1-ol, and 1,*trans*-2,4,4-tetramethylcyclopentan-*r*-1-ol (see Table III for ^{1}H NMR data).

2,5-Dimethylcyclopentyl Tosylhydrazone. This compound was prepared according to the method of Acharya and Brown.[14] The commercial 2,5-dimethylcyclopentanone (6 g, 53.5 mmol) in methanol (30 mL) was treated with *p*-toluenesulfonyl hydrazide (9.3 g, 50 mmol) in THF (50 mL) for 14 h at room temperature. The hydrazone crystal (12 g) gave mp 124–125 °C dec after recrystallization (methanol–hexane). Anal. Calcd for $C_{14}H_{20}N_2O_2S$: C, 59.97; H, 7.19; N, 9.99; S, 11.43. Found: C, 59.67; H, 7.19; N, 9.68; S, 11.45.

1,3-Dimethylcyclopentene. The hydrazone (11.43 g, 41 mmol) obtained above was treated with MeLi (82 mmol) in ether (40 mL) for 3 h at room temperature.[15] After hydrolysis, 1,3-dimethylcyclopentene (1.6 g) was obtained. Anal. Calcd for C_7H_{12}: C, 87.42; H, 12.50. Found: C, 87.67; H, 12.70. Also prepared by this method was 1,3,3-trimethylcyclopentene. Anal. Calcd for C_8H_{14}: C, 87.19; H, 12.80. Found: C, 87.25; H, 12.86.

Results and Discussions

Four methyl-substituted cyclopentanones were treated with MeLi[16] in ether and $LiAlH_4$ in THF at 0 °C. In all the reactions studied, the alcohols were produced in yields greater than 80% and were not isomerized, which are in agreement with the results reported in the literature. Dehydration of the

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Table I. ^{1}H NMR Spectroscopic Data of the Methyl-Substituted Cyclopentanones

Methyl-substituted cyclopentanones	Registry no.	n^{20}D	δ, ppm (J, Hz) 2-Me	3- or 4-Me	5-Me
2-Methyl	1120-72-5	1.4354	1.05 (d, 6)		
cis-2,5-Dimethyl	6672-39-5	1.3415	1.05 (d, 6)		
trans-2,5-Dimethyl	32476-60-1		1.10 (d, 6)		
2,2,5-Trimethyl	4573-09-5	1.4288[a]			
		1.4289	0.94, 1.03		1.08 (d, 6.5)
2,2,4-Trimethyl	4694-12-6	1.4300	0.97, 1.02	1.12 (d, 6)	
2,4,4-Trimethyl		1.4320	1.03 (d, 6.5)	1.07, 1.15	
2,2,4,4-Tetramethyl	4694-11-5	1.4305	1.05	1.12	
2,2,5,5-Tetramethyl	4541-35-9	1.4288[b]	1.00		1.00
		1.4278			

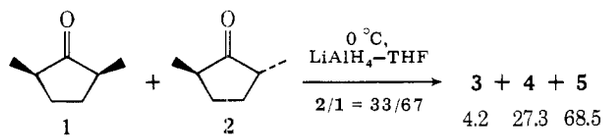
[a] Dr. K. W. Greenlee of Chemical Sample Co. made this value available to the author through Professor H. C. Brown. [b] A. Haller and R. Cornabert, *Bull Soc. Chim. Fr.*, **33**, 1724 (1926).

Table II. ^{1}H NMR Spectroscopic Data of the Methyl-Substituted Cyclopentenes

Methyl-substituted cyclopentene[a]	Registry no.	n^{20}D	1-Me	δ, ppm (J, Hz) 2-H	2-Me	3-H	3-Me	4- or 5-Me
1-Methyl	693-89-0	1.4335	1.72	5.23 ($W_{1/2}$ = 6)				
1,3-Dimethyl	62184-82-1	1.4298	1.67	5.13		2.68	0.95 (d, 6)	
1,2,3-Trimethyl	473-91-6	1.4323[b]	1.57		1.57		0.97 (d, 6)	
1,3,3-Trimethyl	57497-14-0		1.65	5.06			1.00	
1,2,3,3-Tetramethyl	65378-75-8	1.4426	1.57		1.48		0.95	
1,2,4,4-Tetramethyl	65378-76-9	1.4354	1.53		1.53	2.05		1.03
1,3,3,5-Tetramethyl	65378-77-0	1.4285	1.61	4.98			1.03, 0.96	1.00

[a] All the new olefins give satisfactory elemental analyses and are reported in the text. [b] At 25 °C.

Scheme I



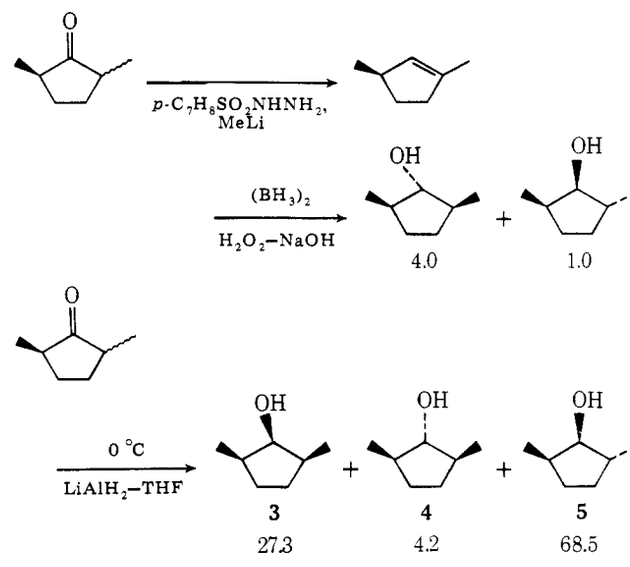
tertiary alcohol during GLC analysis was not observed, as judged from the absence of unknown or olefinic compounds in the chromatogram. The epimeric pair of alcohols was assumed to have equal area response in the GLC analysis.[17]

To determine the structure of these reaction products, an authentic trans alcohol was prepared from the hydroboration–oxidation of the corresponding olefin. In general, the more stable trans alcohols were the preferred reaction products when $LiAlH_4$ was reacted with the ketones. With methyllithium, these cyclopentanones yielded predominantly the cis alcohols with the two methyl groups in a trans relationship.

2-Methylcyclopentyl System. Both secondary[18] and tertiary[19] trans alcohols from 2-methylcyclopentanone have been reported in the literature. Hence structures of the reaction products were determined by comparing their retention times in GLC analysis with the corresponding authentic samples. Using methylmagnesium chloride, Hennion and O'Shea[8] reported 70% of 1,*trans*-2-dimethylcyclopentan-*r*-1-ol from 2-methylcyclopentanone in ether. In our hands, we obtained 67% of the trans alcohol at 0 °C. With methylmagnesium iodide, however, the ketone yielded 52% of the trans alcohol.[16]

2,5-Dimethylcyclopentyl System. The commercial ketones were a mixture of *cis*- and *trans*-dimethylcyclopentanones in a ratio of 33 to 67 according to GLC analysis. Separation of these two ketones by distillation or preparative GLC was unsuccessful. Hence, all the studies in this system were carried out with the isomeric ketone mixture. ^{1}H NMR spectroscopic analysis of the mixture indicated that the two methyl groups of the major component **1** had chemical shift

Scheme II



at a lower field than those of the minor component **2**, 1.10 vs. 1.05 ppm (J = 6 Hz, d). Since the two *cis*-dimethyl groups were expected to be more shielded owing to the bond anisotropy of the C–CH_3 bond,[20] the minor component was believed to be *cis*-2,5-dimethylcyclopentanone. This assignment was further supported by the product distribution of the following reactions. With $LiAlH_4$, the *trans*-dimethyl ketone is expected to yield only one alcohol, **5**, whereas the *cis*-dimethyl ketone would form two isomeric alcohols, **3** and **4**. The ratio of these alcohols, 5/(3 + 4), would correspond to the ratio of the two starting ketones, **1**/**2**, or 67/33 (Scheme I).

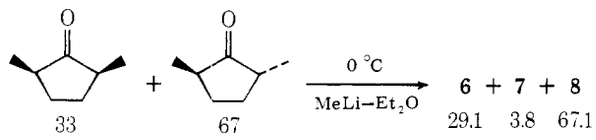
In the actual experiments, three alcohols, **3**–**5**, were obtained from the two starting ketones in 4.2, 27.3, and 68.5% yields, respectively (Scheme I). Unreacted ketones recovered from the reaction showed the same ratio as that of the two starting ketones, **1**/**2** = 67/33, indicating no isomerization.

Table III. Physical Properties and ^{1}H NMR Data of Methyl-Substituted Cyclopentanols

Substituted cyclopentanol	Registry no.	δ, ppm (J, Hz) 1-H	1-Me	2-Me	4-Me	5-Me	n^{20}D	Mp of OPNB, °C[d]
1-H	96-41-3	4.20, 4.18[e]						
cis-2-Methyl	25144-05-2	3.99 (m, $W_{1/2}$ = 4)		0.97 (d, 7)				
trans-2-Methyl	25144-04-1	3.63 (m, $W_{1/2}$ = 9)		0.93 (d, 7)				
cis,cis-2,5-Dimethyl[a]	65404-79-7	3.65 (t, 4.5)		1.00 (d, 7)		1.00 (d, 7)		
cis,trans-2,5-Dimethyl[a]	65378-78-1	3.53 (t, 5.0)		0.95 (d, 7)		0.98 (d, 7)		
trans,trans-2,5-Dimethyl[a]	63057-29-4	2.97 (t, 8.0)		0.92 (d, 7)		0.92 (d, 7)		
2,2,*cis*-5-Trimethyl[b]	65378-79-2	3.34 (d, 4.5)		0.97, 1.00		0.96 (d, 7)		
12,2,*trans*-5-Trimethyl[b]	65378-80-5	3.03 (d, 8.0)		0.97, 1.00		0.90 (d, 7)		
cis-2,4,4-Trimethyl[c]	57905-84-7	4.02[f]		0.95 (d, 7)	0.97, 1.11			
trans-2,4,4-Trimethyl[c]	57905-83-6	3.60[g]		1.02 (d, 7)	1.00, 1.07			
1-Methyl	1462-03-9		1.30					82–83
1,*cis*-2-Dimethyl	16467-13-3		1.21	0.91 (d, 6)			1.4505 1.4506[h]	99.5–100.5
1,*trans*-2-Dimethyl	16467-04-2		1.10	0.86 (d, 6)			1.4538 1.4541[h]	116.5–117
1,*cis,cis*-2,5-Trimethyl	65378-81-6		1.06	0.87 (d, 6)		0.92 (d, 6)	1.4463	113–114
1,*cis,trans*-2,5-Trimethyl	65378-82-7		1.06	0.87 (d, 6)		0.90 (d, 6)	1.4543	104–105
1,*trans,trans*-2,5-Trimethyl	65378-83-8		0.80	0.89 (d, 6)		0.89 (d, 6)	1.4557	116–117
1,2,2,*cis*-5-Tetramethyl	65378-84-9		0.99	0.86, 0.99		0.91 (d, 6)	1.4511	121.5–123.5
1,2,2,*trans*-5-Tetramethyl	65378-85-0		0.87	0.93, 0.93		0.92 (d, 6)	1.4603	108–109
1,*cis*-2,4,4-Tetramethyl	58493-56-4		1.20	0.93 (d, 6)	0.98, 1.11		1.4370	106–107
1,*trans*-2,4,4-Tetramethyl	58493-55-3		1.09	0.92 (d, 6)	1.00, 1.09		1.4453	109–110

[a] Calculated from the cis and trans alcohol mixture. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.67; H, 12.28. [b] Calculated from the cis and trans alcohol mixture. Anal. Calcd for $C_8H_{16}O$: C, 74.13; H, 12.99. Found: C, 73.95; H, 12.92. [c] Calculated from the cis and trans alcohol mixture. Anal. Calcd for $C_8H_{16}O$: C, 74.13; H, 12.99. Found: C, 73.99; H, 13.02. [d] For solvolysis purpose, *p*-nitrobenzoates (OPNB) of all these tertiary alcohols were prepared, and their elemental analyses were found to be satisfactory according to Professor H. C. Brown and Dr. F. J. Chloupek of Purdue University, 1963. [e] H. Booth and J. H. Little, unpublished observation quoted by H. Booth in ref 19. [f] Appears as a quartet with spacing of 4.5 Hz. [g] Appears as a quartet with spacing of 8.0 Hz. [h] Reference 8.

Scheme III



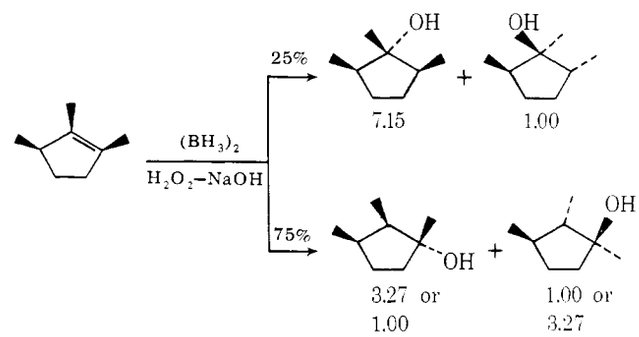
Hence, appropriate grouping of the observed products' distribution should yield a ratio of about 67/33. The only way to group the experimental result is to have **3** and **4** from the same starting ketone and **5** from the other, **5**/(**3** + **4**) = 68.5/31.5. Consequently, one can readily conclude that **5** was from the ketone **1** and had two methyl groups in a trans relationship. The alcohols **3** and **4** are from the ketone **2** and these two compounds had the two methyl groups in a cis relationship.

Having identified compound **5** as *cis,trans*-2,5-dimethylcyclopentan-*r*-1-ol, compound **4** was identified as *trans,trans*-2,5-dimethylcyclopentan-*r*-1-ol by the use of hydroboration–oxidation of 1,3-dimethylcyclopentene which gave both **4** and **5** (Scheme II). Hence compound **3** was *cis,cis*-2,5-dimethylcyclopentan-*r*-1-ol.

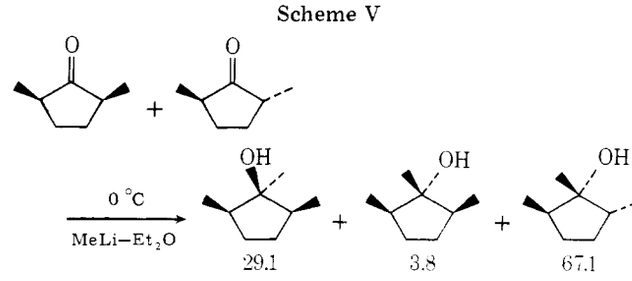
Addition of methyllithium to the *cis*- and *trans*-2,5-dimethylcyclopentanone mixture yielded three alcohols, **6–8**, in a ratio of 29.1, 3.8, and 67.1%, respectively (Scheme III).

As explained earlier, 67% of the starting ketones was 2,5-*trans*-dimethylcyclopentanone; alcohol **8** was readily concluded to be 1,*cis,trans*-2,5-trimethylcyclopentan-*r*-1-ol. From the hydroboration–oxidation raction of 1,2,3-trimethylcyclopentene, four compounds were obtained (Scheme IV). Two of them in a ratio of 7.15 to 1.0 had the same retention times as those of **7** and **8**, respectively. The other two in a ratio of 3.27 to 1.0 were not identified. Consequently, alcohol **7** was identified as 1,*trans,trans*-2,5-trimethylcyclopentan-*r*-1-ol

Scheme IV



Scheme V

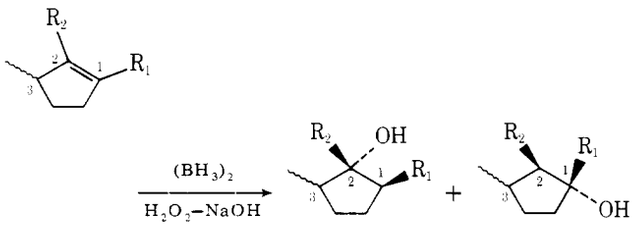


and compound **6** as 1,*cis,cis*-2,5-trimethylcyclopentan-*r*-1-ol.

Thus, the structures of the three alcohols from the reaction of methyllithium and 2,5-dimethylcyclopentanone become clear and are summarized in Scheme V.

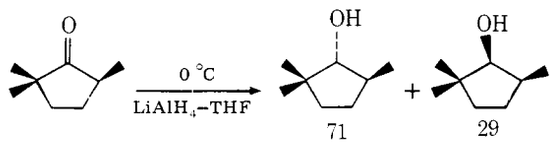
As shown in Scheme VI, as the number of methyl substituents increases, both configurational (trans/cis) and positional

Scheme VI

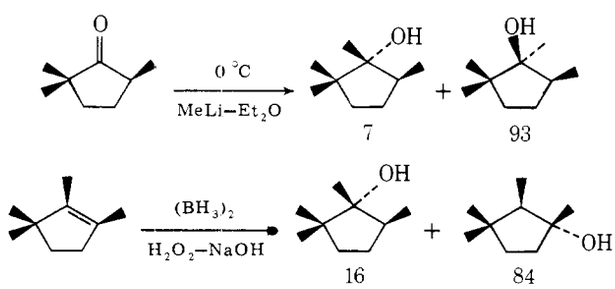


	C-2 trans/cis	C-1 trans/cis	C-1/C-2
$R_1 = R_2 = H$	2.24	1.26	1.1
$R_1 = CH_3$; $R_2 = H$	4.00		0
$R_1 = R_2 = CH_3$	7.15	3.27 or 1/3.27	3.0

Scheme VII



Scheme VIII



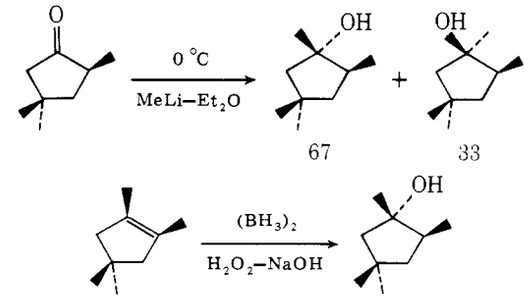
(C-1/C-2) selectivity increase in the hydroboration–oxidation of 3-methylcyclopentene[21] derivatives. Apparently, the methyl substituent in the olefinic bond makes the 3-methyl group exert greater influence on the steric selectivity of the reaction.

Grignard reactions of the 2,5-dimethylcyclopentanones are interesting yet puzzling;[16] the observed results are not understood at the present time. While MeMgCl reacted with the ketones to give a comparable result—**6** (27%), **7** (6%), and **8** (67%) to methyllithium—MeMgI, however, resulted in a different result—**6** (7%), **7** (26%), and **8** (67%). The *cis*-dimethyl ketone forms **7** as the major product with MeLi and MeMgCl, whereas with MeMgI, **6** is the preferred one.

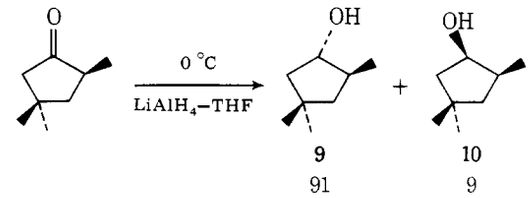
2,2,5-Trimethylcyclopentyl System. $LiAlH_4$ reduction of 2,2,5-trimethylcyclopentanone yielded two alcohols in a 71 to 29 ratio (Scheme VII). The major reaction product was found to be 2,2,*trans*-5-trimethylcyclopentan-*r*-1-ol, after comparing its retention time in the GLC analysis with that of an authentic trans alcohol. The trans alcohol was prepared by the hydroboration–oxidation of 1,3,3-trimethylcyclopentene. The olefin was prepared by the elimination of the tosylhydrazone of the starting ketone.

Addition of methyllithium to the ketone yielded merely 7% of 1,2,2,*trans*-5-tetramethylcyclopentan-*r*-1-ol, in addition to 93% of the cis alcohol (Scheme VIII). The trans alcohol was the minor one of the two reaction products of the hydroboration–oxidation reaction of 1,2,3,3-tetramethylcyclopentene. The olefin was obtained from pyrolytic dehydration of 1,2,2,5-tetramethylcyclopentanols. As in the preceding system, methylmagnesium iodide reacted with the ketone to form 1,2,2,*trans*-5-tetramethylcyclopentan-*r*-1-ol preferentially (72%). Again we do not fully understand the cause of this reversal in the stereochemistry of the reactions when methyllithium is replaced with MeMgI.[16]

Scheme IX



Scheme X



2,4,4-Trimethylcyclopentyl System. At first glance this system could be treated as a 2-methylcyclopentyl system; however, this was found to be oversimplified. The 2,4,4-trimethylcyclopentyl system was found to be the most complex of the four systems studied.

Addition of methyllithium to the ketone gave trans alcohol as the major component (Scheme IX). The trans alcohol was identified by comparison with an authentic sample of 1,*trans*-2,4,4-tetramethylcyclopentan-*r*-1-ol, which was obtained from the hydroboration–oxidation of 1,2,4,4-tetramethylcyclopentene.

The fact that a trans alcohol was the major reaction product of methyllithium with 2,4,4-trimethylcyclopentanone deserves further comment. With this ketone, methylmagnesium iodide also yielded trans alcohol as the major product (78%). Unlike the preceding three systems in which the stereochemistry of the reaction was controlled by the methyl group at the neighboring β position, the stereochemistry of the reaction in the present system is apparently governed by one of the methyl groups at C-4. Conceivably, the methyl group which is trans to the methyl group at C-2 is forced to take a quasi-axial conformation in order to minimize 1,3 interaction between the two *cis*-methyl groups at C-2 and C-4. One sees a similarity in 3,3,5-trimethylcyclohexanone in which the axial methyl group at C-3, but not the sole methyl group at C-5, plays the key role in the determination of conformational energy[2] and the stereochemistry of the reaction.[22]

Lithium aluminum hydride reduction of 2,4,4-trimethylcyclopentanone was highly selective; 91% of *trans*-2,4,4-trimethylcyclopentanol (**9**) was obtained in this reaction (Scheme X). The high stereoselectivity could be attributed to the confluence of both steric strain control and product stability control.[11]

Structural proofs of the reaction products by the methods used in the preceding three systems were unsuccessful. All attempts to prepare and isolate 1,4,4-trimethylcyclopentene by the elimination of 2,4,4-trimethylcyclopentyl tosylates (1) with sodium methoxide in methanol or Me_2SO, (2) with potassium *tert*-butoxide in *tert*-butyl alcohol or Me_2SO, or (3) by refluxing the alcohols with potassium bisulfate resulted in the formation of two olefins; they were assigned as 1,4,4- and 3,3,5-trimethylcyclopentenes in a ratio of 45 to 55, respectively, according to ^1H NMR and GLC analyses. Separation of the two olefins by preparative GLC, unfortunately, was unsuccessful. Due to the expected steric effect of the methyl

group at C-2, elimination of 2,4,4-trimethylcyclopentyl tosylhydrazone was not tried.

cis- and *trans*-2,4,4-trimethylcyclopentan-*r*-1-ols were separated and collected by analytical GLC. Structural determination of these two alcohols was finally accomplished by comparing the chemical shift of 1-H with those of the alcohols mentioned earlier and the europium shift parameter S[23] (or equimolar paramagnetic shift value) of 2-H and 2-Me (Table IV). In Table III, ^{1}H NMR data of all these alcohols are compiled.

As shown in Table III the chemical shifts of 1-H in the secondary alcohols bear a sensitive relationship to the change in the surrounding environment much more so than those of the 2-methyl group. The chemical shifts of 1-H of the cis alcohols are invariably more deshielded by 0.3–0.4 ppm. This could be attributed to the diamagnetic shift of the neighboring 2-methyl group.[20]

The chemical shift of 1-H in compound **9** is 3.60 ppm, whereas that in compound **10** is 4.02 ppm. This agrees well with the general pattern of the cyclopentyl system described below. Chemical shifts of 2-H's of this system merge with other ring protons and were not determined. However, addition of europium shift reagent (Table IV) reveals that the S value of 2-H in compound **9**, 16 ppm, is larger than that in compound **10**, 12.5 ppm. This points out that 2-H in compound **9** is cis to the OH group and that in compound **10** is trans to the OH group.

The 2-methyl group in compound **9**, although less shielded than **10**, 1.02 vs. 0.95 ppm, is expected to be less sensitive to the addition of shift reagent; the S value of the 2-methyl group in compound **9** is 9.6 ppm, whereas that in compound **10** is 15.5 ppm. The S value of 2-H is larger than that of 2-Me in the compound **9**, whereas in compound **10** 2-Me has a larger S value than has 2-H. This means that in compound **9** 2-H is nearer to the OH group than is 2-Me, whereas in compound **10** 2-Me is closer than is 2-H to the hydroxyl group. All these evidences indicate that 2-Me in compound **9** is trans to the OH group and that compound **10** has a cis relationship between the OH group and 2-Me group.

^{1}H NMR Spectroscopy of Methyl-Substituted Cyclopentanols. From Table III one sees a gradual decrease of the chemical shift of 1-H or that of the 1-Me group as the number of methyl substituents at C-2 or C-5 increases, irrespective of its stereochemistry. The larger decrease in the chemical shift of 1-H or 1-Me in the trans alcohol series is caused apparently by the combined effects of the electron-releasing effect of methyl substituents and of the diamagnetic effect of the C–CH_3 bond.

As one would expect, the chemical shifts of 1-H of the secondary trans alcohols are smaller than those of the cis alcohols due to the diamagnetic effect of the neighboring methyl group in the trans series. The differences in the chemical shift between cis and trans alcohols are in the order of 0.3 ppm. Likewise, upfield shifts are also observed for the 1-Me group of the tertiary trans alcohol. However, the differences in the chemical shift of the cis and trans tertiary alcohols are below 0.1 ppm.

In those cases where there are two methyl substituents, one at C-2 and one at C-5, the chemical shift of 1-H is reduced by 0.55 ppm in the *cis,cis*-dimethyl alcohol and 1.23 ppm in the *trans,trans*-dimethyl alcohol, compared to that of the parent unsubstituted cyclopentanol. Such an enormous upfield shift by the double shielding of the neighboring *cis*-dimethyl groups in the *trans,trans*-alcohol is larger than that observed in the cyclohexyl system.[24,25]

In the tertiary system, the double shielding of the 1-Me group by the neighboring *cis*-dimethyl groups causes a 0.5-ppm upfield shift, compared to that of the parent 1-methylcyclopentanol.

Table IV. Paramagnetic Shift (S) of Compounds 9 and 10

Compd	S, ppm 2-H	2-CH_3	4-CH_3
9	16.0	9.6	6.0, 3.8
10	12.5	15.5	7.1, 5.1

The chemical shift of the 2-methyl group is less sensitive to the stereochemistry of the neighboring hydroxyl group at C-1. In general, the chemical shift of the 2-methyl group in the cis alcohol is only about 0.05 ppm less shielded than that of the trans alcohol. The smaller difference in the chemical shift between cis and trans alcohols is, however, unexpected. In the 2,4,4-trimethyl- and 1,2,4,4-tetramethylcyclopentyl systems, the difference in the chemical shift of the 2-methyl group between the cis and trans alcohols is reversed in the former or negligible in the latter. This abnormality could be attributed to a conformational change.

Coupling constants of vicinal protons in the cyclohexyl system have been well studied and successfully applied to evaluate ring torsional angles[26] and conformation.[20] In the cyclopentanol system, a systematic evaluation of the coupling constant remains highly desirable. Furthermore, "... there is hardly an example, involving a simple saturated five-membered ring, in which the shape of the molecule can be said to have been proved satisfactorily by the use of NMR spectra".[20] So often, assignments of J_{trans} and J_{cis} are done in order to make the corresponding dihedral angles (calculated according to the Karplus equation) agreeable with a model of the relatively flattened ring conformation.[27,28]

In this study, structural determinations of the cyclopentanol derivatives were made by an independent approach with one exception being the 2,4,4-cyclopentanols, which were characterized by the use of ^{1}H NMR spectroscopy. Therefore, assignments of J_{cis} and J_{trans} are based on proven structures without the use of ^{1}H NMR data.

In *cis,cis*-2,5-dimethyl- and *trans,trans*-2,5-dimethylcyclopentan-*r*-1-ols, the 1-H couples to two symmetrical protons at C-2 and C-5 with coupling constants of 4.5 and 8.0 Hz, respectively. In 2,2,*cis*- and *trans*-5-trimethylcyclopentan-*r*-1-ols, J_{cis} and J_{trans} are again 4.5 and 8.0 Hz, respectively.

In the cases where 1,3 interaction is not severe, one would expect a gradual flattening of the ring and decrease of J_{cis} and J_{trans}. In *cis,trans*-2,5-dimethylcyclopentan-*r*-1-ol, only one coupling constant of 5 Hz was obtained at room temperature. In the less crowded 2-methylcyclopentanol system, the rings are expected to flatten further. In this system the 1-H appeared as a multiple signal and the coupling constants could not be evaluated. The observed $W_{1/2}$ (4 Hz) indicates a smaller J_{cis}.

In the 2,4,4-trimethylcyclopentanol system, the 1-proton couples to three different protons at C-2 and C-5, and an AMXX′ spectrum would be expected. In reality, the spectra in both the cis and trans alcohols appear as quartets with spacing of 4.5 and 7.5 Hz, respectively. Furthermore, in this system, there are two types of 1,3 interaction, 4-Me with 2-Me and 4-Me with 1-OH. Hence, the molecule in the cis or trans alcohol is expected to be more mobile than in the 2,5-dimethyl- or 2,2,5-trimethylcyclopentanol systems. The observed quartet spectra may be brought about by the averaging of dihedral angles. Detailed study of this system has been undertaken and will be published later.

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Registry No.—2,5-Dimethylcyclopentyl tosylhydrazone, 65378-86-1; 2,2,5-trimethylcyclopentyl tosylhydrazone, 65378-87-2; lithium aluminum hydride, 16853-85-3; methyllithium, 917-54-4.

References and Notes

(1) Address correspondence to the National Science Council.
(2) (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and C. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1965; (b) M. Hanack, "Conformation Theory", Academic Press, New York, N.Y., 1965, p 75 ff; (c) see A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron*, **18**, 705 (1962), for an excellent review of the stereochemistry of nucleophilic addition to cyclic ketones; (d) E. L. Eliel and Y. Senda, *ibid.*, **26**, 2411 (1970); (e) E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, **75**, 521 (1975).
(3) J. A. Berson in "Molecular Rearrangements", P. de Mayo, Ed., Interscience, New York, N.Y., 1963, Chapter 3.
(4) (a) C. G. Le Fivre and R. J. W. Le Fivre, *J. Chem. Soc.*, 3549 (1956); (b) K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959); (c) R. J. Abraham and K. A. McLauchlau, *Mol. Phys.*, **5**, 513 (1962); (d) C. Altona, H. R. Buys, H. J. Hageman, and E. Havinga, *Tetrahedron*, **23**, 2265 (1967).
(5) W. Hückel and E. Mogle, *Justus Liebigs Ann. Chem.*, **649**, 13 (1961).
(6) A. P. Krapcho and D. E. Horn, *Tetrahedron Lett.*, 6107 (1966).
(7) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 1247 (1964).
(8) G. F. Hennion and F. X. O'Shea, *J. Am. Chem. Soc.*, **80**, 614 (1958).
(9) H. C. Brown and H. Deck, *J. Am. Chem. Soc.*, **87**, 5620 (1965).
(10) B. Fuchs and R. G. Haber, *Tetrahedron Lett.*, 1323 (1966).
(11) M.-H. Rei, unpublished results.
(12) In general, a Varian 1200 equipped with a flame ionization detector was used. Quadral (5%) or DEGS (5%) on a Chromosorb W (80–100 mesh) packed column (12 ft × ⅛ in.) was programmed 10°/min from room temperature to 120 °C.
(13) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 4106 (1959).
(14) S. P. Acharya and H. C. Brown, *J. Am. Chem. Soc.*, **89**, 1925 (1967).
(15) R. H. Shapiro and M. J. Heath, *J. Am. Chem. Soc.*, **89**, 5734 (1967).
(16) M.-H. Rei, Ph.D. Thesis, Purdue University, West Lafayette, Ind. More reactions including the uses of three Grignard reagents and other methyl-substituted cyclopentanones were reported herein.
(17) E. L. Eliel, S. H. Shroeter, T. J. Brett, F. J. Biros, and J. C. Richer, *J. Am. Chem. Soc.*, **88**, 3327 (1966).
(18) H. C. Brown and V. J. Varma, *J. Am. Chem. Soc.*, **88**, 2871 (1966).
(19) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2544 (1961).
(20) H. Booth, *Prog. Nucl. Magn. Reson. Spectrosc.*, **5**, 144, 214 (1970).
(21) W. J. Hammer, Ph.D. Thesis, Purdue University, West Lafayette, Ind., 1967.
(22) (a) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965). (b) S. R. Landor, P. W. O'Connor, A. R. Tatchell, and I. Blair, *J. Chem. Soc., Perkin Trans. 1*, 473 (1973).
(23) A. F. Cockerill and D. M. Rackham, *Tetrahedron Lett.*, 5149 (1970).
(24) N. Mueller and W. C. Tosch, *J. Chem. Phys.*, **37**, 1167 (1962).
(25) H. Haubenstook and E. L. Eliel, *J. Am. Chem. Soc.*, **84**, 2363 (1962).
(26) J. B. Lambert, *Acc. Chem. Res.*, **4**, 87 (1971).
(27) (a) J. B. Lambert, J. J. Papay, S. A. Khan, K. A. Kappauf, and E. S. Magyar, *J. Am. Chem. Soc.*, **96**, 6112 (1974); (b) R. Steyn and H. Z. Sable, *Tetrahedron*, **25**, 3579 (1969); (c) H. J. Jakobsen, *Tetrahedron Lett.*, 1991 (1967).
(28) (a) R. L. Lipnick, *J. Am. Chem. Soc.*, **96**, 2941 (1974); (b) *J. Mol. Struct.*, **21**, 411, 423 (1974).
(29) The nomenclature of the stereochemistry of these alcohols follows the 1974 IUPAC Commission. The hydroxyl group of the alcohol is used as the reference and is indicated by *r* before its locant. The steric relationship of the methyl substituent to the hydroxyl group is affixed by a cis or trans, followed by the locant of the methyl group. For the ketone, the carbonyl group is used as the starting point of the numering system, and the plane of the ring is the reference of the stereochemistry. Affixes cis or trans are used to indicate the stereochemistry of the methyl substituent in the ring.

New Mass Spectrometric Rearrangements Involving Silicon. A Study of Trimethylsilylated Di- and Polyamines and Their Isotopically Labeled Analogues

Ronald G. Smith and G. Doyle Daves, Jr.*

Department of Chemistry and Biochemical Sciences, Oregon Graduate Center, Beaverton, Oregon 97005

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The electron-impact spectra of six trimethylsilylated di- and polyamines and 12 deuterium labeled analogues have been examined. Structures of several ions in the spectra of the unlabeled compounds, unexplained by simple fragmentations, have been assigned consistent with the observed changes in *m/e* values of the corresponding labeled ions. The composition of these ions suggests molecular decomposition processes not previously reported for trimethylsilylated compounds. These include a McLafferty rearrangement involving hydrogen migration to an even-electron siliconium center and a 1,5-alkyl migration of a methyl group initially bonded to silicon. The primary impetus for these rearrangements is the high reactivity of the silicon center; however, in addition, the proximities of the various amine centers affect the fragmentation processes.

Trimethylsilyl (TMS) groups are widely utilized for protection of polar functions during synthetic and chromatographic (including coupled gas chromatography–mass spectrometry) procedures, and the mass spectra of a large number of trimethylsilylated compounds have been recorded. In many instances, primarily involving *O*-trimethylsilyl compounds, electron-impact induced rearrangements have been described which involve interaction between a TMS group and a second functional group.[1] Such interactions between functional groups are also observed in mass spectra of alkanes possessing multiple polar substituents,[2] e.g., the di- and polyamines[3] and their N-substituted derivatives.[4]

In view of our interest in the analysis of physiological polyamines using GC–MS techniques[5] and the impressive detection sensitivity reported for trimethylsilyldiamines,[6] we have investigated extensively the electron-impact mass spectrometry of TMS derivatives of selected di- and polyamines. Mass spectrometric data for the compounds studied (1–18, Chart I), which include a variety of specifically deuterated analogues, are recorded in Tables I–VI.

The novel rearrangements described in this study are excellent examples of the versatility of silicon-containing compounds upon activation by electron impact and provide some interesting insights into the *N*-trimethylsilyl group.[7] The migration of a TMS methyl group to a γ-methylene carbon represents one of a limited number of authenticated 1,5-alkyl rearrangements.[9–11] Another decomposition process is a McLafferty rearrangement, different in that a hydrogen migrates to a dimethylsiliconium center.

Results and Discussion

Isotopic Analyses. The per cent deuterium incorporation into the di- (**7** and **10**) and polyamines (**13**, **16**, and **17**) was determined from the intensities of ions in the $[M - CF_3\cdot]^+$ ion

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