

## Meerwein-Ponndorf-Verley Reduction of Mono- and Bicyclic Ketones. Rate of Reaction<sup>1a,b</sup>

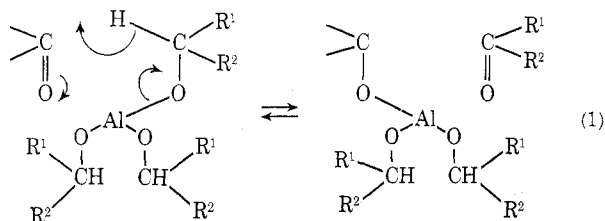
V. HACH

Department of Chemistry, University of British Columbia, Vancouver 8, British Columbia Canada

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The Meerwein-Ponndorf-Verley (MPV) reduction rates of eight representative mono- and bicyclic ketones 1-8 were established at  $82.3 \pm 0.4^\circ$  under nonequilibrating conditions resembling preparative utilization of this reaction. Results obtained enabled, for the first time, a systematic comparison of substituent effects and stereochemistry in the vicinity of the CO group. The following reaction half-lives ( $t_{1/2}$ , min) for the pseudo-first-order disappearance of 0.213 M ketone in *i*-PrOH containing 0.252 M  $\text{Al}(\text{O-}i\text{-Pr})_3$  were observed: 3-isothujone (7), 20.7; isomenthone (5), 21.9; menthone (4), 24.4; 3-thujone (8), 47.7; and camphor (6), 145.8. Reduction of cyclohexanone (2) and 2-methylcyclohexanone (3) was immeasurably rapid. Thus, in contrast to commonly held views, the MPV reduction of these ketones proceeds at a relatively high rate. The reduction of cyclopentanone (1) led to extensive by-product formation. Reduction of ketones 7 and 8 was studied in more detail at various ketone (0.483 and 0.0971 M) and  $\text{Al}(\text{O-}i\text{-Pr})_3$  (0.407, 0.147, and 0.0818 M) concentrations. It was found that the ratio of epimeric alcohols formed in the MPV reduction of ketones 7 and 8 was dependent on the concentration of ketone and  $\text{Al}(\text{O-}i\text{-Pr})_3$ , their ratio being constant. In dilute solution the preponderance of *cis* alcohol was more pronounced than at higher concentration. The reduction rate of thujone 8 was also measured at  $100 \pm 0.5^\circ$  in *sec*-BuOH with  $\text{Al}(\text{O-}sec\text{-Bu})_3$  as catalyst. The reduction was more stereospecific than with  $\text{Al}(\text{O-}i\text{-Pr})_3$  under comparable conditions. Various aspects of these findings are briefly discussed.

The Meerwein-Ponndorf-Verley (MPV) reduction<sup>2</sup> of ketones and aldehydes, formally described<sup>3</sup> by eq 1,

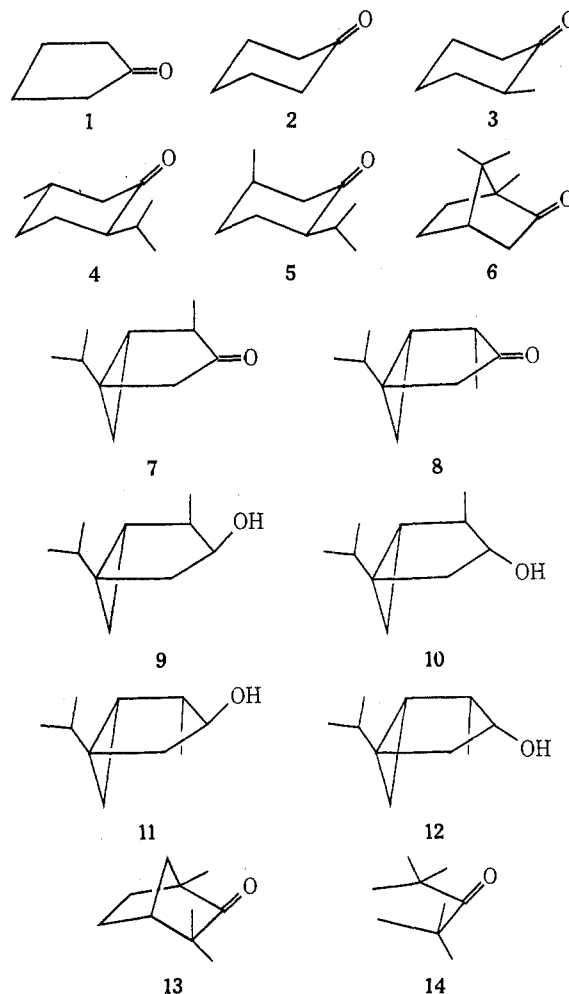


was introduced almost 50 years ago. Although in recent years its importance has declined due to the introduction of complex hydrides, there appear to be several instances where its application is preferable. Generally, *i*-PrOH and  $\text{Al}(\text{O-}i\text{-Pr})_3$  ( $\text{R}^1 = \text{R}^2 = \text{CH}_3$ ) serve as reducing agent and catalyst, respectively. Other secondary alcohols ( $\text{R}^1, \text{R}^2 = \text{alkyl}$ ) may be applied as well.

Two important aspects of this reaction remain obscure: first, its detailed mechanism including the rate-determining step and overall reaction order and, second, the relationship between the steric environment of the CO group and rate of reduction. Considerable efforts have been expended to elucidate the reaction mechanism.<sup>4</sup> In contrast, very little work has been done in regard to the second point.<sup>4g</sup>

In this study we addressed ourselves to the latter problem. We measured MPV reduction rates of eight

mono- and bicyclic ketones 1-8, which represent examples of stereochemical conditions in the vicinity of the CO group with regard to steric hindrance and strain. Bearing in mind the synthetic potential of the MPV reduction we aimed at developing experimental conditions resembling its preparative utilization characterized by continuous removal of acetone formed according to eq 1, a prerequisite for reaction completion. In previous kinetic work<sup>4a,c-e,g</sup> acetone or any other ketone



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(2) (a) H. Meerwein and R. Schmidt, *Justus Liebigs Ann. Chem.*, **444**, 221 (1925); (b) W. Ponndorf, *Angew. Chem.*, **39**, 138 (1926); (c) M. Verley, *Bull. Soc. Chim. Fr.*, **37**, 537, 871 (1925); (d) A. L. Wilds, *Org. React.*, **2**, 178 (1944).

(3) (a) E. D. Williams, K. A. Krieger, and A. R. Day, *J. Amer. Chem. Soc.*, **75**, 2404 (1953), and references therein; (b) W. von E. Doering and T. C. Aschner, *ibid.*, **75**, 393 (1953).

(4) (a) L. M. Jackman and A. K. Macbeth, *J. Chem. Soc.*, 3252 (1952); (b) D. E. Pickart and C. K. Hancock, *J. Amer. Chem. Soc.*, **77**, 4642 (1955); (c) W. N. Moulton, R. E. VanAtta, and R. R. Ruch, *J. Org. Chem.*, **26**, 290 (1961); (d) M. S. Bains and D. C. Bradley, *Chem. Ind. (London)*, 1032 (1961); (e) V. J. Shiner, Jr., and D. Whittaker, *J. Amer. Chem. Soc.*, **85**, 2337 (1963); (f) V. J. Shiner, Jr., D. Whittaker, and V. P. Fernandez, *ibid.*, **85**, 2318 (1963); (g) B. J. Yager and C. K. Hancock, *J. Org. Chem.*, **30**, 1174 (1965); (h) V. J. Shiner, Jr., and D. Whittaker, *J. Amer. Chem. Soc.*, **91**, 394 (1969); (i) L. Otvos, L. Gruber, and J. Meisel-Agoston, *Acta Chim. (Budapest)*, **43**, 149 (1965); *Chem. Abstr.*, **63**, 6803 (1965).

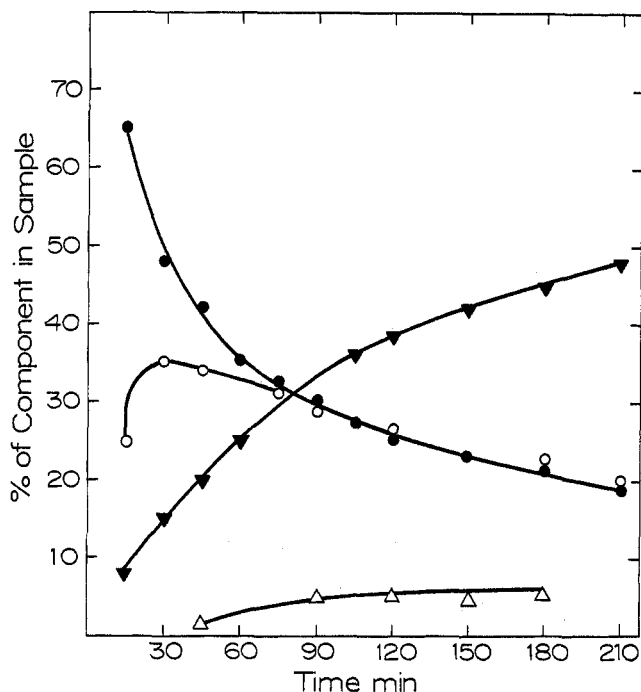


Figure 1.—MPV reduction of (+)-3-thujone (0.483 *M*) by  $\text{Al}(\text{O-}i\text{-Pr})_3$  (0.407 *M*) in *i*-PrOH under equilibrating conditions without acetone removal. Relationship between percentages of epimeric alcohols formed and reaction time: ●, (+)-3-thujone (8); ○, (+)-3-neothujanol (12); ▲, (+)-3-thujanol (11); △, (-)-3-neoisothujanol (9).

formed from the corresponding alcohol-alkoxide reducing system was not removed from the reaction mixture. Such measurements established only the difference between the forward and reverse reactions. We thought that separation of the equilibrating influence of the reverse reaction was an important condition for drawing relevant conclusions about structure-reactivity relationships. In addition, determination of the ratio of epimeric alcohols formed in the reduction was expected to yield information about stereochemistry of product formation and kinetic product control. Consequently, the choice of methods available for kinetic measurement and of applicable analytical methods became rather limited.<sup>5</sup> We chose to work up samples withdrawn from kinetic runs resembling preparative reaction conditions and analyze them by glpc. The percentages of starting ketone, epimerized ketone where applicable, both epimeric alcohols and by-products formed in the reaction mixture were easily determined. This would hardly be possible by polarographic, spectroscopic, and polarimetric methods applied previously.<sup>4a,c,e,g,h</sup>

## Results and Discussion

**Rate of Reduction.**—In preliminary experiments with the two isomeric thujones 7 and 8 carried out under reflux without removal of acetone considerable equilibration of the epimeric alcohols formed took place. The kinetically controlled formation of the less stable *cis* alcohols 9 and 12, respectively, prevailed only in the earlier phase of the reaction as exemplified by Figure 1 for the reduction of 3-thujone (8). Pseudo-first-order plots of ketone disappearance obtained

(5) Problems involved in the determination of MPV reduction rates were succinctly summarized by Jackman, *et al.*,<sup>4a</sup> and others.<sup>4b</sup>

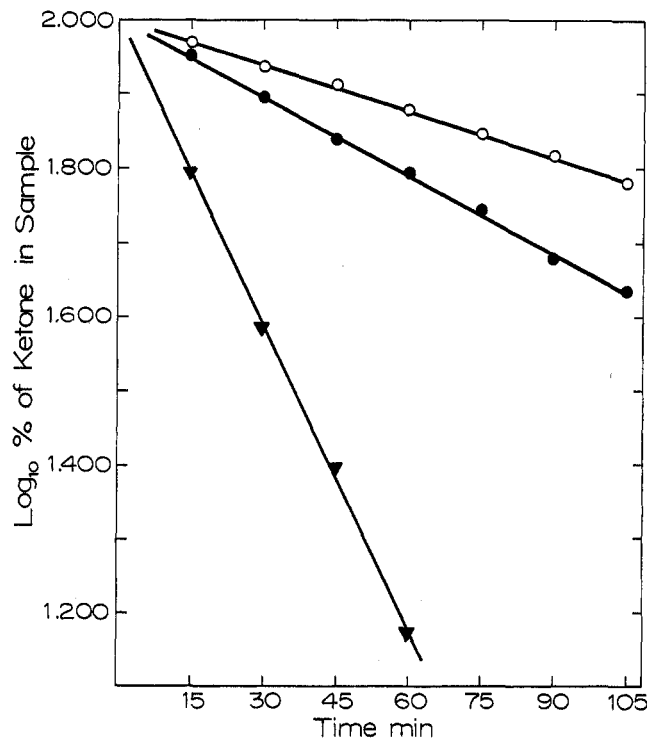


Figure 2.—MPV reduction of isomenthone, camphor, and (+)-3-thujone at  $82.3 \pm 0.4^\circ$  with  $\text{Al}(\text{O-}i\text{-Pr})_3$  in *i*-PrOH. Representative pseudo-first-order plots of ketone disappearance: ○, camphor 0.252 *M*,  $\text{Al}(\text{O-}i\text{-Pr})_3$  0.213 *M*; ▲, isomenthone 0.252 *M*,  $\text{Al}(\text{O-}i\text{-Pr})_3$  0.213 *M*; ●, (-)-3-thujone 0.0971 *M*,  $\text{Al}(\text{O-}i\text{-Pr})_3$  0.0818 *M*.

from these runs showed nonlinear inconsistencies extending over the first 15–20% of reaction, similar to those that had been noted by Jackman, *et al.*<sup>4b</sup> This confirmed our suspicion that equilibrating conditions were not suitable for rate measurements.

Results (all with continuous acetone removal) obtained with ketones 1–8 are summarized in Table I. A representative run, the reduction of thujone 8, is presented in Table II. A sample of pseudo-first-order plots of ketone disappearance obtained from the reduction of isomenthone (5), camphor (6), and 3-thujone (8) is portrayed in Figure 2.

Two principal observations emerge from these data. First, very good pseudo-first-order linear plots of ketone disappearance are obtainable using the distillation technique combined with glpc analysis of withdrawn samples. Second, in contrast to common opinion—Wilds<sup>2d</sup> indicates a standard reaction time of 12 to 24 hr for the reduction of ketones—purported by long reaction times given in the literature<sup>6</sup> the MPV reduction of simple mono- and bicyclic ketones is a relatively rapid reaction.<sup>9</sup> Only in sterically hindered and rigid systems like cam-

(6) Where shorter reaction times were noted a 15-fold excess of  $\text{Al}(\text{O-}i\text{-Pr})_3$  was applied,<sup>7</sup> shifting the equilibrium in favor of alcohol formation. Also, some ketone-alcohol pairs are characterized by an equilibrium favoring the alcohol even in the absence of larger amounts of alkoxide. The dependency of this equilibrium on the structural setting of the CO group was explored by Yager, *et al.*,<sup>4e</sup> and Adkins, *et al.*<sup>8</sup> Little useful generalization regarding steric effects came up from this work. All this only adds to the uncertainty about structure-reactivity relationships and impedes reasonable predictions of reduction rates.

(7) W. L. Truett and W. N. Moulton, *J. Amer. Chem. Soc.*, **73**, 5913 (1951).

(8) H. Adkins, R. M. Elofson, A. G. Rossow, and C. C. Robinson, *ibid.*, **71**, 3622 (1949).

(9) In fact, the reduction of ketones 2 and 3 may be viewed as instantaneous.

TABLE I  
 MEERWEIN-PONNDORF-VERLEY REDUCTION OF MONO- AND BICYCLIC KETONES 1-8<sup>a</sup>

Entry no.	Ketone	Alkoxide + alcohol <sup>b</sup>	[Ketone], M	[Alkoxide], M	Rate of pseudo-first-order disappearance of ketone	
					k, min <sup>-1</sup>	t <sub>1/2</sub> , min
1	Cyclopentanone (1)	A	0.253	0.215		... <sup>c</sup>
2	Cyclohexanone (2)	A	0.253	0.215		3 <sup>d</sup>
3	2-Methylcyclohexanone (3)	A	0.253	0.215		3 <sup>d</sup>
4	(±)-Menthone (4)	A	0.252	0.213	2.8 × 10 <sup>-2</sup>	24.4
5	(±)-Isomenthone (5)	A	0.252	0.213	3.1 × 10 <sup>-2</sup>	21.9
6	(-)-Camphor (6)	A	0.252	0.213	4.7 × 10 <sup>-3</sup>	145.8
7	(-)-3-Isothujone (7)	A	0.483	0.407	4.4 × 10 <sup>-2</sup>	15.5
8		A	0.252	0.213	3.3 × 10 <sup>-2</sup>	20.7
9		A	0.0971	0.0818	2.5 × 10 <sup>-2</sup>	27.0
10	(+)-3-Thujone (8)		0.483	0.407	2.0 × 10 <sup>-2</sup>	34.2
11		A	0.252	0.213	1.4 × 10 <sup>-2</sup>	47.7
12		A	0.0971	0.0818	8.4 × 10 <sup>-3</sup>	81.8
13		A	0.252	0.147	1.2 × 10 <sup>-2</sup>	53.6
14		A	0.252	0.0837	6.6 × 10 <sup>-3</sup>	107.4
15		B	0.252	0.213	1.5 × 10 <sup>-2</sup>	43.5
16		B	0.0971	0.0818	1.1 × 10 <sup>-2</sup>	62.3

<sup>a</sup> Reaction rates at 82.3 ± 0.4° in isopropyl alcohol and at 100.0 ± 0.5° in *sec*-butyl alcohol with the corresponding aluminium alkoxides as catalysts. <sup>b</sup> A = Al(O-*i*-Pr)<sub>3</sub> + *i*-PrOH; B = Al(O-*sec*-Bu)<sub>3</sub> + *sec*-BuOH. <sup>c</sup> For detailed description of products see Results and Discussion. <sup>d</sup> Estimated from yield of corresponding alcohol after a reaction time of 15 min.

 TABLE II  
 MEERWEIN-PONNDORF-VERLEY REDUCTION OF (+)-3-THUJONE 8 (0.0971 M) WITH Al(O-*i*-Pr)<sub>3</sub> (0.0818 M) IN *i*-PrOH AT 82.3 ± 0.4°. COMPLETE KINETIC RUN

Reaction time, min	Component % in isolated sample <sup>a</sup>					
	(+)-3-Thujone <sup>b</sup> (8)	(+)-3-Neothujanol <sup>c</sup> (12)	(+)-3-Thujanol <sup>c</sup> (11)	(-)-3-Isothujone (7)	(-)-3-Neoisothujanol (9)	Unknown <sup>d</sup>
15	89.0	8.1	1.9	0.2	0.2	0.4
30	78.4	16.5	3.9	0.4	0.2	0.8
45	68.6	23.2	5.8	0.3	0.5	1.1
60	62.0	29.2	7.0	0.2	0.6	1.5
75	55.1	34.3	8.3	0.3	0.8	1.4
90	47.5	40.2	10.1	0.4	1.3	1.5
105	43.0	43.1	10.8	0.3	1.5	1.8

<sup>a</sup> Determined by glpc; see Experimental Section. <sup>b</sup> See also Figure 2. <sup>c</sup> Ratio of alcohols; see Table IV. <sup>d</sup> Total of several unidentified reduction by-products.

phor the rate decreases considerably. Some values characteristic for this comparison<sup>10-12</sup> are summarized in Table III.<sup>13-20</sup> In this we projected from our results a time of 5 reaction half-lives corresponding to a yield of 96.8%. This is mostly above the yields indicated by the various authors. Also, alkoxide and ketone concentrations used by them were generally higher than in our measurements. Under comparable conditions our projected reaction times would be lower and the contrast more pronounced.

The discrepancy between high reaction rates observed here and long reaction times recorded in the literature is explicable when we consider the nature and application of the "acetone test" used in monitoring the progress of MPV reductions.<sup>2d,21,22</sup> Let us consider a reaction carried out with 0.1 mol of ketone (mol wt 200) in a

0.5 M solution, *i.e.*, 20 g of ketone in 200 ml of *i*-PrOH. After 8 reaction half-lives 0.4% (0.08 g) of ketone will still be present and will produce in the next reaction half-life *ca.* 0.02 ml of acetone. When this amount is distilled over with 20 ml of *i*-PrOH, the concentration of acetone in the tested distillate will be 1 ppt. This is within or above the sensitivity limit of the 2,4-dinitrophenylhydrazine reagent used in this test.<sup>2d,21,23</sup> For preparative purposes a 98.6% conversion of the starting ketone corresponding to a mere 6 reaction half-lives would appear sufficient. Beyond this more harm is perhaps done by side reactions, and the production of acetone is in itself no proof that the starting ketone is still present.<sup>24</sup> We conclude without doubt that the traditional "acetone test" is not well suited for monitoring the progress of MPV reductions because of, paradoxically, its high sensitivity. Fortunately, more sophisticated methods are presently available for this purpose.

Discussion of relationships between structure and MPV reduction rate will be based on entries 2-6, 8 and 11 of Table I. Cyclopentanone 1 was the only ketone

(10) Reduction of 3-isopropylcyclohexanone and 3-bicyclo[3.1.0]hexanone required 8 and 17 hr, respectively.<sup>11,12</sup> Both ketones are structurally related to ketones of this study.

(11) W. Hüchel and K. Thiele, *Chem. Ber.*, **94**, 96 (1961).

(12) S. Winstein and J. Sonnenberg, *J. Amer. Chem. Soc.*, **83**, 3235 (1961).

(13) L. M. Jackman, A. K. Macbeth, and J. A. Mills, *J. Chem. Soc.*, **2641**, 2646 (1949).

(14) W. Hüchel and A. Hubele, *Justus Liebig's Ann. Chem.*, **613**, 27 (1958).

(15) D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.*, **72**, 5743 (1950).

(16) P. Anziani and R. Cornubert, *Bull. Soc. Chim. Fr.*, **12**, 359 (1945).

(17) W. Hüchel and Ch. Z. Khan, *Chem. Ber.*, **91**, 311 (1958).

(18) O. Zeitschel and H. Schmidt, *ibid.*, **59**, 2303 (1926).

(19) D. V. Banthorpe and H. F. S. Davies, *J. Chem. Soc. B*, 1356 (1968).

(20) (a) W. Hüchel and S. Geiger, *Justus Liebig's Ann. Chem.*, **624**, 142 (1959); (b) W. Hüchel, H. Feltkamp, and S. Geiger, *ibid.*, **637**, 1 (1960).

(21) H. Lund, *Chem. Ber.*, **70**, 1520 (1937).

(22) Reaction times given in the literature and quoted here are mostly based on this "acetone test." The reaction is considered complete when no acetone is detected in the distillate.

(23) We found that the limit of detectability of acetone is about 1 part in 2000. Wilds<sup>2d</sup> states that "1 part in 1000 is easily detected."

(24) Shiner and Whittaker<sup>2b</sup> pointed out that Al isopropoxide trimer 15 is a catalyst for ketone condensations.

TABLE III  
COMPARISON OF REACTION TIMES RECORDED IN THE LITERATURE AND REACTION TIMES BASED ON THE PRESENT STUDY

Ketone	[Ketone], <sup>a</sup>	[Al(O- <i>i</i> -Pr) <sub>3</sub> ], <sup>a</sup>	Reaction time,		Ratio		Author
	<i>M</i>	<i>M</i>	min × 10 <sup>2</sup>	Yield, %	<i>cis</i> alcohol/ <i>trans</i> alcohol		
2-Methylcyclohexanone	1.35	0.45	1.8	95.0	1.0	Jackman, <i>et al.</i> <sup>13</sup>	
	0.82	0.28	1.5	93.0	2.1	Hückel, <i>et al.</i> <sup>14</sup>	
	0.82	0.28	1.5	85.0	1.3	Noyce, <i>et al.</i> <sup>15</sup>	
	0.77	0.88	3.6	...	0.16 <sup>c</sup>	Anziani, <i>et al.</i> <sup>16</sup>	
	0.253	0.215	0.15	96.8	1.3	This work	
Menthone	1.35	0.45	2.1	92.0		Jackman, <i>et al.</i> <sup>13</sup>	
	0.14	0.95	86.4	80.0		Hückel, <i>et al.</i> <sup>17</sup>	
	2.17	0.32	7.2	96.0		Zeitschel, <i>et al.</i> <sup>18</sup>	
	0.252	0.213	1.2	96.8		This work	
Isomenthone	0.54	0.16	18.0	92.0		Hückel, <i>et al.</i> <sup>20</sup>	
	0.252	0.213	1.0	96.8		This work	
Camphor	1.35	0.83	...	100.0 <sup>e</sup>		Lund <sup>21</sup>	
	1.35	0.45	5.4	...	2.3	Jackman, <i>et al.</i> <sup>13</sup>	
	0.252	0.213	7.2	96.8	3.0	This work	
(+) -3-Thujone	0.0026	0.0078	2.4 <sup>g</sup>	...	2.7	Banthorpe, <i>et al.</i> <sup>19</sup>	
	0.0971	0.0818	4.0	96.8	4.0	This work	
(-) -3-Isothujone	0.0026	0.0078	2.4	...	6.7	Banthorpe, <i>et al.</i> <sup>19</sup>	
	0.0971	0.0818	1.3	96.8	8.1	This work	

<sup>a</sup> Molar concentrations were calculated from amounts and/or concentrations of reagents given by the authors and relate to conditions at the beginning of reaction. Any change in concentration due to distillation was not taken into account. <sup>b</sup> Yield not given. <sup>c</sup> Extensive equilibration apparently took place. Noyce, *et al.*,<sup>15</sup> found a value of 0.30 for an Al(O-*i*-Pr)<sub>3</sub> and acetone equilibrated mixture. <sup>d</sup> Rate quoted as "exceedingly slow." <sup>e</sup> Purity of product not documented. <sup>f</sup> Yield quoted as "nearly quantitative but a clean distillation could not be achieved." <sup>g</sup> Note excess of alkoxide used in reaction. <sup>h</sup> Yield of glpc isolated product not given. Reduction was carried out with 10–20 mg of ketone and was qualified as "completed."

that showed anomalous behavior. After a 15-min reaction time two unidentified by-products comprised 75 and 15%, respectively, of the reaction mixture, and only a trace of cyclopentanol was observed.<sup>25,26</sup> After 75 min 57% of cyclopentanol was formed,<sup>27</sup> the two original by-products decreased to 6 and 3%, respectively, and a third by-product emerged (26%). Upon further reaction these percentages remained unchanged. Reduction of ketones 2–8 was clean and the expected alcohols predominated as reaction products.

Reduction of cyclohexanone 2 and 2-methyl-cyclohexanone (3) was immeasurably rapid under our conditions. This indicates a negligible steric effect of the 2-Me group in 3 and is in sharp contrast with reaction times of 2.5–6 hr given in the literature for ketone 3 (see Table III). An isopropyl group adjacent to CO lowers the reaction rate sufficiently so as to enable its measurement under the present conditions. This is illustrated by results obtained with menthone (4) and isomenthone (5). We believe that in relation to 2-methyl-cyclohexanone the additional effect of the Me groups in ketones 4 and 5 is negligible. The rate difference between menthone (4) and isomenthone (5) can be explained by taking into account the two possible conformers of each of the two ketones. In 4 the Me and *i*-Pr groups will be either both equatorial in the more stable conformer or both axial in the less stable one, thus, in the latter case, providing an effective shielding of both sides of the molecule. In isomenthone (5) only one alkyl group, preferably Me, will be in axial conformation at any given time and, consequently, the total shielding will be less effective.

Turning to the more rigid bicyclic system of 3-isothujone (7) and 3-thujone (8), 7 shows the higher rate of

reduction. This is instructive with regard to the possible steric influence of the cyclopropane methylene C-6 and the *i*-Pr group at the C-1 bridgehead. In ketone 7 the reagent approaches *trans* to the Me group adjacent to CO and produces a preponderance of *cis* alcohol 9 in accordance with previous observations on the directive effect of CO neighboring alkyl groups in MPV reductions.<sup>28</sup> Together with higher rate of reduction, this stereospecificity is more pronounced (see Table IV) than in the isomeric 3-thujone 8. Alcohols 9 and 10 are formed in a ratio of 7:1, respectively, whereas thujone 8 yields alcohols 12 and 11 in a ratio of 3.2:1, respectively. This indicates that in 7 there is very little steric hindrance caused by the  $\alpha$  H of the C-6 methylene when the reagent approaches from the  $\alpha$  face and that the *i*-Pr group at C-1 assists in the primary directing effect of the CO adjacent CH<sub>3</sub> group. In ketone 8 the primary directing effect of this Me group (reagent approaching from the  $\beta$  side) is less pronounced. A larger proportion of the alkoxide is forced to approach and/or transfer its hydride anion from the  $\alpha$  side. This confirms the negligible steric influence of the  $\alpha$  H at C-6 and indicates that the rigidly positioned *i*-Pr group at C-1 contributes through substantial shielding of the  $\beta$  face to a decrease in rate as well as in stereospecificity of reduction of ketone 8.<sup>29,30</sup>

(28) W. Hückel, M. Maier, E. Jordan, and W. Seeger, *Justus Liebigs Ann. Chem.*, **616**, 46 (1958), presents a valuable discussion and many leading references.

(29) In this brief discussion we are aware of our disregard for the subtle conformational problems involved in the adequate description of thujones 7 and 8. Their conformation may range from an overall boatlike through an L-shaped (essentially flat five-membered ring) to a chairlike molecule. Although nmr studies indicated a boatlike conformation, this has not been proved conclusively.<sup>30</sup> Banthorpe, *et al.*,<sup>19</sup> in their study on the reduction of 7 and 8 by various reagents, including the MPV reduction, concluded that 7 prevails in a chairlike whereas 8 in a boatlike conformation. Our present results appear to be consistent with an L-shaped conformation in both ketones. Results of our recently completed and detailed conformational study of these two ketones support this latter view.

(30) V. Hach, F. R. Raimondo, D. M. Cartledge, and E. C. McDonald, *Tetrahedron Lett.*, 3175 (1970).

(25) Self-condensation of cyclopentanone in the presence of base is known<sup>26</sup> to be about  $1.4 \times 10^4$  more rapid than that of 2-methylcyclohexanone.

(26) J. M. Conia, *Rec. Chem. Progr.*, **24**, 43 (1963).

(27) Yields of cyclopentanol from the MPV reduction of cyclopentanone given in the literature<sup>7,9,13</sup> are in the 30–60% range.

TABLE IV  
RATIO OF EPIMERIC ALCOHOLS FORMED IN THE REDUCTION OF KETONES 6, 7, AND 8 AND ITS DEPENDENCY ON REACTANT CONCENTRATION

Ketone	Concn, <i>M</i>	Alkoxide	Concn, <i>M</i>	Ketone reacted, %	Ratio <sup>a</sup> of cis alcohol/trans alcohol
Camphor (6)	0.252	Al( <i>O-i-Pr</i> ) <sub>3</sub>	0.213	25	2.9
				50	3.0
				75	... <sup>b</sup>
3-Isothujone (7)	0.0971	Al( <i>O-i-Pr</i> ) <sub>3</sub>	0.0818	25	7.9
				50	7.9
				75	8.1
3-Isothujone (7)	0.252	Al( <i>O-i-Pr</i> ) <sub>3</sub>	0.213	25	... <sup>c</sup>
				50	7.0
				75	6.8
3-Isothujone (7)	0.483	Al( <i>O-i-Pr</i> ) <sub>3</sub>	0.407	25	... <sup>c</sup>
				50	5.9
				75	5.8
3-Thujone (8)	0.0971	Al( <i>O-i-Pr</i> ) <sub>3</sub>	0.0818	25	4.1
				50	4.0
				75	... <sup>b</sup>
3-Thujone (8)	0.252	Al( <i>O-i-Pr</i> ) <sub>3</sub>	0.213	25	3.5
				50	3.2
				75	2.9
3-Thujone (8)	0.483	Al( <i>O-i-Pr</i> ) <sub>3</sub>	0.407	25	3.0
				50	2.7
				75	2.0
3-Thujone (8)	0.0971	Al( <i>O-sec-Bu</i> ) <sub>3</sub>	0.0818	25	5.0
				50	5.0
				75	4.4
3-Thujone (8)	0.252	Al( <i>O-sec-Bu</i> ) <sub>3</sub>	0.213	25	... <sup>c</sup>
				50	4.5
				75	3.8

<sup>a</sup> In the case of camphor ratio of exo/endo alcohol, *i.e.*, isoborneol/borneol. In the case of 3-isothujone and 3-thujone ratio of 9:10 and 12:11, respectively. <sup>b</sup> Only 60% of reaction was followed. <sup>c</sup> Due to relatively high reaction rate the ratio at 25% ketone reacted was not established.

Camphor shows by a considerable margin the lowest rate of reduction indicating the effect of rigidity and steric hindrance in the vicinity of the CO group and along the reaction path. However, in its ultimate effect rigidity of a cyclic system may be a key factor enabling reagent approach by locking CO neighboring groups in a fixed position. This is revealingly demonstrated by results obtained with fenchone (13) and di-*tert*-butyl ketone (14). Yager, *et al.*,<sup>48</sup> were unable to reduce 14 or, for that matter, to oxidize di-*tert*-butylcarbinol despite a reaction time of "several days." Consequently, one could be tempted to predict that fenchone (13) would not be reduced as well. However, fenchone 13 was reduced by two groups.<sup>31,32</sup> Apparently, the free rotation of *t*-Bu groups around the C-CO axis in ketone 14 can block the reagent approach completely whereas the "locked positions" of CH<sub>3</sub> and CH<sub>2</sub> groups in fenchone (13) leave a marginal opportunity for reagent attack from the endo side of the molecule to yield 95% of exo alcohol as shown by Hückel and Meinhardt.<sup>32</sup>

Finally, we may take a brief note of entries 7-14 in Table I. These results are in agreement with observations made by previous workers<sup>48,c,8</sup> who detected pseudo-first-order disappearance of ketone and dependency of reaction rate on concentration and ratio of reagents. As stated in the previous the overall reaction rate has not been established conclusively.

(31) P. Hirsjärvi and N. J. Toivonen, *Suom. Kemistilehti B*, **23**, 14 (1950); *Chem. Abstr.*, **45**, 1545 (1951).

(32) W. Hückel and G. Meinhardt, *Chem. Ber.*, **90**, 2025 (1957).

**Ratio of Epimeric Alcohols.**—Results obtained in studies on the ratio of epimeric alcohols formed in the MPV reduction of camphor (6), isothujone 7, and thujone 8 are briefly summarized in Table IV. Some stereochemical implications of these results have already been mentioned in the preceding discussion. Two additional aspects will be considered here.

First is dependency of the epimeric alcohol ratio on reaction time. To our best knowledge this facet of the MPV reduction has not previously received any attention.<sup>33,34</sup> Constancy of this ratio throughout the reduction would be a strong proof of nonequilibrating conditions and, consequently, of kinetic product control. Indeed, it follows from results in Table IV that this condition was achieved. As had been expected reduction with the bulkier Al(*O-sec-Bu*)<sub>3</sub> in *sec*-BuOH was more stereospecific. A slight downward drift of the cis/trans ratio was occasionally observed. However, when contrasted with experiments carried out under truly equilibrating conditions (Figure 1) this appeared to be of little significance.

Second is influence of concentration of reactants on the epimeric alcohol ratio. This was studied in more detail using ketones 7 and 8. Surprisingly, this ratio was dependent on the absolute concentration of reactants, the ratio of reactants being constant. In

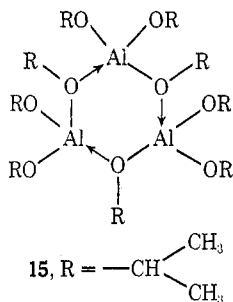
(33) Recently, Rickborn and Wuesthoff<sup>34</sup> studied the dependency between ratio of epimeric alcohols formed in NaBH<sub>4</sub> reductions of alkylcyclohexanones and reaction time. Surprisingly, a continuous change in the ratio of epimeric alcohols during the course of reduction was observed.

(34) B. Rickborn and M. T. Wuesthoff, *J. Amer. Chem. Soc.*, **92**, 6894 (1970).

dilute solutions the *cis* alcohol/*trans* alcohol ratio was higher, and thus the stereospecificity of reduction was more pronounced than in concentrated solutions. This observation may be of serious consequence in two respects: practical utilization of the MPV reduction and stereochemical interpretation of results published in previous literature. Regarding the first point it will be advisable to carry out MPV reductions at the highest dilution compatible with acceptable reaction rate when pursuing an increase in stereospecificity. Regarding the second point, it will be reasonable to reconsider ratios of epimers obtained from MPV reductions and recorded in the literature with respect to reactant concentration applied. Also, conclusions drawn from comparisons between ratios of epimers obtained by other reducing agents, particularly complex hydrides,<sup>35-37</sup> and by MPV reductions should perhaps be more cautious.<sup>38</sup>

Limited results of Jackman, Noyce, and Hüchel and their collaborators with 2-methyl-cyclohexanone as well as our and Jackman's results on camphor (Table III) seem to support our observation that stereospecificity of MPV reduction is more pronounced in dilute solutions.<sup>39</sup>

We believe that the key factor governing the relation between product stereochemistry and reactant concentration will be the concentration-dependent association of  $\text{Al}(\text{O}-i\text{-Pr})_3$  with *i*-PrOH. Shiner and Whitaker<sup>40,41</sup> have shown that at the boiling point of *i*-PrOH Al isopropoxide as a reactive species is trimeric **15**.



Apparently, this trimer will be subject to a high degree of solvation by solvent alcohol in addition to direct coordination through available d orbitals of aluminum. In support of this view Shiner, *et al.*, observed that the reaction between a ketone and trimer **15** had a higher rate in benzene than in a 1:1 mixture of benzene and *i*-PrOH, and they assumed that this rate acceleration was caused by greater accessibility of the trimer to coordination with ketone as *i*-PrOH was removed from its association with the trimer. A similar solvent asso-

ciation mechanism could possibly explain the results of Bains and Bradley<sup>42</sup> who found that within a narrow range of 16–32° the reaction order of MPV reduction with respect to alkoxide changed by more than 50%. It is reasonable to assume that a higher degree of solvation of the bulky trimer **15** in dilute solution will require that its approach<sup>40,41</sup> by and coordination with a ketone<sup>42</sup> be more stereoselective. The same would apply to the subsequent hydride transfer step. This then could determine the higher degree of reaction stereospecificity<sup>43</sup> in dilute solution.

## Experimental Section

**Materials.**—Ketones 1–6 were of commercial origin. Standard purification methods were applied when necessary so that materials used in rate measurements were at least 99% pure determined by glpc. Pure (+)-3-thujone (**8**) was obtained as described previously.<sup>44</sup> (–)-3-Isothujone (**7**) was obtained either by spinning band column distillation of Western red cedar (*Thuja plicata* Donn) leaf oil or by Brown oxidation<sup>45</sup> of crystalline (–)-3-neoisothujanol (**9**). Details of this work will be reported subsequently.

Aluminium isopropoxide and  $\text{Al}(\text{O}-\textit{sec}\text{-Bu})_3$  were prepared *in situ* by dissolving Al cleaned by washing with  $\text{CCl}_4$  in the corresponding alcohol. The solutions were used immediately. The main reason for this approach was the fact that crystalline  $\text{Al}(\text{O}-i\text{-Pr})_3$  is tetrameric whereas in solution at the boiling point of *i*-PrOH it is trimeric. In addition, the conversion of tetramer into trimer is slow, and its actual rate under our projected conditions is not known.<sup>41,42</sup> However, according to previous results<sup>41,42</sup> our procedure provided a solution of the trimer **15** only. To initiate the dissolution of Al a trace of  $\text{HgCl}_2$  was used as catalyst. It is generally accepted that the MPV reduction is not influenced by its presence.<sup>28</sup> To support this point control experiments were carried out in which the dissolution of Al was initiated by  $\text{I}_2$  or  $\text{CCl}_4$ . No difference in reaction rate was observed with any of these three catalysts.

**Procedure.**—A ground-glass joint apparatus consisting of a three-necked flask and a distilling condenser was used. The flask was equipped with a calibrated dropping funnel, thermometer reaching into the reaction mixture, and a magnetic stirring bar. The distilling condenser head was fitted with a thermometer, and the condenser receiving end was equipped with a calibrated receiver enabling distillate volume measurement. Reaction samples were withdrawn from the flask *via* a septum-like attachment. The whole apparatus was protected by a  $\text{CaCl}_2$  tube. The flask was placed in an oil bath located on a thermostatically controlled stirrer–heater combination.

Aluminum alkoxide solutions were prepared by dissolving the necessary amount of Al in the appropriate amount of dry *i*-PrOH or *sec*-BuOH. In the calculation of molarity the volume of subsequently added ketone was accounted for. Change in alcohol volume caused by dissolution of Al was found to be negligible. The amount of  $\text{HgCl}_2$  used as catalyst was 12.6 mg/0.1 mol of Al alkoxide. The time necessary to complete dissolution of Al was about 1 hr, and the practically clear alkoxide solution was then stirred for another hour at 45°. Throughout the dissolving process very little heat had to be supplied. The amount of alcohol that distilled off was exactly measured and

(35) Rickborn, *et al.*,<sup>34</sup> brought into serious doubt another common belief purported in the literature, that is, that the ratio of epimeric alcohols formed in hydride reductions is independent of the ratio hydride/ketone. Rickborn, *et al.*, have shown that this may be true in a few specific ketones but must not be accepted as a general rule; see ref 36 also. Snyder<sup>37</sup> has shown that the ratio of *cis*- and *trans*-cyclopentane- and -cyclohexane-1,2-diols formed by MPV reduction of the corresponding 1,2-diones was dependent on the ratio dione/alkoxide.

(36) (a) H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, **84**, 2368 (1962); E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970), and references therein.

(37) (a) C. H. Snyder, *J. Org. Chem.*, **31**, 4220 (1966); (b) C. H. Snyder and M. H. Micklus, *ibid.*, **35**, 264 (1970).

(38) W. Hüchel, *et al.*,<sup>28</sup> relates numerous examples and provides an extensive background on this topic.

(39) Banthorpe's and our results on thujones in Table III are not comparable. Banthorpe, *et al.*, carried out the reduction of both ketones under reflux and, apparently, brought about equilibration of the epimeric alcohols despite the fact that they worked in a more dilute solution than we did.

(40) Steric influence during such an approach are remotely illustrated by the findings of Bradley<sup>41</sup> who has shown that branched and sterically hindered alcohols interchange with Al alkoxides more slowly than straight-chain alcohols.

(41) D. C. Bradley, *Progr. Inorg. Chem.*, **2**, 303 (1960).

(42) Undoubtedly, solvation of the ketone itself will also be a contributing factor.

(43) There seems to be somewhat more evidence available in the area of complex hydride reductions in regard to solvation influencing the ratio of epimeric alcohols formed, although, a coherent picture is still missing. These aspects were admirably discussed by Eliel, *et al.*,<sup>38</sup> and there is little doubt that the nature of solvent and its association with complex hydride indeed plays a role in determining the ratio of epimeric alcohols.

(44) V. Hach, R. W. Lockhart, E. C. McDonald, and D. M. Cartledge, *Can. J. Chem.*, **49**, 1762 (1971). In the present paper as in our previous papers we adopted the thujone–thujanol nomenclature proposed by H. C. Brown; see also ref 30.

(45) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

was replaced by fresh dry alcohol after the completed dissolution. This amount was never more than a few milliliters.

Kinetic runs were carried out as follows. The solution was brought to gentle boiling and stirred magnetically to assure its smoothness. The rate of stirring was estimated at about 200 rpm and was kept constant throughout the experimental series. Immediately after the boiling point was reached the calculated amount of ketone was introduced and this moment was taken as time zero. The amount of ketone was mostly between 5 and 10 g depending on the desired molarity. Volume of the reaction mixture varied between 135 and 270 ml. Samples were withdrawn at 15-min intervals. In all cases eight samples were sufficient to establish very good kinetic plots. The mixture of acetone or 2-butanone formed in the reaction and the corresponding alcohol distilled off at an average rate of 8 ml per 15 min with limits of 5–11 ml. After each sampling in the standard 15-min interval a volume of dry alcohol was added to the reaction mixture equal to the volume of distillate collected in the preceding 15-min interval. This kept the volume of the reaction mixture essentially constant and guaranteed the continuous removal of acetone or butanone formed by the reaction. In control experiments total amounts of acetone in the distillate were found to be in rough agreement with the amounts expected. Obviously, losses of acetone in the reaction mixture may occur as a consequence of side reactions.<sup>4b,46</sup>

Each sample (about 5 ml) withdrawn from the reaction mixture was quenched in a 10% solution of tartaric acid containing 1.5 g of acid/0.1 g of Al in the sample. The products were extracted with ether; the extract was washed with a 3% NaHCO<sub>3</sub> solution, dried with Na<sub>2</sub>SO<sub>4</sub>, and evaporated. Material balance experiments confirmed complete extraction. In the resulting sample starting ketone, epimerized ketone where applicable, alcohols produced and total percentage of by-products formed were determined by glpc analysis using procedures described by us previously.<sup>30,44,47</sup> No attempt was made to identify the individual by-products. All kinetic runs were duplicated. A precision of 4% or better was usually achieved in corresponding determinations at specific time intervals. When necessary the run was repeated for a third time or more in case of any doubt. Typical analytical results from the reduction of 3-thujone (8) are given in Table II. Reaction constants in Table I were established graphically from semilogarithmic plots of percentage of disappearing ketone *vs.* time as exemplified by Figure 2. Best fits were obtained according to Livingston.<sup>48</sup> Reaction half-lives were calculated using the standard equation  $t_{1/2}(\text{min}) = 2.303 \log 2/k$  (min).

In preliminary experiments without acetone removal the apparatus was similar except that a reflux condenser was used instead of a distilling condenser. Also, the procedure was similar and a typical result is exemplified by Figure 1.

**Criticism of Method.**—Three topics warrant a more detailed discussion: concentration of reagents, epimerization of starting ketones, and by-product formation.

The principle of our approach, *viz.*, the exclusion of equilibrating conditions, necessitated the continuous removal by distillation of acetone or 2-butanone formed in the reduction. A batch-type reaction rate measurement brings about the inherent problem

of maintaining a constant reactant concentration. In extreme cases the change of volume during the 15-min interval in which the volume was being adjusted amounted to about 10% and thus to a corresponding 10% change towards higher molar concentration of reactants. From entries 7, 8, 10, and 11 of Table I it appears that a 100% rise in reactant concentration led to a 33% enhancement of rate constant. Consequently, 10% would cause approximately a 3% error in a rate constant. We reiterate that these conditions were applicable only in a few cases of lower reaction volumes and in the latter part of the reaction. Further, due to averaging of reaction times at lower and higher concentration the potential error will actually be lower. With reaction volumes of 250 ml a change of 8 ml would lead to a reaction rate constant uncertainty of about 1%. In regard to the starting concentration of Al alkoxide the assumption was made that all Al was converted into the alkoxide in accordance with established knowledge.<sup>41</sup> Unfortunately, there is no method available that would enable an accurate estimation of Al alkoxide in solution. In all previous kinetic work<sup>40,42</sup> only the total content of Al in solution was estimated by absolutely irrelevant nonspecific procedures as Al<sub>2</sub>O<sub>3</sub>. The only loss in concentration of alkoxide could possibly occur by hydrolysis. However, traces of moisture would manifest themselves promptly by inhibiting the dissolution of Al and, subsequently, the reaction itself. Therefore, careful avoidance of moisture was one of the main prerequisites which was rigidly controlled.

Epimerization of ketones like 4, 5, 7, and 8 by Al alkoxide would obviously distort the rate measurement. Fortunately enough its extent was in the 1.5–3% range, the higher value resulting from reductions with 0.407 M alkoxide beyond 60% ketone disappearance. This value is in accord with findings of Hüchel<sup>18</sup> and Banthorpe<sup>17</sup> on the isomeric menthones and thujones respectively. As shown in Table II epimerization demonstrates itself predominantly by the presence of alcohols corresponding to the epimerized ketone.

As in the case of epimerization by-product formation was directly proportional to alkoxide concentration and stage of reduction. With alkoxide concentration of 0.407 M by-product formation reached about 3% after 75% reaction completion. Otherwise by-products were in the 1–2% range with the exception of cyclopentanone reduction discussed previously.

In conclusion, taking into account the outlined points and the accuracy of the glpc method used, which was established to be  $\pm 3\%$ , we estimate an uncertainty limit of about  $\pm 10\%$  for the rate constants at highest (0.407 M) alkoxide concentrations. The basis for our structure-reactivity discussion were rates obtained with 0.213 M alkoxide. These have a lower uncertainty limit and allow for a meaningful and conclusive discussion of the relationship between sterical environment of the CO group and its rate of reduction by the MPV method.

**Registry No.**—1, 120-92-3; 2, 108-94-1; 3, 583-60-8; 4, 1074-95-9; 5, 36977-92-1; 6, 464-48-2; 7, 546-80-5; 8, 471-15-8; Al(O-*i*-Pr)<sub>3</sub>, 13431-86-2; *i*-PrOH, 67-63-0; Al(O-*sec*-Bu)<sub>3</sub>, 36977-99-8; *sec*-BuOH, 78-92-2.

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(46) E. F. Kutepov, *Med. Prom. SSSR*, **18**, 26 (1964); *Chem. Abstr.*, **66**, 37029e (1967).

(47) K. L. McDonald and D. M. Carlidge, *J. Chromatogr. Sci.*, **9**, 440 (1971).

(48) R. Livingston in "Techniques of Organic Chemistry," Vol. VIII, 2nd ed, part 2, S. L. Friess, S. L. Lewis and A. Weissberger, Ed., Interscience, New York, N. Y., pp 126, 127.