

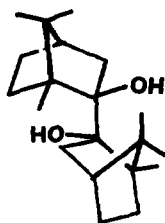
DIMERIC PRODUCTS FROM THE DISSOLVING METAL  
REDUCTION OF CAMPHOR

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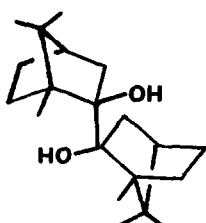
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ABSTRACT: Various dissolving metal reductions of (+)-camphor afford one of two pinacols frequently accompanied by a dimeric product in which one bicycloheptane unit has been cleaved. Similar reductions of (±)-camphor afford various mixtures of (+)-exo-endo, (+)-endo-endo and meso endo-endo pinacols. The structures of two of these products were confirmed by X-ray crystallography.

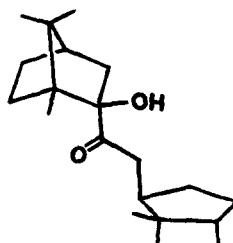
A number of studies of the mechanism of dissolving metal reduction of ketones to secondary alcohols have been carried out, frequently using camphor as substrate<sup>2</sup>. In addition to mixtures of alcohols it is known that reduction of (+)-camphor under various conditions affords two diastereomeric pinacols.<sup>3</sup> On the basis of NMR data, Rautenstrauch assigned exo-endo structure 1



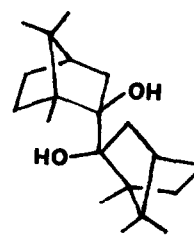
1



2



3



4

to the pinacol, mp 113-115<sup>o</sup>, obtained by Li/NH<sub>3</sub> reduction of (+)-camphor.<sup>2c,3b</sup> The second pinacol was assigned endo-endo structure 2<sup>2c</sup> and is presumably the same pinacol, mp 157<sup>o</sup>, obtained by Beckmann<sup>3a</sup> and later by Hückel *et al.*<sup>3b</sup> using Na/Et<sub>2</sub>O or Na/NH<sub>3</sub>. The relative yields and stereochemistry of these pinacols appear to be very sensitive to the conditions of reduction.<sup>2</sup>

Ketyls are implicated in the production of both secondary alcohols and pinacols and an investigation of the factors governing pinacol formation should provide additional insight

into the mechanistic course of the dissolving metal reduction of ketones.<sup>2a,b</sup> While this work was in progress, Pradhan reported that with Li/THF (+)-camphor gave exclusively pinacol 2, which was also the only dimeric product when camphor was added to Li/NH<sub>3</sub>.<sup>4</sup> The structure of pinacol 2 was confirmed by crystallography and conditions for the formation of pinacol 1 were described. Pradhan also made the remarkable observation that reduction of (+)-camphor gave exclusively racemic pinacols 1 and 2 unaccompanied by the diastereomeric pinacols resulting from coupling of (+) and (-)-camphor units.<sup>4</sup>

In our hands, and in general agreement with Pradhan's results,<sup>4</sup> we find that reduction of (+)-camphor with Li/THF, (0.4 equiv) on stirring or sonication affords pinacol 2 in approximately 20% yield, accompanied by 4% of a second dimeric reduction product, mp 77-79°. This material was clearly not a pinacol (m<sup>+</sup> 306, <sup>13</sup>C NMR at δ 214) and the presence of a ketonic carbonyl group was confirmed by IR peaks at 1696 and 1707 cm<sup>-1</sup>.<sup>5</sup> The structure was determined by crystallography to be that depicted in 3 with the ORTEP projection in Figure I.<sup>6</sup>

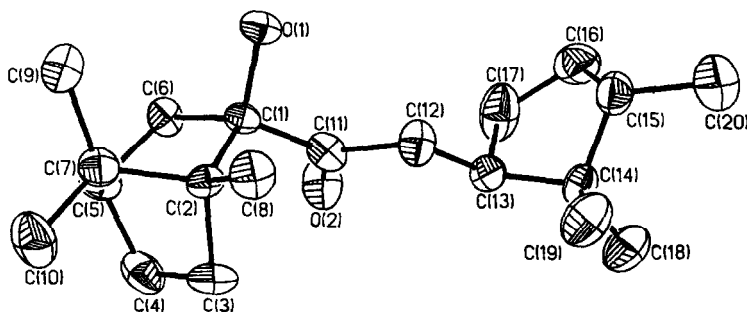


Figure I  
ORTEP Structure of 3

Careful repetition of Pradhan's procedure for the preparation of pinacol 2 by addition of (+)-camphor to a 0.5 M solution of Li/NH<sub>3</sub> (1 equiv of Li) gave 2, contaminated with ca 10% (<sup>13</sup>C NMR) of pinacol 1. In one of five apparently identical runs pinacol 1 was obtained as the major dimeric product. We have no explanation for this apparently anomalous run, however it emphasizes the sensitivity of these reactions to the conditions under which they are carried out.

Under the usual conditions for the Li/NH<sub>3</sub> reduction of (+)-camphor (addition of Li to a stirred solution of camphor in THF/NH<sub>3</sub>) the principal dimeric product was pinacol 1, in agreement with, earlier work,<sup>2c,3c,4</sup> accompanied by varying amounts of ketone 3 and pinacol 2 (ca. 10%). The yield of ketone 3 was increased to 25-30% by adding a 1.8 M solution of (+)-camphor to approximately 50 ml of a 0.14 M solution of Li/NH<sub>3</sub> at a rate of 2.5-4.0 ml/min (syringe pump). In a number of experiments carried out under similar conditions it was found that decreasing the rate of addition of substrate (0.5 ml/min) decreased the relative amount of ketone 3 (13%) and increased the amount of pinacol to 40-60%. In these, and other similar experiments, mixtures of pinacols 1 and 2 were obtained in which 1 was the major (90%) component.

In contrast to Pradhan's report, reduction of (+)-camphor using 0.4 equiv Li/THF with sonication or stirring at room temperature gave in addition to 13% yield of racemic endo-endo pinacol 2, 17% of a second pinacol, mp 119-121°. The <sup>13</sup>C NMR was very similar to that of pinacol 2 and this material was tentatively assigned meso-endo-endo structure (4) which was confirmed by crystallography as depicted in Figure II.<sup>6</sup> Pinacol 4 (19%) was obtained in addition to 13% of (+)-2 by Li/NH<sub>3</sub> reduction of (+)-camphor under Pradhan's conditions for the preparation of 2.<sup>4</sup>

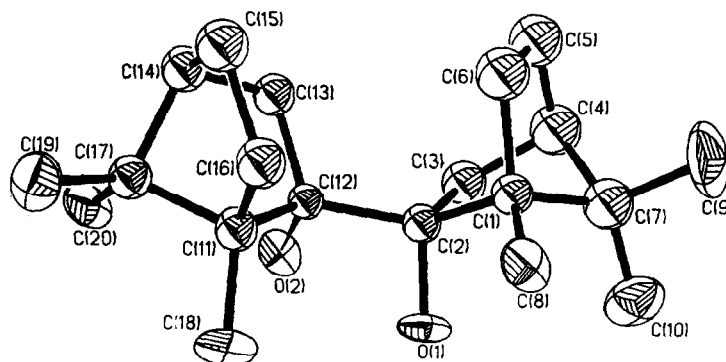
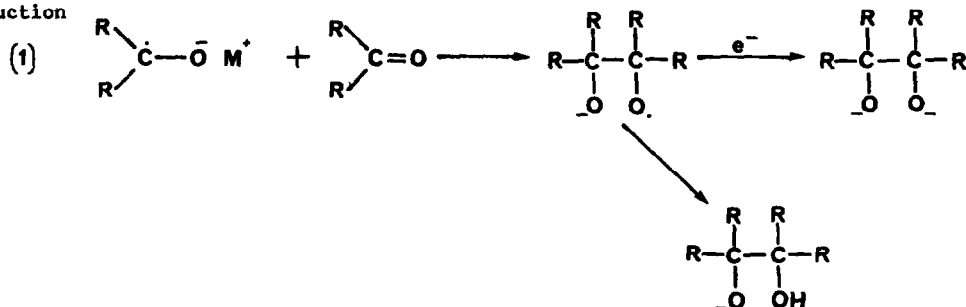


Figure II  
ORTEP Structure of 4

Although reductions of (+)-camphor which afforded endo-endo pinacol invariably gave mixtures of (+)-2 and 4, both exo-endo pinacol 1 and ketone 3 were obtained as racemates with no detectable amount of products arising from coupling of (+)- and (-)-camphor units.<sup>7</sup>

As noted by Pradhan,<sup>4</sup> reduction of (+)-camphor in the presence of relatively concentrated solutions of Li/NH<sub>3</sub> leads to formation of endo-endo pinacol (2). Lower concentrations of metal give exo-endo pinacol 1, accompanied by varying amounts of ketone 3.<sup>4</sup> It has been suggested, and appears probable, that the endo-endo pinacol arises via direct coupling of two ketyl units which are formed rapidly and essentially irreversibly in the presence of excess reducing agent.<sup>4</sup>

Exo-endo pinacol 1 is formed in the presence of relatively low concentrations of reducing agent and we suggest that both pinacol 1 and ketone 3 arise via the path outlined in equation 1. Initial attack of the radical center of a ketyl on an unreduced ketone molecule, followed by reduction



or hydrogen transfer affords the pinacol derivative.  $\beta$ -Cleavage of the alkoxy radical and hydrogen abstraction<sup>9</sup> leads to ketone 3. The addition of a ketyl to a carbonyl group is a known reaction,<sup>10</sup> however this appears to be the first example identified in a metal-ammonia reduction.

These results, particularly the observation that the exo-endo pinacols apparently arise by radical attack on a ketonic carbonyl imply that secondary alcohol formation in the absence of added proton donors may be occurring by hydrogen transfer from a ketone to a ketyl, rather than from one ketyl to another, as previously suggested.<sup>2a-c</sup>

#### REFERENCES AND NOTES

- (1) To whom inquiries regarding the crystallographic studies should be directed.
- (2) (a) Huffman, J.W. Acc. Chem. Res. 1983, 16, 399 and references therein. (b) Huffman, J.W.; Liao, W.-P.; Wallace, R.H. Tetrahedron Lett. 1987, 28, 3315. (c) Rautenstrauch, V.; Willhalm, B.; Thommen, W.; Burger, U. Helv. Chim. Acta. 1981, 64, 2109. (d) Pradhan, S.K. Tetrahedron, 1986, 42, 6351.
- (3) (a) Beckmann, E. Liebigs Ann. Chem. 1896, 292, 1. (b) Hüchel, W.; Maier, M.; Jordan, E.; Seeger, W. ibid. 1958, 616, 46. (c) Murphy, W.S.; Sullivan, D.F. J. Chem. Soc. Perkin Trans. I 1972, 999.
- (4) Pradhan, S.K.; Thakker, K.R.; McPhail, A.T. Tetrahedron Lett. 1987, 28, 1813.
- (5) In all cases, mixtures of the epimeric alcohols and recovered camphor were obtained. The composition of these mixtures was the same, within experimental error, as those reported previously (ref. 2a-c). The reduction mixtures were analyzed by GLC, the crude bimolecular reduction products were isolated as described by Rautenstrauch (ref 2c) and purified by MPLC. Pinacols 1 and 2 were characterized by mp and <sup>13</sup>C NMR.
- (6) Crystallographic data have been deposited with the Cambridge Crystallographic Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 IEW, England.
- (7) Racemic products were compared (IR, mmp) with samples prepared by mixing equal parts of material obtained by reduction of (+) and (-)-camphor.
- (8) The results in THF are more difficult to assess since the reactions are heterogeneous and reaction may be occurring on the metal surface.
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