205. Alkali Metal/Ammonia Reductions of Ketones Should Be Run in the Presence of Ammonium Ion

by **Valentin Rautenstrauch**[1], **Bruno Willhalm** and **Walter Thommen**
Firmenich SA, Research Laboratories, CH-1211 Geneva 8
and **Ulrich Burger**
Département de Chimie Organique, Université de Genève, CH-1211 Genève 4

Dedicated to Professor *George Büchi* on the occasion of his 60th birthday

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Summary

Reduction of (+)-[3,3-$^2H_2$]camphor ([3,3-$^2H_2$]**1**) with lithium, sodium or potassium in ammonia and a co-solvent gave: 1) the enolate of [3,3-$^2H_2$]**1** and the alcoholates of (–)-[2,3,3-$^2H_3$]isoborneol ([2,3,3-$^2H_3$]**2**) and (+)-[2,3,3-$^2H_3$]borneol ([2,3,3-$^2H_3$]**3**); 2) the alcoholates of [3,3-$^2H_2$]**2** and [3,3-$^2H_2$]**3**; 3) the dialcoholates of the pinacols [3,3,3′,3′-$^2H_4$]**4** and [3,3,3′,3′-$^2H_4$]**5**. It is proposed that these are formed from the ketyls [3,3-$^2H_2$]$\mathbf{1}^{\cdot-}M^+$, by: 1) disproportionation; 2) H-atom abstraction from the medium; 3) dimerization. Protonation upon work-up afforded [*endo*-3-^{2}H]**1**, [2,3,3-$^2H_3$]**2**, [2,3,3-$^2H_3$]**3**, [3,3-$^2H_2$]**2**, [3,3-$^2H_2$]**3**, [3,3,3′,3′-$^2H_4$]**4** and [3,3,3′,3′-$^2H_4$]**5**. Pinacol [3,3,3′,3′-$^2H_4$]**5** was the main and pinacol [3,3,3′,3′-$^2H_4$]**4** a minor product in the reductions with lithium and both were minor products in the reductions with sodium; pinacols were not formed in the reductions with potassium. Parallel reductions of **1**, unlabeled, analogously led to **2**, **3**, **4** and **5**, and the ratios **2**/**3** differed from the ratios ([2,3,3-$^2H_3$]**2** + [3,3-$^2H_2$]**2**)/([2,3,3- $^2H_3$]**3** + [3,3-$^2H_2$]**3**) under certain conditions. Different values for these ratios were found in the reductions with each metal, all of which corresponded to low overall diastereoselectivities. Reactions 1 and 3 persisted when the reductions were carried out in ammonia/water/co-solvent mixtures and the enolate formed *via* reaction 1 was protonated and the resulting [*endo*-3-^{2}H]**1** recycled. Reaction 2 cannot be monitored under these conditions. Reactions 1 and 3, and by inference also reaction 2, were almost completely suppressed when analogous reductions were carried out in the presence of ammonium chloride, [3,3-$^2H_2$]**2** and [3,3-$^2H_2$]**3** being obtained almost exclusively, in a 6:94 ratio, with all three metals. A parallel reduction of **1** afforded **2** and **3** in a 6:94 ratio. It is proposed that the mechanism outlined in *House* [1] was dominant when, and only when, ammonium ion was the proton source; it may have competed when water was the proton source.

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[1] Author to whom correspondence should be addressed.

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1. Introduction, background. – 1.1. *Alkali metal/ammonia and* Bouveault-Blanc *reductions.* In a number of methods that serve to transform saturated ketones into the corresponding secondary alcohols, alkali metals function as the sources of electrons [1]. One such, the *Bouveault-Blanc* reduction, was the first general method for reducing ketones to alcohols. These methods continue to be used because of their stereochemical outcome, namely, that when diastereoisomeric alcohols can be formed, it is usually the thermodynamically more stable one that is formed predominantly.

In the *Bouveault-Blanc* procedure, metallic sodium is added to a solution of the substrate in an alcohol (ethanol, propanol, *etc.*, dissolving metal reduction). The metal dissolves/reacts and two complex reactions take place. The substrate is transformed into the corresponding sodium alcoholate(s) (overall stoichiometry: $R^1R^2C{=}O + 2Na + R^3OH \rightarrow R^1R^2HC{-}ONa + R^3ONa$) and molecular hydrogen is formed ($2\ R^3OH + 2\ Na \rightarrow 2\ R^3ONa + H_2$), the sodium alcoholate derived from the solvent being generated in both. Water is added when the sodium is consumed and this liberates the alcohols.

The side reaction to give molecular hydrogen is less important in alkali metal/ammonia reductions and this is probably the main reason why these are now preferred. In these, the alkali metals (usually lithium or sodium, sometimes potassium) are either added to a solution of the substrate in ammonia and a co-solvent (dissolving metal reduction, normal addition) or a solution of the substrate in a co-solvent is added to a solution of the metal in ammonia (inverse addition). In either addition mode, an alcohol (methanol, ethanol, *t*-butyl alcohol) may, but need not, constitute a further component of the reducing system. To minimize the reaction of the alcohols with the dissolved metals to give molecular hydrogen and the metal alcoholates, the substrate and the alcohol are jointly combined with the metals in both addition modes. Thus the metals are either added to a solution of the substrate in an ammonia/alcohol/co-solvent mixture, or a solution of the substrate in an alcohol/co-solvent mixture is added to a solution of the metal in ammonia. Water or ammonium chloride are sometimes, but rarely, used in place of the alcohols and for reasons of solubility, this is only possible in the normal addition mode.

The alcohols, water, and ammonium chloride are thought to serve as proton sources. The overall stoichiometry of these reductions then corresponds to that of the *Bouveault-Blanc* reduction. In the reductions without a proton source, the stoichiometry was unclear until recently (see *1.2*), the origin of the H-atoms that are introduced into the substrate not having been established. The function of the co-solvents – diethyl ether (DEE) or tetrahydrofuran (THF) or dioxan are commonly used – is to enhance the solubility of the substrate. Dissolution of the alkali metals in ammonia gives solutions containing solvated electrons and solvated alkali metal cations [1] [2]. The solvated electrons react rapidly, but not at diffusion-controlled rates, with ketones [3]. Solvated electrons may also be the active species in the *Bouveault-Blanc* reduction. The mechanism of the reaction between solvated electrons and proton sources to give molecular hydrogen is not well understood.

The currently accepted mechanism [1] of *Bouveault-Blanc* and metal/ammonia reductions of ketones has its origins linked with those of conformational analysis [4], through the stereochemical outcome, and is summarized below as *Mechanism A*. Accordingly, the reductions proceed *via* the sequence, 1) electron transfer (ketone→ketyl), 2) proton transfer (from a proton source, ketyl→ketyl radical), 3) electron transfer (ketyl radical→hydroxycarbanion) and, 4) proton transfer (hydroxycarbanion→alcoholate anion or alcohol). The stereochemical outcome is explained by postulating that the pyramidal, diastereoisomeric ketyl radicals and/or hydroxycarbanions equilibrate *via* inversion (the ketyls are probably planar), that their thermodynamic stabilities parallel those of the corresponding alcohols, and that the equilibrium populations are trapped by reduction or protonation, respectively[2]). Pinacol coupling, which often competes with the reduction to give the alco-

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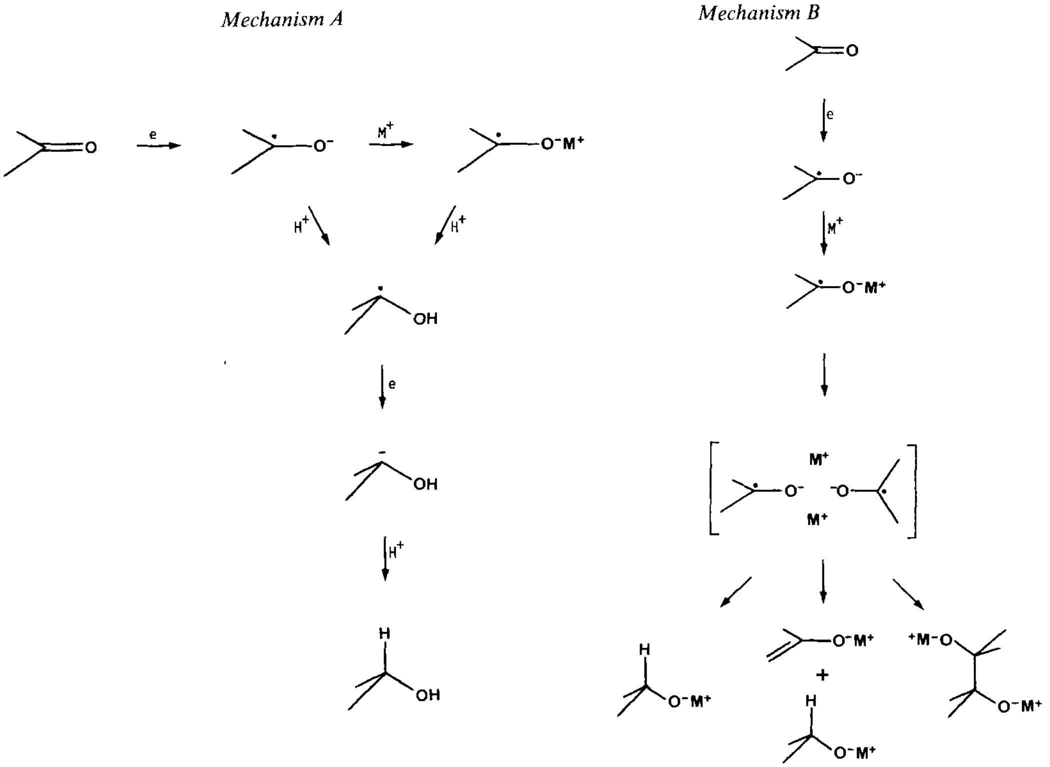
[2]) Another proposal is that the protonation rates of the rapidly interconverting hydroxycarbanions determine the product ratios [1].

hol(s), is rationalized by postulating that the ketyls and/or the ketyl radicals dimerize to some extent, giving pinacolates and/or pinacols.

Mechanism A implies that pinacol coupling should be the main reaction when the first protonation step is slow but the bulk of published work[3]) appears to contradict this conclusion. The substrates always appear to be partially or completely transformed into the corresponding alcohols, regardless of whether proton sources of widely differing acidities (pK_A: alcohols 16–19, water 15.74, ammonium ion 9.24) are present or not (pK_A of ammonia: 34).



1.2. *Ketyl disproportionation.* We resolved this contradiction between theory and experiment *(1.1)*. We found [6] that the textbook *Mechanism A* is normally not the dominant one. We examined the behaviour of a suitable ketone upon exposure to lithium, sodium or potassium in ammonia/THF at –75° and discovered that in the absence of proton sources, the main primary products are the corresponding alcoholate and the corresponding enolate, as a 1:1 mixture, pinacolates being only formed in sizeable amounts with lithium as the reducing agent. Deuterium labeling showed that the alcoholate/enolate mixture was formed *via* the transfer of a ^{2}H-atom from one of the C-atoms flanking the oxygen-bearing C-atom of one ketone or

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[3]) A comprehensive compilation of published work does not exist and we are unable to provide one here. The compilation by *Starr* [5a], the short reviews by *Dryden* [5b] and *Caine* [5c], and [1] and [4] provide a somewhat dated coverage of the literature.

ketyl unit to the oxygen-bearing C-atom of another ketone or ketyl unit. We also identified [6] a second, usually minor pathway by which a further fraction of alcoholate is formed and which seems to involve the transfer of a H-atom from the medium, *i. e.* from the ammonia and/or the THF, to the oxygen-bearing C-atom of a ketyl unit, in a way which is clearly different from that of *Mechanism A*.

The likeliest interpretation of our experiments [6] is that these transformations take place *via* the sequence formulated in *Mechanism B*. The gist of *Mechanism B* is that the ion-pairing and the association of the ketyl ion pairs are rapid and efficient and that the first associated species that can be formed, namely the ion quadruplets ("dimers"), rapidly undergo three intraionic (intramolecular) decay reactions which lead to the observed primary products.

We suggest that the two ketyl units that are associated within the ion quadruplet undergo intraionic dimerizations to give the pinacolates, and intraionic disproportionation(s) *via* the transfer of a H-atom from one unit to the other to give the alcoholate(s) and the enolate. The abstraction of a H-atom from the medium seems also to involve both ketyl units and a solvent molecule in the solvent shell. These hypothetical decay reactions correspond exactly to the dimerizations, disproportionations, and H-abstractions by which normal, uncharged radicals decay.

Furthermore, we found [6] that upon metal/ammonia reduction of the same substrate in the presence of massive amounts of alcohols (30–50 mol-equiv. of methanol or ethanol or *t*-butyl alcohol, normal addition), the three processes outlined above persist while *Mechanism A* may be competing inefficiently. The enolate formed by disproportionation, however, is protonated to give back the substrate (or its enol, see *2.4.1*), which is then reduced again.

The three reactions outlined above probably intervened in all previous experiments in which ammonia/co-solvent or ammonia/alcohol/co-solvent mixtures were used – probably the majority of all published work [5].

1.3. *Suppressing ketyl disproportionation and dimerization.* From the practical standpoint, the reactions interpreted in *Mechanism B*, and especially pinacol coupling (as a side reaction), are not desirable, while reduction *via Mechanism A* – were it feasable – is. We therefore now define conditions which suppress the reactions interpreted in *Mechanism B*, and which appear to render *Mechanism A* or a variant dominant. Two independent, convergent arguments suggest what these conditions should be.

To block *Mechanism B*, rapid protonations must be made to intervene after the first electron transfer, at the level of the free ketyl or of the ketyl ion pair (see *Mechanisms A* and *B*). The resulting ketyl radicals could then still undergo dimerizations and disproportionations, the latter of two kinds [7], but, having very low reduction potentials, should be rapidly reduced under conditions where the first electron transfer to the substrate takes place.

To our knowledge, kinetic studies of metal/ammonia reductions of ketones have not been carried out[4]); in particular, the rates of the critical proton transfers[4]) are

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[4]) For a kinetic study of the reactions of *N,N*-dimethylformamide and -acetamide with sodium in ammonia, see [8]. The dynamics of the equilibrium, ketyl radical + $OH^- \leftrightharpoons$ ketyl + H_2O, at about 20° (in water), were established for two simple cases [9].

unknown and difficult to estimate. Since the transformation(s) of the substrate into the corresponding alcohol(s) alsways took place, previous workers therefore concluded that one of the critical proton transfers (to the free ketyl, or to the ion pair, *etc.*) was always rapid enough.

Our results with alcohols as proton sources provide a qualitative calibration, showing that proton transfers from the alcohols to the ketyls – if they take place at all – are slow with respect to the reactions interpreted in *Mechanism B* – which provides an alternative pathway for the overall reduction. This calibration can then be coupled with a thermodynamic argument. Basically, the only way to increase the rates of the critical proton transfers is to make them thermodynamically more favorable. The pK_A values of ketyl radicals (11–12) are about five units lower than those of the alcohols with a C–H bond in place of the radical site [10]. Ketyl radicals are thus much stronger acids than alcohols and a proton transfer from an alcohol to a ketyl to give the ketyl radical (see *2.5.7*) is thus thermodynamically unfavorable and kinetically slow with respect to the reverse step [9]. Parenthetically, we note that on the same basis, the protonation of the ketyls by ammonia itself (pK_A 34) which has sometimes been postulated (to complete the stoichiometry, see *1.1*), can be assumed to be negligibly slow. For more rapid protonations, stronger acids than alcohols (pK_A 16–19) must be used^5) and there are only two reasonable choices; water (pK_A 15.74) must be tried although it is still a weaker acid than the ketyls but the best possible choice is ammonium ion (pK_A 9.24). Because of the leveling effect of the medium, this is the strongest acid that is available in ammonia.

Both water and ammonium chloride have been used as proton sources [1] [5] (see *1.1*), but rarely, and it is clear why. The rates of the ill-understood reactions between solvated electrons and proton sources to give molecular hydrogen appear to be roughly proportional to their acidities, and therefore presumably reach their upper limits in the case of ammonium ion. The reaction with ammonium chloride is indeed rapid and is usually used to destroy unreacted dissolved metal before work-up.

The disproportionation of ketyls as interpreted in *Mechanism B* only becomes evident when the substrates have a deuterium or tritium label in the α-position(s) and, to the best of our knowledge, such substrates have not been used previously. Published results with unlabeled substrates can nevertheless be evaluated on the basis of *Mechanism B* requiring that ketyl dimerization and disproportionation be jointly suppressed. Proton sources in whose presence pinacol coupling was reported to be suppressed may therefore be taken to block *Mechanism B* and to render *Mechanism A* dominant. *Murphy & Sullivan* [12g] reported that pinacol coupling of the substrate used in the present work is suppressed in the presence of ammonium ion. Further discussion of this result is postponed (see *2.5.1*).

The present work confirms these conclusions and demonstrates again that the reactions interpreted in *Mechanism B* intervene in the presence of weaker acids.

1.4. *Substrate.* We used (+)-camphor (**1**) as the substrate, because of the results of *Murphy & Sullivan* (see *1.3*), because camphor is an established ketonic model

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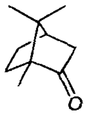
^{5}) An entropic counterpart, namely, to use a weak, intramolecular proton source in combination with a still weaker, external proton source in the medium, may also be feasable. For a possible example, see [11].

substrate from which diastereoisomeric alcohols can be formed and most methods[6]) for reducing a ketone to the corresponding alcohol(s) have been tried with it, and because two groups (*Ourisson-Rassat-Coulombeau* [12a, b, d, e] and *Murphy-Sullivan* [12f, g]) reported that the stereochemical outcome of the metal/ammonia reduction of **1** is abnormal under certain conditions, the thermodynamically less stable diastereoisomeric alcohol being formed predominantly, a finding which evoked considerable interest and discussion at the time, and which was contested by a third group (*Huffman-Charles-McWhorter* [12c, h]).



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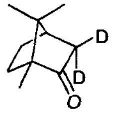
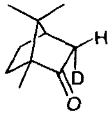
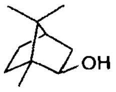


[3,3-$^{2}H_{2}$]**1**



[*endo*-3-^{2}H]**1**



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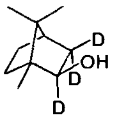
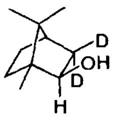
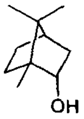


[2,3,3-$^{2}H_{3}$]**2**



[3,3-$^{2}H_{2}$]**2**



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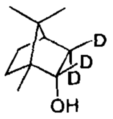
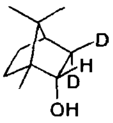
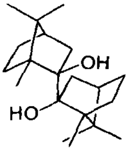


[2,3,3-$^{2}H_{3}$]**3**



[3,3-$^{2}H_{2}$]**3**



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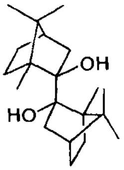

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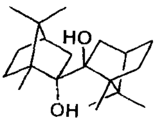

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[6]) The following procedures related to metal/ammonia reductions were reported. *Bouveault-Blanc* reduction (**1**, sodium in ethanol) [13a], addition of a solution of (±)-camphor in DEE/*t*-butyl alcohol to a solution of lithium, sodium or potassium in hexamethylphosphoramide (HMPA)/DEE and treatment of the resulting mixture with aqueous HCl-solution [13b], addition of (–)-camphor to a suspension in THF of potassium intercalated in graphite, followed in addition of water to the resulting suspension [13c], electrochemical reduction of **1** [or (–)- or (±)-camphor] in 2-propanol containing tetraethylammonium *p*-toluenesulfonate [13d] or in HMPA/ethanol containing lithium chloride [13e].

Reduction of **1** can lead to (–)-isoborneol (**2**) and (+)-borneol (**3**) [14]. In the earlier reports, alkali metals in ammonia and a co-solvent alone [12] or in combination with ethanol [12a, c], *t*-butyl alcohol [12a, c] or ammonium chloride [12a, c, g] were used for reduction. ΔH and ΔS for the equilibrium between **2** and **3** are known [15] and **2**/**3** is calculated to be 29:71 at 100°, 16:84 at –33°, and 11:89 at –75°.

Defining conditions which apparently render *Mechanism A* dominant, with **1** as the substrate, establishes the stereochemical outcome under these conditions, and whether it is in fact in agreement with the textbook explanation (see *1.1*).

1.5. *Strategy.* We first show that the reactions observed with the previously used substrate [6] also take place with a labeled derivative of **1**, both under the conditions used in our previous report and those in the published work with camphor [12]. These reactions are best observed in ammonia/co-solvent media alone and in much of the previous work with camphor, such media were in fact used. We thus first establish the behaviour of **1** upon metal/ammonia reduction in these media, then in media containing water, and finally in a medium containing ammonium chloride. We only employ the commonly used alkali metals, lithium, sodium and potassium.

1.6. *Labeling.* To detect the disproportionations and distinguish them from the reactions with the medium *(Mechanism B)*, the labeled (+)-camphor, [3,3-$^2H_2$]**1** [16], was used as the substrate[7]). Two overall disproportionation pathways can then be distinguished: one gives the alcoholate of (–)-[2,3,3-$^2H_3$]isoborneol, c-([2,3,3-$^2H_3$]**2**)$^-$ M$^+$[8]), and the enolate of [3,3-$^2H_2$]**1**, c-([3-^{2}H]**1**)$^-$M$^+$, the other gives the alcoholate of (+)-[2,3,3-$^2H_3$]borneol, c-([2,3,3-$^2H_3$]**3**)$^-$M$^+$and again the enolate c-([3-^{2}H]**1**)$^-$M$^+$. These pathways are formulated in *Mechanism C* which is a reformulation of the general *Mechanism B*. The use of this substrate thus permits the observation of the stereochemical outcome of the ketyl disproportionations at the termini – but not at the starting points – of the migrations of the ^{2}H-atoms[7]).

The products and the stereochemical course of the reactions with the ammonia and/or the co-solvent *(Mechanism B)* can be fully identified. There are again two pathways, which now lead to the alcoholates of (–)-[3,3-$^2H_2$]isoborneol, c-([3,3-$^2H_2$]**2**)$^-$M$^+$, and of (+)-[3,3-$^2H_2$]borneol, c-([3,3-$^2H_2$]**3**)$^-$M$^+$, and which are also depicted in *Mechanism C*.

Pinacol coupling of [3,3-$^2H_2$]**1** can in theory lead to three diastereoisomeric pinacols, namely [3,3,3′,3′-$^2H_4$]**4**, [3,3,3′,3′-$^2H_4$]**5**, and [3,3,3′,3′-$^2H_4$]**6**, with the hydroxyl groups in the *exo,exo-*, *exo,endo-*, and *endo,endo*-positions. Two unassigned diastereoisomers were reported[9]) and we also found only two, namely [3,3,3′,3′-$^2H_4$]**4** and [3,3,3′,3′-$^2H_4$]**5**, and *Mechanism C* depicts their dialcoholates. Structure assignments are postponed (see *2.2.3*).

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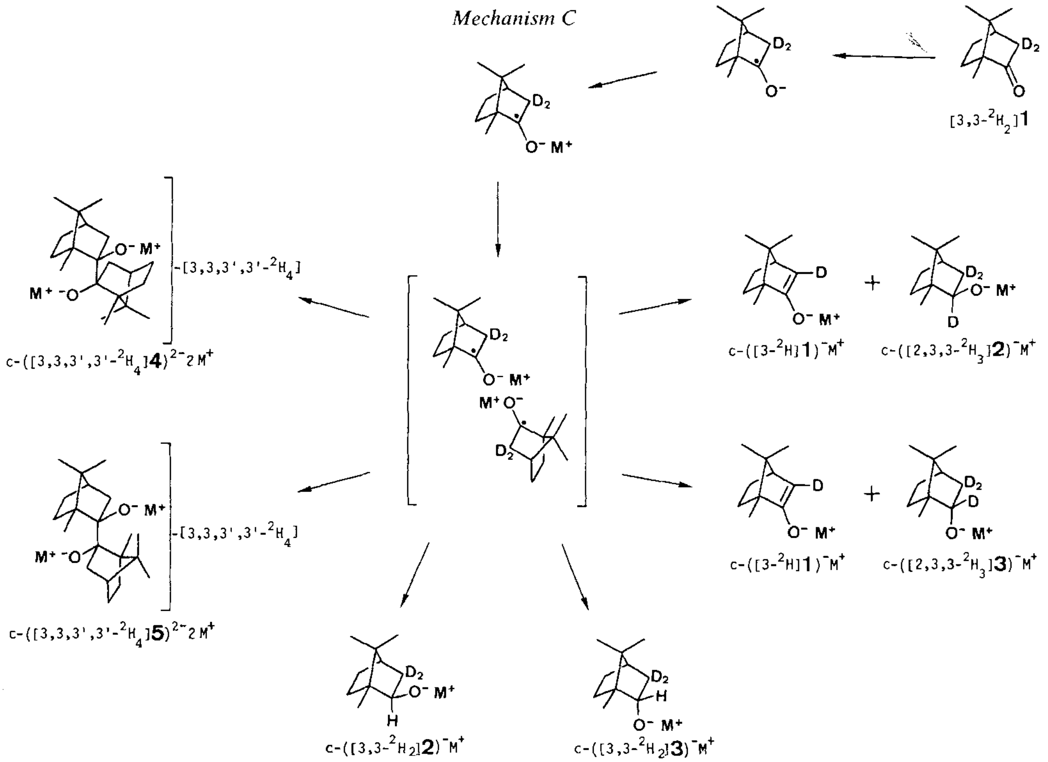
[7]) In principle, a complete stereochemical analysis of the disproportionations can be made by using [*exo*-3-^{2}H]**1** and [*endo*-3-^{2}H]**1** as additional substrates, and correcting for the overall $k_H/k_{^2H}$.

[8]) The prefix c-designates the conjugate bases, – the enolate, alcoholates, and pinacolates – derived from the camphors, isoborneols, borneols, and pinacols, respectively.

[9]) a) Reaction of metallic sodium with a solution of **1** in DEE and subsequent treatment of the resulting mixture with water gave a single (?) camphor pinacol, m.p. 157–158° [17a]; b) addition of a solution of **1** or (–)-camphor in DEE to a solution of sodium in ammonia and subsequent treatment of the resulting mixture with methanol and water led to the same (?), single (?) pinacol or the enantiomer, m.p. 157° [17b]; reaction of metallic lithium with a solution of **1** in ammonia/DEE and treatment of the resulting mixture with water gave a second, single (?) (–)-pinacol, m.p. 114–115° [12f, g].

Mechanism C



1.7. *Protonation of the alcoholates, the pinacolates and the enolate; $^2H/H$ exchange in the substrate; results concerning the exchange and the protonation of the enolates.* At some stage of our experiments, the alcoholates, the pinacolates, and the enolate formed as outlined in *Sect. 1.6 (Mechanism B/C)* are protonated to give the corresponding alcohols, pinacols, and ketone, which are then isolated.

We used two types of media, namely ammonia with a co-solvent, and ammonia with a co-solvent and a proton source – ethanol, water or ammonium chloride. In the former, the acid/base equilibria with ammonia, the strongest acid in these systems, lie largely on the side of the alcoholates, the pinacolates, and the enolate, which should therefore accumulate in the course of the experiments – barring exchange in the enolate *via* protonation and dedeuteronation for the moment (see below) – and only be protonated at the end, when ammonium chloride is added for this purpose. In the latter, the acid/base equilibria with the proton sources lie largely or completely on the side of the alcohols, the pinacols, and the ketone, and their conjugate bases should therefore be protonated *in situ*, soon after they are formed.

In the case of the alcoholates and the pinacolates, the timing of these protonation steps is of no particular importance because the alcoholates[10]) and the pinaco-

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[10]) *Meerwein-Ponndorf-Verley* equilibrations between alkali metal alcoholates and ketones, expected to occur only at much higher temperatures [1] [18], are excluded by the data in *Table 1*. Exposure of c-**2**⁻Li⁺ and/or c-**3**⁻Li⁺ to lithium in ammonia/DEE at –33.5° was reported to give traces of bornane [12g]; we did not investigate these deoxygenations under our conditions.

lates[11]) as well as the corresponding conjugate acids are essentially inert under the conditions of the experiments, and because the outcome of these protonations is evident; each gives a single product. In the case of the enolates c-([3-^{2}H]**1**)$^-$M$^+$, however, the timing of the protonation affects the outcome of the experiment because the resulting ketone (or enol, see *2.4.1*) is not stable under the conditions of the experiment. Protonation of the enolate in solution, in ammonia and a co-solvent, on addition of ammonium chloride at the end of the experiment should give [^{2}H]camphors that can be isolated. The same [^{2}H]camphors should be formed *in situ* in the media containing a proton source and then be reduced again. Moreover, the protonation of the enolates can in principle lead to two [^{2}H]camphors; this is discussed further on.

This problem of the timing and of the stereochemical course of the protonation of the enolate is directly related to another, namely that of the stability of the substrate itself. The disproportionations *(Mechanism B/C)* can only be observed if the substrate – and its enolate – do not lose their label(s) in the course of the experiment. In principle, [3,3-^{2}H$_2$]**1** can undergo base-catalyzed ^{2}H/H exchange[12]) and the enolate c-([3-^{2}H]**1**)$^-$ which is independently generated by disproportionation, is also the intermediate that would be formed during such exchange.

To our knowledge, base-catalyzed exchanges in ketones in general and in **1** and [3,3-^{2}H$_2$]**1** in particular, in ammonia (N^{2}H$_3$, NH$_3$), have not been studied. *Shatenshtein* [21] demonstrated, however, that exchanges involving carbanion intermediates are rapid in ammonia when “uncatalyzed” and are catalyzed by alkali metal alcoholates and especially efficiently by alkali metal amides. The exchange rates are such that exchanges in much weaker C-acids than ketones were examined. Solutions of the alkali metals in ammonia inevitably decompose to some extent to give the alkali metal amides and molecular hydrogen. Moreover, the very reactions of *Mechanism C* produce alcoholates and pinacolates. The species that catalyze exchange are thus present in ammonia/co-solvent media; they are not present in the media buffered by water or ammonium ion.

To our knowledge, our previous experiments [6] provided the first pertinent results. Exchange in the substrate used there and in the derived enolate, on alkali metal/ammonia reduction at –75°, was slow enough to maintain the integrity of the label(s) in the substrate and its enolate.

Both alkali metal deuteroxide-catalyzed H/^{2}H exchange between deuterium oxide and **1** and alkali metal hydroxide-catalyzed ^{2}H/H exchange between water and [3,3-^{2}H$_2$]**1** have been investigated thoroughly [22] and we extrapolate from these studies. That this is sound is justified by our findings.

In water and deuterium oxide, exchange at the 3-*exo* position is much more rapid than at the 3-*endo* position. Both key steps of the exchange must therefore preferentially involve the 3-*exo* position. In the case of [3,3-^{2}H$_2$]**1**, a deuteron must be pref-

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[11]) Pinacol coupling of saturated ketones *via* the reduction by alkali metals is irreversible [19].

[12]) Direct dedeuteronation of [3,3-^{2}H$_2$]**1**, presumably coupled with evolution of molecular ^{2}HH or ^{2}H$_2$, by analogy to [13b] and [20] apparently does not take place in metal/ammonia reductions.

erentially abstracted from the 3-*exo* position to give the enolate c-([3-^{2}H]**1**, to which a proton must then be delivered in such a way that it ends up preferentially in the 3-*exo* position [23].

By analogy, base-catalyzed exchange in [3,3-$^2H_2$]**1** in ammonia should lead rapidly to [*endo*-3-^{2}H]**1** and then slowly to **1** and protonation of the enolate c-([3-^{2}H]**1**$^-$, generated independently, by disproportionation or otherwise, should also lead to [*endo*-3-^{2}H]**1**.

It turns out that exchange in [3,3-$^2H_2$]**1** can be minimized or avoided if precautions are taken but [3,3-$^2H_2$]**1** appears to be more susceptible to exchange than the substrate we used previously. It is necessary to carry out the reductions at –75° and when sodium and potassium are the reducing agents, only the normal addition mode is feasable[13]). Furthermore, the metals must be used in less than stoichiometric amounts and even then, some exchange is unavoidable when potassium is the reducing agent. When lithium is the reducing agent, exchange does not occur when it is used in modest excess – up to four mol-equiv. which, however, suffice to effect complete conversion of the substrate – in either addition mode.

Using these precautions (the procedure is fully specified in *2.2.1*), the reductions in media not containing a proton source and subsequent quenching with ammonium chloride at the end led to [*endo*-3-^{2}H]**1** only (see *2.2.2*). Appropriate book-keeping (see *2.2.5*) shows that it must have been formed exclusively or largely by disproportionation and protonation. It must thus have been formed by protonation of the enolates c-([3-^{2}H]**1**)$^-$M$^+$ (M$^+$ = Li$^+$, Na$^+$, K$^+$)[14]) by ammonium ion[15]) at the end of the experiments and the stereochemical course of these protonations is the one observed in the exchange experiments in water and deuterium oxide. This in turn justifies the assumption that base-catalyzed exchange between [3,3-$^2H_2$]**1** and ammonia (which involves sodium and potassium amides or alcoholates or pinacolates as the bases and ammonia as the acid) shows the same stereochemical preference.

1.8. *Distinction between isoborneols and borneols formed* via Mechanisms, A/D *and* B/C. The products ([3,3-$^2H_2$]**2**, [3,3-$^2H_2$]**3**) and the product ratios in the reaction with the medium interpreted in *Mechanism B/C* (see *1.6*) can be determined because the ammonia/co-solvent media alone can be used. In the derived media containing proton sources, *Mechanisms A* and *B/C* may compete. Reduction of [3,3-$^2H_2$]**1** *via Mechanism A* is reformulated in *Mechanism D* and leads to the same isoborneol ([3,3-$^2H_2$]**2**) and borneol ([3,3-$^2H_2$]**3**) as does *Mechanism B/C*. The ratios of the two may differ. The pathways can be distinguished if they do and by reference to the other products formed *via Mechanism B/C*.

2. Results. – 2.1. *(+)-[3,3-$^2H_2$]Camphor.* Samples containing *ca.* 97% of [3,3-$^2H_2$]**1** and *ca.* 3% of {[^{2}H]**1**}[16]), mainly [*exo*-3-^{2}H]**1** (see 1.7), obtained by a single, complete, sodium deuteroxide-catalyzed exchange in deuterium oxide under somewhat forc-

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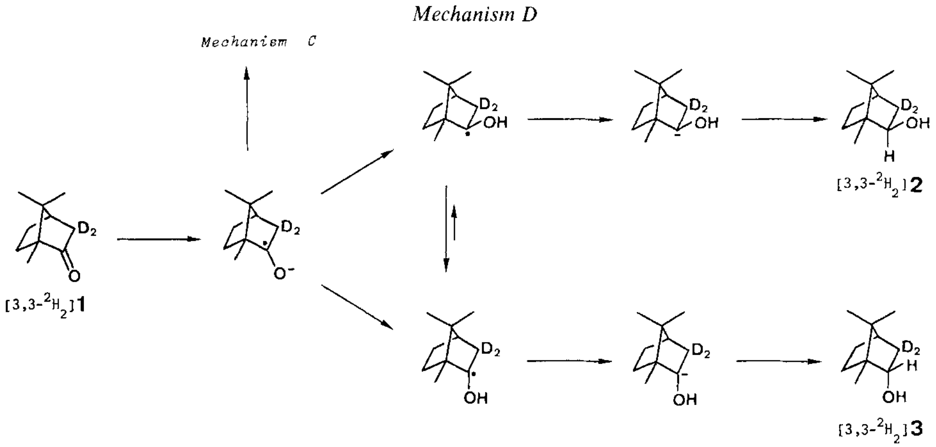
[13]) Exposure of the substrate to the alkali metal amides is minimized in the normal addition mode.

[14]) The experiments were carried out for M$^+$ = Li$^+$, Na$^+$.

[15]) To our knowledge, no such direct protonation experiments – treatment of the enolates with acids – have been reported with any of the ketones that show base-catalyzed, unsymmetrical exchange.

[16]) Brackets { } designate unseparated mixtures of differently labeled isomers derived from a single substrate and containing the same or different numbers of ^{2}H-atoms located at C(2) and/or C(3).



ing conditions [22] (see *4.6*), were used[17]). The ^{2}H-content was determined by low resolution mass spectrometry (MS., estimated analytical error ±3%, molecular ion intensities (see *4.10* and *4.11.1*)). The location of the labels[18]) was confirmed by 360-MHz-^{1}H-FT- and ^{1}H noise-decoupled 55.28-MHz-^{2}H-FT-NMR. spectrometry. The ^{2}H-NMR. spectrum (*Fig. 1*) was primarily recorded in order to be able to contrast it with the ^{2}H-NMR. spectra of the derived {borneols} (see *2.2.2.2* and *2.5.4.2*). In most experiments, the impurity in the substrate was neglected.

2.2. *Experiments in ammonia/THF.* These experiments with [3,3-$^2H_2$]**1** and **1** provide the link to the earlier, more elaborate set of experiments with a different substrate [6]. The experimental procedure was essentially the same[19]). The results of the experiments with [3,3-$^2H_2$]**1** are summarized in *Table 1*.

2.2.1. *Procedure* (see 4.7 for further details). – *Normal addition.* Lithium, sodium or potassium in the amounts indicated in *Table 1* was added to stirred solutions[19]) [20]) of 1 mmol of [3,3-$^2H_2$]**1** in 35 ml of ammonia and 6 ml of THF (*ca.* 0.024 M), at –75° under Ar. The metals, added at once as one or two pieces dissolved/reacted in *ca.* 10 min in/with the stirred solution (–75°), leaving a blue-black trail of dissolved, rapidly reacting metal (decoloration). A fine white precipitate appeared when most of the metal had reacted. In runs 1, 2 and 9 to 11, the amount of metal was adjusted[21]) in such a way that the metals dissolved/reacted without a blue solution ever being formed and on complete disappearance of the metal excess solid ammonium chloride was immediately added to the resulting mixture (–75°). In runs 3 and 4, a blue solution of lithium was formed which lost its color upon additional stirring (–75°, total time *ca.* 10 min) when excess ammonium chloride was again added to the resulting mixtures. In runs 6 (carried out on thrice the normal scale), 7 and 8, dark-blue solutions of lithium were obtained which were treated with excess ammonium chloride after 7 to 12 min (total time).

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[17]) In the following, these samples are referred to as [3,3-$^2H_2$]**1**.

[18]) Exchanges at positions other than C(3), *via* homoenolates as intermediates [24], expected to take place only at much higher temperatures, are thus excluded.

[19]) The initial concentration in [3,3-$^2H_2$]**1** in the experiments in the normal addition mode was somewhat lowered because [3,3-$^2H_2$]**1** is somewhat less soluble than the substrate previously used.

[20]) The solution was homogeneous as judged visually.

[21]) By trial and error. Lithium and sodium were weighed in the air and potassium in mineral oil. The potassium was then rinsed in THF. The weighing is not accurate and the amounts given in the *Tables* are approximate. The rate of the reaction of the solvated electrons with the ammonia to give molecular hydrogen seems to vary from run to run when the same metal is used, and varies strongly when different metals are used.

Table 1. *Reaction of (+)-[3,3-^{2}H$_{2}$]camphor with alkali metals in ammonia/THF at –75°; camphors, isoborneols, and borneols obtained after treatment with ammonium chloride and work-up*

Run		1	2	3	4	5	6	7	8	9	10	11
Metal mol-equiv. Addition mode		Li 0.8 normal	Li 0.8 normal	Li 1.0 normal	Li 0.9 normal	Li 1.2 inverse	Li 2.9 normal	Li 3.0 normal	Li 4.0 normal	Na 0.8 normal	K 1.1 normal	K 0.7 normal
Weight %, ± 1–2%	{[3,3-^{2}H$_{2}$]**1**, [*endo*-3-^{2}H]**1**}	62	78	42	71	55	39	28	38	56	69	84
	{[2,3,3-^{2}H$_{3}$]**2**, [3,3-^{2}H$_{2}$]**2**, [^{2}H]**2**}	10 27	5 21	13 23	7 25	10 22	12 19	13 18	13 20	19 44	20 64	10 64
	{[2,3,3-^{2}H$_{3}$]**3**, [3,3-^{2}H$_{2}$]**3**, [^{2}H]**3**}	28 73	17 79	45 77	22 75	35 78	49 81	59 82	49 80	25 56	11 36	6 36
Mol fraction in %, ± 3%	[3,3-^{2}H$_{2}$]**1**	69	82	–	80	39	–	–	–	63	42	75
	[*endo*-3-^{2}H]**1**	31	18	100	20	61	100	100	100	37	58	25
	1	–	–	–	–	–	–	–	–	–	–	–
Mol fraction in %, ± 3–5%	[2,3,3-^{2}H$_{3}$]**2**	75	86	91	68	90	82	81	86	65	77	85
	[3,3-^{2}H$_{2}$]**2**	25	14	9	27	10	18	19	14	31	23	15
	{[^{2}H]**2**}	–	–	–	5	–	–	–	–	4	–	–
Mol fraction in %, ± 3–5%	[2,3,3-^{2}H$_{3}$]**3**	72	78	88	61	81	81	69	86	58	63	78
	[3,3-^{2}H$_{2}$]**3**	28	22	12	34	13	13	20	14	37	32	22
	{[^{2}H]**3**}	–	–	–	5	6	6	11	–	5	5	–
Mol fraction in %, ± 5–8%	[*endo*-3-^{2}H]**1**	34 42	40 46	43 45	35 45	43 48	44 48	30 36	40 44	33 44	58 65	58 62
	[2,3,3-^{2}H$_{3}$]**2**	13 16 28	11 12 22	12 13 23	12 15 27	11 12 24	10 12 22	11 13 21	9 10 18	20 27 47	21 24 64	23 25 66
	[2,3,3-^{2}H$_{3}$]**3**	35 42 72	36 42 78	39 42 78	31 40 73	36 40 76	37 40 78	43 51 79	43 46 82	23 29 53	10 11 36	12 13 34
	[3,3-^{2}H$_{2}$]**2**	5 25	2 15	1 18	5 21	1 13	2 24	3 18	1 18	9 40	6 56	4 56
	[3,3-^{2}H$_{2}$]**3**	13 75	11 85	5 82	17 79	9 87	7 76	13 82	7 82	15 60	5 44	3 44

Inverse addition. In run 5, 1.2 mmol of lithium was dissolved with stirring in 35 ml of ammonia and 3 ml of THF at –75° under Ar and a solution of 0.95 mmol of [3,3-$^2H_2$]**1** in 2.9 ml of THF was added dropwise over a period of 36 min to the stirred, blue-black, opaque mixture, up to the moment when the blue color disappeared („titration", almost all of the solution (3 ml) of the weighed-in substrate (1 mmol) had been added) whereupon excess ammonium chloride was added.

Evaporation of the ammonia, addition of water, and work-up (see *4.7*) afforded crude isolates consisting of mixtures of {camphors}[16]), {isoborneols}, {borneols}, and pinacols.

2.2.2. *Product analyses.* – 2.2.2.1. *Gas chromatography (GC.), distillation, column chromatography.* The crude isolates were first analyzed by GC. (see *4.2*) which gives the proportions (weight %) in which the mixtures of camphors, {[3,3-$^2H_2$]**1**, [*endo*-3-^{2}H]**1**}[16]), isoborneols, {[2,3,3-$^2H_3$]**2**, [3,3-$^2H_2$]**2**}, and borneols, {[2,3,3-$^2H_3$]**3**, [3,3-$^2H_2$]**3**}, each in turn an unseparated (see *4.10*) mixture consisting of (mainly, see below) two differently labeled isomers, were present in the crude isolates. *Table 1* (first entry) gives the proportions of the above components and also the corresponding {isoborneol}/{borneol} ratios (estimated analytical error ± 1–2%).

In the reductions with lithium, the pinacol [3,3,3′,3′-$^2H_4$]**5** was a major product and the pinacol [3,3,3′,3′-$^2H_4$]**4** was formed in traces and the reductions with sodium, both were formed in small amounts. Determination of the proportions of these pinacols in the crude isolates by GC. was sometimes grossly unreliable and this problem could not be resolved. Approximate yields of the pinacols based on the analyses by GC. (see *4.2*), isolation by distillation (see *4.8*), and chromatography (see *4.9*) are given later (see *2.2.3*) since they must be related to the other reaction modes which must be unraveled first.

After distillation (see *4.8*) – material balances were 75 to 95% – analytical samples of the {camphors}, {isoborneols}, and {borneols} were isolated. In all runs, this was done by preparative GC. (see *4.2* and *4.10*) and in one run also by column chromatography (see *4.9*). The pinacols were isolated by the same techniques.

2.2.2.2. *Mass and NMR. spectrometry.* The compositions of each of these mixtures isolated by GC. or chromatography (see *2.2.2.1*), of the {camphors}, {isoborneols}, and {borneols}, were then determined as follows. Low resolution MS. was used in every run. This provides accurate ratios of isomers differing in ^{2}H-content ([$^2H_0$], [^{2}H], *etc.*) but does not readily indicate the location(s) of the ^{2}H-atom(s) and therefore does not readily distinguish between positional isomers containing the same number of ^{2}H-atoms. ^{1}H-NMR. spectrometry was therefore employed in addition in the majority of runs. It permits the location of the ^{2}H-nuclei – they give no signals and the spectra must be correlated with those of the unlabeled series – but is less accurate. This means in particular that it cannot detect small amounts of deuterium at C-atoms other than C(2) and C(3) (see below). ^{2}H-NMR. spectrometry was therefore used in one case. This would be the best method – it shows (only) the ^{2}H-nuclei and their locations directly – were it not also the most expensive one[22]). The results of the analyses by all three methods were consistent with each other. This ensures that the data obtained by MS. only, or by MS. in combination with ^{1}H-NMR. spectrometry only, are reliable.

{*Camphors*}. Analysis by MS. (using the molecular ion intensities (see *4.11.1*), estimated analytical error ± 3%) of the {camphor(s)} obtained in runs 3 and 6 to 8 showed that they consisted of [^{2}H]species – one or several positional isomers – only. 360-MHz-^{1}H-FT-NMR. spectrometry showed that they (and also one from a run with sodium not included in *Table 1*) consisted, within the larger analytical error of

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[22]) The cost (size of the sample, instrument and operator time) of the analyses increases in the order, low resolution MS., 360-MHz-^{1}H-, 55.28-MHz-^{2}H-NMR. spectrometry.

this method, of [*endo*-3-^{2}H]**1** only. The signals of the 3-*exo* and 3-*endo* H-nuclei in the 360-MHz-^{1}H-NMR. spectrum of **1** are well resolved and the spectra of the above samples lack the latter signal. We estimate that we would have detected *ca.* 5% of [*exo*-3-^{2}H]**1** in a mixture of the two[23]). Analysis of the {camphors} (see *4.11.1*) obtained in the other runs by MS. showed that they consisted of unreacted substrate and of [^{2}H]species. That again only one [^{2}H] species, [*endo*-3-^{2}H]**1**, was present, can be deduced from the experiments in which it was the only component and was confirmed by ^{1}H-NMR. spectrometry as above. *Table 1* (second entry) lists the compositions (mol fractions, in %) as obtained by MS. (estimated analytical error ± 3%).

{*Isoborneols*} *and* {*borneols*}. The analyses of the {isoborneols} and {borneols} by MS. were carried out by measuring the (M-CH$_3$)$^+$ fragment intensities (see *4.11.2*). In most runs, we found only [^{2}H$_3$]- and [^{2}H$_2$]-isoborneols and -borneols. In each case, MS. does not distinguish between one and/or several positional isomers. Both 360-MHz-^{1}H- (majority of runs) and ^{1}H noise-decoupled 55.28-MHz-^{2}H-FT-NMR. spectrometry (run 6, {borneols}) showed, in each case, within the larger analytical error of these methods, the presence of single [^{2}H$_3$]species, [2,3,3-^{2}H]**2** and [2,3,3-^{2}H$_3$]**3**, and of single [^{2}H$_2$]species, [3,3-^{2}H$_2$]**2** and [3,3-^{2}H$_2$]**3**. All signals in the 360-MHz-^{1}H-NMR. spectrum of borneol (**3**. in CDCl$_3$) are fully resolved and were assigned [25] and the absence of the signals of the 2-*exo*, 3-*exo*, and 3-*endo* H-nuclei in the case of [2,3,3-^{2}H$_3$]**3** and the presence of the signal of the 2-*exo* and the absence of the signals of the 3-*exo* and 3-*endo* H-nuclei in the case of [3,3-^{2}H$_2$]**3** is readily seen. Conversely, the signals of the 2-*exo*, 3-*exo*, and 3-*endo* ^{2}H-nuclei in the case of [2,3,3-^{2}H$_3$]**3** and the signals of the 3-*endo* and 3-*exo* ^{2}H-nuclei in the case of [3,3-^{2}H$_2$]**3** ({borneols} from run 6), and the absence of signals of ^{2}H-nuclei in other positions in the case of both are directly seen in the ^{2}H-NMR. spectrum[23]). The latter spectrum and that of the substrate are depicted in *Figure 1*.

The corresponding analyses of the {isoborneols} lead to strictly analogous conclusions but are less straightforward because the signals of the 3-*exo* and 3-*endo* H-nuclei in the 360-MHz-^{1}H-NMR. spectrum of **2** overlap with each other and with a further, unassigned signal. A full assignment was not made and we did not attempt to provide one but we identified the signals of the 3-*exo* and 3-*endo* H-nuclei from the spectra of reference samples of [*endo*-3-^{2}H]**2** and [3,3-^{2}H$_2$]**2**. The presence or absence of the signal of the 2-*endo* H-nuclei was readily established. These ^{1}H-NMR. spectrometric analyses are only qualitative.

Table 1 (third and fourth entries) lists the compositions of the {isoborneols} and {borneols} (mol fractions, in %) as obtained by MS. (estimated analytical error ± 3–5%).

In some of the runs (4 to 7, 9, 10), we found {[^{2}H]isoborneols} and/or {[^{2}H]borneols} in amounts that are in most cases only slightly larger than the estimated analytical error. We leave the corresponding structure(s) unassigned; we know that they have the ^{2}H-atom only at C(2) or C(3).

2.2.2.3. *Product compositions*. Combination of the data from the analyses by GC. (see *2.2.2.1*) with those from the analyses by mass and NMR. spectrometry (see *2.2.2.2*) gives the proportions of each individual component, the (unreacted) substrate and the five products (pinacols excepted), in the crude isolates. The proportions of the products, [*endo*-3-^{2}H]**1**, [2,3,3-^{2}H$_3$]**2**, [2,3,3-^{2}H$_3$]**3**, [3,3-^{2}H$_2$]**2**, and [3,3-^{2}H$_2$]**3**, expressed as mol fractions (in %), are listed in *Table 1* (fifth entry, estimated analytical error ± 5–8%). For convenience, the derived, equivalent proportions of the three products formed by disproportionation, [*endo*-3-^{2}H]**1**, [2,3,3-^{2}H$_3$]**2**, and [2,3,3-^{2}H$_3$]**3**, and two isoborneol/borneol ratios, [2,3,3-^{2}H$_3$]**2**/[2,3,3-^{2}H$_3$]**3** and [3,3-^{2}H$_2$]**2**/[3,3-^{2}H$_2$]**3** are also listed, each again expressed as mol fractions (in %).

2.2.3. *Pinacols* **4**(*[3,3,3',3'-^{2}H$_4$]***4**) *and* **5**(*[3,3,3',3'-^{2}H$_4$]***5**). The structures of the two pinacols formed (see *1.6* and *2.2.2.1*) can be assigned on the basis of the 360-MHz-^{1}NMR. spectra.

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[23]) Here and from here on, we neglect the possibility that small amounts of isomers having ^{2}H at C-atoms other than C(3) in the case of the {camphors} and other than C(2) and C(3) in the case of the {isoborneols} and {borneols} are present.

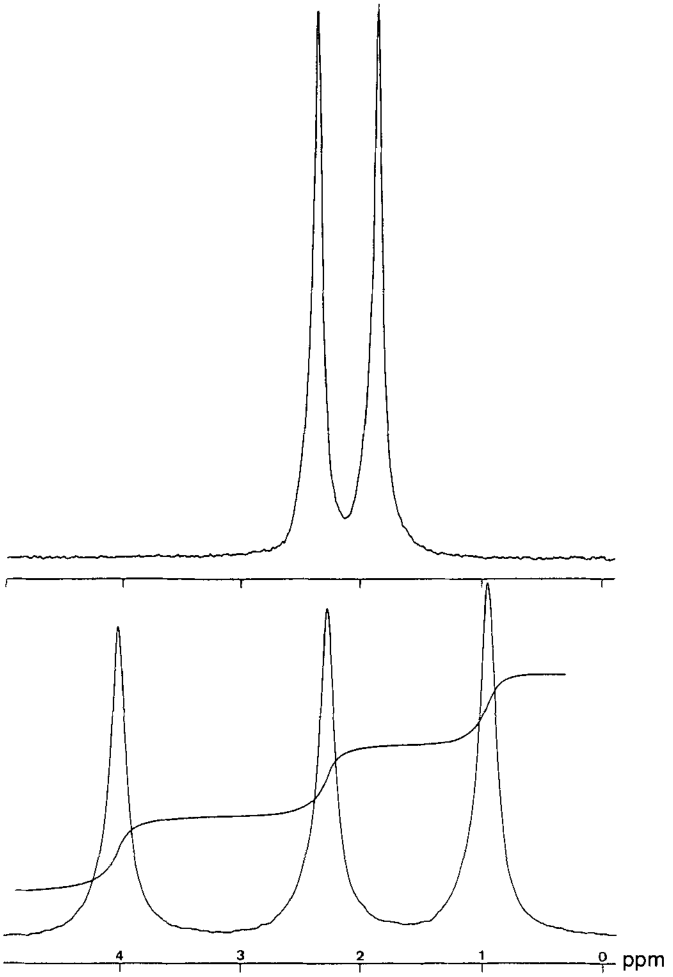

Fig. 1. *^{1}H-Noise decoupled 55.28-MHz-^{2}H-FT-NMR. spectra of [3,3-$^2H_2$]***1** *[above, 1,85 (3-*endo*-^{2}H), 2.35 ppm (3-*exo*-^{2}H)] and of the {borneols} from run 6 [below, 0.95 (3-*endo*-^{2}H), 2.25 (3-*exo*-^{2}H), 4.00 ppm (2-*exo*-^{2}H)]*

Both the unlabeled pinacols and the [$^2H_4$]-pinacols were characterized by their spectra and in each case the two sets of spectra were consistent with each other. The NMR. spectra of one pair of pinacols ([$^2H_0$], [$^2H_4$]) show three methyl signals. They therefore must have a C_2-axis and must possess either structure **4**([3,3,3′,3′-$^2H_4$]**4**) or structure **6**([3,3,3′,3′-$^2H_4$]**6**). The spectra resemble those of **2**([3,3-$^2H_2$]**2**) which have the hydroxyl group in the *exo*-position, and structure **4**([3,3,3′,3′-$^2H_4$]**4**), with both hydroxyl groups *exo*, can therefore be assigned to this pair, provided that extrapolation from the spectra of the alcohols to those of the pinacols is justified. That it is, is supported by the spectra of the other pair of pinacols which show approximately the signal patterns of **2**([3,3-$^2H_2$]**2**) and **3**([3,3-$^2H_2$]**3**) superimposed upon each other, and in particular, show five resolved methyl signals one of which corresponds to two methyl groups. These must be the unsymmetrical pinacols **5**([3,3,3′,3′-$^2H_4$]**5**), with an *exo* and an *endo* hydroxyl group. Pinacol **5**, m.p. 113–115°, was previously isolated by *Murphy & Sullivan* [12g], and pinacol **4**^{24}) may have been isolated by *Beckmann* [17a] and *Hückel et al.* [17b].

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^{24}) We did not isolate enough of **4**([3,3,3′,3′-$^2H_4$]**4**) to be able to determine a reliable m.p.

On the basis of erratic analyses by GC. and the yields of distilled and/or chromatographed material (see *2.2.2*), we estimate that in all runs with lithium, 0.3 mol ±0.1 mol of $[3,3,3',3'\text{-}{}^{2}\mathrm{H}_{4}]$**5** (or **5**) was formed per mol of $[3,3\text{-}{}^{2}\mathrm{H}_{2}]$**1** (or **1**) transformed *via* all three pathways[25]). Traces of $[3,3,3',3'\text{-}{}^{2}\mathrm{H}_{4}]$**4**(**4**) were formed in the runs with lithium; the ratios $[3,3,3',3'\text{-}{}^{2}\mathrm{H}_{4}]$**4**/$[3,3,3',3'\text{-}{}^{2}\mathrm{H}_{4}]$**5** (**4**/**5**), *ca.* 5:95, could be determined by GC. Both pinacols were formed in small amounts, in a *ca.* 50:50 ratio, in the runs with sodium.

2.2.4. *Experiments with unlabeled (+)-camphor.* The disproportionations proceed *via* the transfer of a ${}^{2}\mathrm{H}$-atom when $[3,3\text{-}{}^{2}\mathrm{H}_{2}]$**1** is the substrate and that of a H-atom when **1** is the substrate. The two should proceed at different rates and the latter are probably more rapid (overall, $k_{\mathrm{H}}/k_{{}^{2}\mathrm{H}}$ probably > 1 [6]). Product distributions could therefore differ depending on whether **1** or $[3,3\text{-}{}^{2}\mathrm{H}_{2}]$**1** is the substrate. That they do was shown by experiments with **1** parelleling those with $[3,3\text{-}{}^{2}\mathrm{H}_{2}]$**1** in the normal addition mode (see *2.2.1*), which are reported in *Table 2. Table 2* gives the proportions (weight %) in which **1**, **2**, and **3** were found in the crude isolates. In the runs with lithium, the (–)-isoborneol/(+)-borneol ratio (*Table 2*, **2**/**3** = (20–21):(80–79)) is similar to the {isoborneol}/{borneol} ratios found with $[3,3\text{-}{}^{2}\mathrm{H}_{2}]$**1** (*Table 1*, (18–27):(82–73)). In the runs with sodium, the ratios differ somewhat ((33–34):(67–66) *vs.* 44:56), and in the runs with potassium, markedly ((46–48):(54–52) *vs.* 64:36). As far as we can tell (see *2.2.3*) the yields and proportions of the pinacols **4** and **5** correspond to those observed for $[3,3,3',3'\text{-}{}^{2}\mathrm{H}_{4}]$**4** and $[3,3,3',3'\text{-}{}^{2}\mathrm{H}_{4}]$**5**.

Table 2. *Reaction of (+)-camphor with alkali metals in ammonia/THF at –75°; (+)-camphor, (–)-isoborneol, and (+)-borneol obtained after treatment with ammonium chloride and work-up*

Run		12	13	14	15	16	17
Metal mol-equiv.		Li 0.7	Li 0.8	Na 0.5	Na 0.8	K 0.7	K 0.7
Weight %,	**1**	72	87	70	53	70	71
± 1–2%	**2**	6 21	2 20	10 33	16 34	14 46	14 48
	3	22 79	11 80	20 67	31 66	16 54	15 52

2.2.5. *Summary and discussion.* The results in *Table 1* demonstrate that under the conditions used in our earlier study [6], $[3,3\text{-}{}^{2}\mathrm{H}_{2}]$**1** behaves exactly like the substrate used there. Ketyl disproportionation as outlined in *Sect. 1.2* and *1.6* is a major reaction when lithium is the reducing agent and the main one when sodium and potassium are the reducing agents. The ${}^{2}\mathrm{H}$-NMR. spectrum of the {borneols} isolated in run 6 (*Fig. 1*) strikingly illustrates the phenomenon. With all three metals, the reaction with the medium outlined in *Sect. 1.2* and *1.6* is a side reaction. With lithium, pinacols **5**($[3,3,3',3'\text{-}{}^{2}\mathrm{H}_{4}]$**5**) are the main products and pinacols **4**($[3,3,3',3'\text{-}{}^{2}\mathrm{H}_{4}]$**4**) are formed in traces. With sodium, both are formed in small amounts, and with potassium, pinacols are not formed[26]).

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[25]) *I. e.*, per mol of $[3,3\text{-}{}^{2}\mathrm{H}_{2}]$**1** consumed, *ca.* 0.4 mol was transformed into [*endo*-3-${}^{2}\mathrm{H}$]**1**, $[2,3,3\text{-}{}^{2}\mathrm{H}_{3}]$**2**, $[2,3,3\text{-}{}^{2}\mathrm{H}_{3}]$**3**, $[3,3\text{-}{}^{2}\mathrm{H}_{2}]$**2**, and $[3,3\text{-}{}^{2}\mathrm{H}_{2}]$**3**, and *ca.* 0.6 mol into $[3,3,3',3'\text{-}{}^{2}\mathrm{H}_{4}]$**5**.

[26]) The occurrence of pinacol coupling can apparently be correlated with the size of the alkali metal ions. This is reasonable: the larger the bridging metal ions in the ketyl "dimers" [7a] [6] are, the more difficult it is for the C-atoms C(2) of the ketyl units to approach each other.

The molar ratios [*endo*-3-^{2}H]**1**/([2,3,3-$^2H_3$]**2** + [2,3,3-$^2H_3$]**3**) should be 1:1 if [*endo*-3-^{2}H]**1** is formed exclusively *via* disproportionation and protonation and are (36–48):(64–52) (expressed in %, ±5–8%) in the runs with lithium and sodium (*Table 1*). A distinctly larger ratio, (62–65):(38–35), is found in the runs with potassium and this must be due to partial exchange in the substrate (see *1.7*).

The series of runs with lithium show that, in contrast to those with the previously used substrate, the product distributions vary somewhat from run to run. An possible explanation for which we did not attempt to provide experimental support is the following. The camphor ketyls are more sterically encumbered than those derived from the previously used substrate and the camphor-derived ion quadruplets could therefore have longer life times, of the order of minutes rather than seconds. This could have two consequences: association to give more highly associated species could occur, the intraionic decay reactions could then take place within several associated species and the extent of such association could vary from run to run; alternatively, a fraction of the associated ketyl species could survive up to the moment of quenching with ammonium chloride and the ketyl radicals formed by protonation could then undergo disproportionation to give [3,3-$^2H_2$]**1**, [3,3-$^2H_2$]**2**, and [3,3-$^2H_2$]**3** [7a].

Intuition led us to expect that ketyl dimerization would preferentially involve bond formation between the two units at their less hindered side, to give **4**([3,3,3',3'-$^2H_4$]**4**), but these are only formed in traces. It turns out that the main product, **5**([3,3,3',3'-$^2H_4$]**5**), is formed *via* the coupling of one ketyl unit at the less hindered side to another at the more hindered side.

2.3. *Published procedures.* – 2.3.1. *Procedure of* Huffman & Charles. We checked (see *1.5*) the reductions in ammonia/DEE alone [12c, h], using [3,3-$^2H_2$]**1** as the substrate and potassium as the reducing agent, because the contradictory reports on the stereochemical outcome (see *1.4*) mainly concern these experiments with this metal [12h]. The product distribution was determined in principle as in *Sect. 2.2.2* but is only qualitative in this case.

A solution of 1 mmol of [3,3-$^2H_2$]**1** in 3.5 ml of DEE was added over a period of *ca.* 1 min to the stirred, dark-blue, opaque mixture obtained by dissolving 50 mmol of potassium in 35 ml of ammonia (formally 1.43 M), at the temperature of boiling ammonia (–33.5°), under Ar. The resulting, dark-blue, opaque mixture was kept at reflux and stirred for 30 min when ethanol was slowly added until the blue color disappeared. Evaporation of the ammonia, addition of water and work-up afforded a mixture of {isoborneols} and {borneols}. These were analyzed ({isoborneols}/{borneols} = 56:44) and isolated by GC. as in *Sect. 2.2.2.1.* Each mixture was then analyzed by MS. as in *Sect. 2.2.2.2,* but without control by NMR. spectrometry. MS. showed, qualitatively, in each case, the presence of [$^2H_3$]-, [$^2H_2$]-, [^{2}H]-, and [$^2H_0$]-species; we were unable to determine the compositions quantitatively by MS. (see *4.11.2*). 360-MHz-^{1}H-NMR. spectrometry is not suitable for this task either, nor for making structural assignments. We therefore leave open structure assignments for the [^{2}H]- and [$^2H_2$]-species; we know that these species have the ^{2}H-atom at C(2) and C(3) only. The structures of the [$^2H_3$]- – by analogy to the previous series of experiments (see *2.2*) – and [$^2H_0$]-species can be assigned ([2,3,3-$^2H_3$]**2**, [2,3,3-$^2H_3$]**3**, **2**, **3**).

The qualitative analysis by MS. shows that disproportionation does take place, and furthermore, that [3,3-$^2H_2$]**1** undergoes exchange and the resulting [*endo*-3-^{2}H]**1** and **1** (see *1.7*) then react in a manner analogous to *Mechanism B/C* but presumably involving all three species with the proportions of the three changing in the course of the experiment; the enolate resulting from disproportionation may be protonated *in situ* by the ammonia or when ethanol is added, and the resulting ketone is then recycled.

We did not carry out a parallel run with **1** using this procedure, but did so using that of *Rassat et al.* (see *2.3.2*); according to *Huffmann* [12 h], the two procedures give the same results.

2.3.2. *Procedure of* Coulombeau & Rassat. We investigated the reductions without a proton source [12a, b, d, e] in more detail. The procedure is similar to that of

Huffman & Charles (see *2.3.1*), employing the same addition mode, temperature, and co-solvent, and a similar initial concentration of the substrate, but much less of the metal, namely five mol-equiv., which, however, is more than enough for complete conversion of the substrate[27]. For the reasons given in *Sect. 2.3.1*, we again only used potassium as the reducing agent in the experiments with [3,3-$^2H_2$]**1**. Product distributions were determined by using or adapting the methodology used before. The results are collected in *Table 3*.

Table 3. *Reaction of (+)-[3,3-$^2H_2$]camphor with potassium in ammonia/DEE at –35°; camphors, isoborneols and borneols obtained after treatment with ammonium chloride or ethanol and work-up*

Run		18		19		20	
Mol-equiv. of K		1.2		2.4		4.1	
Weight %,	{[3,3-$^2H_2$]**1**, [*endo*-3-^2H]**1**, **1**}	91		41		33	
± 1–2%	{[2,3,3-$^2H_3$]**2**, [$^2H_2$]**2**, [^2H]**2**}	6	62	40	68	44	66
	{[2,3,3-$^2H_3$]**3**, [$^2H_2$]**3**, [^2H]**3**}	3	38	19	32	23	34
Mol fraction in %,	[3,3-$^2H_2$]**1**	91		–		–	
± 3%	[*endo*-3-^2H]**1**	9		22		–	
	1	–		78		100	
Mol fraction in %,	[2,3,3-$^2H_3$]**2**	56		73		69	
± 3–5%	{[$^2H_2$]**2**}	34		15		14	
	{[^2H]**2**}	10		12		17	
Mol fraction in %,	[2,3,3-$^2H_3$]**3**	52		57		48	
± 3–5%	{[$^2H_2$]**3**}	37		17		13	
	{[^2H]**3**}	11		26		39	

Solutions of 0.5 to 1.2 mmol of [3,3-$^2H_2$]**1** in 2 to 3.5 ml of DEE were added (*ca.* 1 min) to stirred solutions obtained by dissolving 1 to 4 mol-equiv. of potassium in 35 ml of ammonia (formally 0.016 to 0.11 M), at 35°, under Ar. In run 20, 4 mol-equiv. of potassium was used; the solution was still blue when all the substrate had been added and was then stirred at –35° until the blue color disappeared (20 min) and then for another 10 min when 0.5 ml of ethanol was added. Less potassium was used in runs 18 and 19 and the solution became colorless before all of the weighed-in substrate had been added (the remaining substrate was not added, "titration"); the solutions were treated immediately with excess ammonium chloride once the color had disappeared. Evaporation of the ammonia, addition of water, and work-up afforded mixtures of {camphors}, {isoborneols}, and {borneols}.

Product distributions were then determined quantitatively as in *Sect. 2.2.2*, but without control by NMR. spectrometry. We found [$^2H_2$]-, [^2H]-, and [$^2H_0$]-camphors and [$^2H_3$]-, [$^2H_2$]-, and [^2H]-, but no [$^2H_0$]-isoborneols and -borneols by MS. In the case of the {camphors}, the structures of the [$^2H_2$]- and [$^2H_0$]-species, [3,3-$^2H_2$]**1** and **1**, are evident and the [^2H]species can be identified as [*endo-3*-^2H)**1** on the basis of the experiments in ammonia/THF (see *2.2*). In the case of the {isoborneols} and {borneols}, only the [$^2H_3$]-species can be assigned structures, [2,3,3-$^2H_3$]**2** and [2,3,3-$^2H_3$]**3**, again on the basis of the experiments in ammonia/THF (see *2.2*), while those of the [$^2H_2$]- and [^2H]-species must be left unassigned, although we again know that they have the ^2H-atoms at C(2) and C(3) only; complementary analyses of these probably complex mixtures by NMR. spectrometry are not possible. As in the runs with potassium in ammonia/THF at –75°, pinacols are not formed.

The camphors completely lose their label by exchange (see *1.7*) when four mol-equiv. of potassium are used, and the exchange can be slowed down by using less potassium. The ketyls disproportionate and the enolate c-([3-^2H]**1**)$^-K^+$ so formed is

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[27] We carried out the reductions at –35°, and used a maximum of 4 mol-equiv. of potassium (run 20) rather than 5 in the runs with [3,3-$^2H_2$]**1** in order to not have to quench the excess of potassium, used 5 mol-equiv. in the runs with **1** (run 23), and quenched with ethanol or ammonium chloride.

apparently partially protonated by the ammonia and the resulting [*endo*-3-^{2}H]**1** is then recycled.

2.3.3. *Experiments with unlabeled camphor.* We have also carried out parallel experiments with unlabeled **1**, using the procedure of *Coulombeau & Rassat* (see *2.3.2*) but in this case employing lithium, sodium, and potassium, in order to see whether the product distributions using potassium as the reducing agent and unlabeled or labeled substrate differ (see *2.2.4*), and whether we could reproduce the results in the literature. Our results are collected in *Table 4*. Contrary to the results in ammonia/THF at –75°, the (–)-isoborneol/(+)-borneol ratio observed with **1** as the substrate (59:41) is similar to the {isoborneol}/{borneol} ratio found with [3,3-$^{2}H_2$]**1** as the substrate (*Table 3*, (62–68):(38–32)) in the runs with potassium. In run 23 we used 5 mol-equiv. of potassium (blue solution, quench with ethanol)[27]). Runs 21 (colorless solution, quench with ammonium chloride) and 22 (blue solution, quench with ethanol) correspond to runs 19 and 20 *(Table 3)*, and runs 24 and 25 (colorless solutions, quench with ammonium chloride) are similar runs with lithium and sodium.

Table 4. *Reaction of (+)-camphor with alkali metals in ammonia/DEE at –35°; (+)-camphor, (–)-isoborneol, and borneol obtained after treatment with ammonium chloride or ethanol and work-up*

Run		21		22		23		24		25	
Metal mol-equiv.		K 1.6		K 3.9		K 5.1		Li 1.5		Na 1.5	
Weight %,	**1**	48		29		–		51		43	
± 1–2%	**2**	31	59	42	59	59		11	22	22	39
	3	21	41	29	41	41		38	78	35	61

The (–)-isoborneol/(+)-borneol ratios in *Table 4* are close to those reported by *Ourisson & Rassat* [12a] and by *Coulombeau & Rassat* [12b, e] and also by *Murphy & Sullivan* [12f, g] who used a similar procedure. *Huffman et al.* [12c, h] reported different ratios using their procedure (see *2.3.1*) which is also similar and that of *Ourisson, Rassat & Coulombeau*. The differences in the reported ratios are greatest in the reductions with potassium. (All three procedures do not use a proton source.)

We did not resolve this discrepancy despite our expectation that the phenomena uncovered in the present work might be responsible (treatment of the blue solution obtained upon reduction in ammonia/DEE with ethanol [12] leads to protonation of the enolate formed by disproportionation and the resulting **1** may then be reduced again). We have, however, demonstrated that ketyl disproportionation as interpreted in *Mechanism B/C* is the main reaction under the conditions used by *Rassat et al.* and by *Huffman et al.* (without a proton source) and we show below that when it is suppressed and the textbook *Mechanism A/D* is apparently dominant, a strikingly different product ratio is observed.

2.3.4. Bouveault-Blanc *reduction* [13a]. Compound [3,3-$^{2}H_2$]**1** underwent rapid exchange under *Bouveault-Blanc* conditions (sodium/propanol at reflux). Analysis by MS. showed recovered (+)-camphor to be unlabeled and the {isoborneols} and {borneols} – again only qualitatively – to consist of [$^{2}H_2$]-, [^{2}H]-, and [$^{2}H_0$]-, but not of [$^{2}H_3$]-species. The presence of the latter would have proved that disproportionation occurs. The rapid exchange precludes this test. An analogous reduction using lithium in place of sodium was therefore tried because the occurrence of pinacol coupling would have pointed indirectly to disproportionation taking place *(Mechanism B/C)* and because solutions of lithium in ammonia caused the least exchange in [3,3-$^{2}\mathrm{H}_{2}$]**1**. In the event, exchange but no reduction whatsoever was observed.

2.4. *Water as the proton source.* In two runs, [3,3-$^{2}\mathrm{H}_{2}$]**1** was reduced with lithium in ammonia in the presence of a large excess of water. The product compositions are given in *Table 5.*

Table 5. *Reaction of (+)-[3,3-$^{2}H_{2}$]camphor with lithium in ammonia/THF/water and in ammonia/ethanol/water at –75°; isoborneols and borneols obtained after work-up*

Run		26	27
Weight %,	{[2,3,3-$^{2}\mathrm{H}_{3}$]**2**, [$^{2}\mathrm{H}_{2}$]**2**, [^{2}H]**2**}	27	13
±1–2%	{[2,3,3-$^{2}\mathrm{H}_{3}$]**3**, [$^{2}\mathrm{H}_{2}$]**3**, [^{2}H]**3**}	73	87
Mol fraction in %,	[2,3,3-$^{2}\mathrm{H}_{3}$]**2**	47	37
±3–5%	{[$^{2}\mathrm{H}_{2}$]**2**}	36	50
	{[^{2}H]**2**}	17	13
Mol fraction in %,	[2,3,3-$^{2}\mathrm{H}_{3}$]**3**	41	22
±3–5%	{[$^{2}\mathrm{H}_{2}$]**3**}	33	55
	{[^{2}H]**3**}	26	23

In run 26, 3 mmol of lithium was added to a stirred, solution of 1 mmol of [3,3-$^{2}\mathrm{H}_{2}$]**1** in 35 ml of ammonia, 8 ml of THF and 2 ml of water, under Ar at –75°. The lithium dissolved/reacted in/with the stirred solution (–75°) in 26 min, the appearance of a blue color almost coinciding with the complete disappearance of the metal. The blue color disappeared upon stirring an additional 0.5 min when the ammonia was allowed to evaporate. In run 27, the reaction medium was a mixture of 35 ml of ammonia, 6 ml of ethanol and 2 ml of water. The run was otherwise analogous to run 26. The lithium dissolved/reacted in/with the stirred solution (–75°) in 58 min. The resulting solution never became blue but a white suspension appeared. On complete dissolution of the metal, excess ammonium chloride was added.

Evaporation of the ammonia, addition of water, and work-up afforded a mixture of {isoborneols}, {borneols}, and pinacols.

The product distributions were determined quantitatively as in *Sect. 2.3.2.* The yields of the pinacols were not determined. We find sizeable amounts of [2,3,3-$^{2}\mathrm{H}_{3}$]**2** and [2,3,3-$^{2}\mathrm{H}_{3}$]**3** which demonstrates that disproportionation persists. This is in line with the finding that pinacol coupling also persists *(Mechanism B/C).* The proton source(s) protonated the enolate formed by disproportionation and the resulting ketone(s) were then probably recycled. *Mechanism A/D* may have competed.

2.4.1. *Reduction of the enol?* Protonation of the enolate formed by disproportionation probably leads first to the enol which then rearranges to give the ketone. The simplest hypothesis is that this ketone is then recycled when the protonation takes place in the presence of solvated electrons but it could be that the enol is instead intercepted directly. We have no evidence for the latter pathway.

2.5. *Ammonium chloride as the proton source.* – 2.5.1. *Experiments of* Murphy & Sullivan. We now discuss the results of *Murphy & Sullivan* [12g] (see *1.3*). These authors reported that product distributions in alkali metal/ammonia reductions of **1** differ markedly[28]) when carried out in the presence or absence of ammonium chlo-

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[28]) The same changes in the ratios **2**/**3** were reported by *Ourisson & Rassat* [12a]. Similar ratios **2**/**3** in reductions in the presence of ammonium chloride were reported by *Huffman & Charles* [12c].

ride. Reduction with lithium in ammonia/DEE alone (–33.5°, normal addition) afforded **2** and **3** in a 20:80 ratio in 25% combined yield and pinacol **5** in 70% yield, while otherwise analogous reduction in the presence of 3 mol-equiv. of ammonium chloride gave **2** and **3** in a 6:94 ratio in 95% combined yield and none of the pinacol. With sodium, pinacol coupling was similarly suppressed (20% yield in the absence of ammonium chloride) and the ratio **2**/**3** changed, from 40:60 (absence) to 10:90. With potassium, pinacols were not formed in the absence (or presence) of ammonium chloride but the ratio **2**/**3** again changed, from 58:42 (absence), again to 10:90. These results suggested to us (see *1.3*) that in the presence of ammonium ion *Mechanism B/C* is suppressed and *Mechanism A/D* is dominant. Note that the ratios **2**/**3** are similar in the reductions with all three metals in the presence of ammonium chloride, and that the thermodynamically more stable isomer is formed with high diastereoselectivity, in accord with the textbook explanation (see *1.1*). Prior to our discovery of the disproportionation of ketyls, the significance of these results could not be assessed.

2.5.2. *Experiments with* [$3,3$-$^2H_2$]**1**. For reasons of solubility, the normal addition mode must be used (see *1.1*) and we continued to carry out the reductions at –75° in order to minimize exchange although the system is buffered with respect to the build-up of base and in order to slow down the reaction between the solvated electrons and ammonium ions to give molecular hydrogen. We have the impression that by lowering the temperature, this reaction is indeed slowed down while the reductions of **1** and [$3,3$-$^2H_2$]**1** are not, or at least not substantially. The evolution of molecular hydrogen was distinctly more violent when potassium rather than lithium or sodium dissolved/reacted in the normal addition mode in the presence of ammonium chloride and we therefore concentrated on the use of sodium and especially of lithium because reductions with lithium in the absence of ammonium chloride afford large amounts of the pinacol [$3,3,3',3'$-$^2H_4$]**5**(**5**) and suppression of such pinacol coupling is an additional criterion for the suppression of *Mechanism B/C*. The results are summarized in *Table 6*.

2.5.3. *Procedures*. In runs 28 to 31 and 33 to 35, lithium, sodium or potassium in the amounts indicated in *Table 6* was added to stirred solutions of 1 mmol of [$3,3$-$^2H_2$]**1** in 35 ml of ammonia and 5 ml of THF[29]) (*ca.* 0.025 M) containing ammonium chloride in the amounts indicated in *Table 6*, at –75°, under Ar. In runs 28 to 30, 33, and 35, the ammonium chloride was first added in a single charge after the substrate and the metal was then added in a single charge of one or two pieces to the resulting solution. In runs 28, 30, and 33, the metal dissolved/reacted in/with the stirred solution (–75°) in 9 to 14 min leaving a blue trail, to give a white suspension, and in run 29, the lithium dissolved/reacted in 3 min, otherwise in the same manner. Excess ammonium chloride was added in each case immediately after the metal had disappeared. In run 35, the potassium dissolved/reacted rapidly (*ca.* 1 min) to give a dark-blue, opaque mixture and stirring was then continued at –75° for 75 min when the still dark-blue mixture was treated with excess ammonium chloride. In runs 31 and 34, the ammonium chloride and the metal were each added in three batches; after addition of the first batches as in runs 28 to 30 and after the metal had disappeared, a second batch of ammonium chloride (to give a white suspension) followed by a second batch of metal, and then a third batch of each was added. In run 32, the concentration of [$3,3$-$^2H_2$]**1** was

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[29]) It is necessary to warm the mixture to dissolve the substrate and the ammonium chloride and to then cool the solution again to –75° and we may have been working with supercooled solutions. It was also necessary to use somewhat less THF than in the previous experiments (see *2.2.1*) to dissolve the ammonium chloride.

Table 6. *Reaction of (+)-[3,3-$^2H_2$]camphor with alkali metals in ammonia/THF containing ammonium chloride at –75°; camphors, isoborneols, and borneols obtained after work-up*

Run		28	29	30	31	32[a])	33	34	35
Metal mol-equiv.		Li 3	Li 3	Li 4	Li 3,3,1	Li 3.5, 8	Na 4	Na 3,3,3	K 4
Mol-equiv. NH_4Cl		3	3	4	3,3,1	3.5, 8	4	3.5, 3.5, 3.5	4
Weight %,	{[3,3-$^2H_2$]**1**, [*endo*-3-^{2}H]**1**}	10	29	44	–	4	48	9 –	
± 1–2%	{[2,3,3-$^2H_3$]**2**, [3,3-$^2H_2$]**2**, [^{2}H]**2**}	5 6	4 6	3 6	6	6 6	3 6	5 6	6
	{[2,3,3-$^2H_3$]**3**, [3,3-$^2H_2$]**3**, [^{2}H]**3**}	85 94	67 94	53 94	94	90 94	49 94	86 94	94
Mol fraction	[3,3-$^2H_2$]**1**	91	93	94		93	96	94	
in %, ± 3%	[*endo*-3-^{2}H]**1**	9	7	6		7	4	6	
Mol fraction	[2,3,3-$^2H_3$]**2**	4	6	–	4	4		4	–
in %, ± 3–5%	[3,3-$^2H_2$]**2**	91	89	100	90	90		90	92
	{[^{2}H]**2**}	5	5	–	6	6		6	8
Mol fraction	[2,3,3-$^2H_3$]**3**	–	–	–	–	3	–	–	–
in %, ± 3–5%	[3,3-$^2H_2$]**3**	93	93	94	95	92	95	94	93
	{[^{2}H]**3**}	7	7	6	5	5	5	6	7

[a]) Higher concentration, more THF.

doubled (*ca.* 0.05 M). To increase the solubility of the substrate, the proportion of THF was also raised (2 mmol of [3,3-$^2H_2$]**1** in 35 ml of ammonia and 7 ml of THF) and this lowers the solubility of the ammonium chloride. On adding first batches as before, the ammonium chloride dissolved only partially, and after 8 min, the first batch of lithium not having completely reacted, a large excess of ammonium chloride which remained largely undissolved, and the rest of the lithium was added. The lithium dissolved/reacted in/with the stirred (–75°) solution in 25 min. Evaporation of the ammonia, addition of water, and work-up afforded crude isolates.

2.5.4. *Product analyses.* We used or adapted the methodology used in the previous runs.

2.5.4.1. *Gas chromatography, distillation, column chromatography.* GC. showed that pinacol [3,3,3′,3′-$^2H_4$]**5** was formed in traces in the runs with lithium and exact yields could again not be determined (see *2.2.2.1*). Material balances after distillation were *ca.* 95%. In all runs, samples of the {camphors}, {isoborneols}, and {borneols} were isolated by preparative GC. (see *4.2.* and *4.10*) and in one run (run 32) also by column chromatography (see *4.9*).

2.5.4.2. *Mass and NMR. spectrometry. – {Camphors}.* The {camphors} were analyzed by MS. only (see *4.11.1*). It showed that they consisted largely of unreacted substrate and of small amounts, just above the analytical error of the method, of [^{2}H]species. One component among those must be [*endo*-3-^{2}H]**1** (see below). Another must be the [*exo*-3-^{2}H]**1** present as an impurity in the samples of [3,3-$^2H_2$]**1** used (*ca.* 3%, see *2.1*).

{Borneols} and {isoborneols}. The composition of the {borneols} and {isoborneols} was determined as in *Sect. 2.2.2.2*, by combination of low resolution mass spectometry with 360-MHz-^{1}H- and 55.28-MHz-^{2}H-NMR. spectrometry. MS. was used in every run, ^{1}H-NMR. spectrometry in most runs (on the {borneols}, the main components, in five and on the {isoborneols} in two) and ^{2}H-NMR. spectrometry in one ({borneols}, run 32).

The analyses of the {isoborneols} and {borneols} by MS. show in each case [$^2H_2$]species as the main components, and [$^2H_3$]- and [^{2}H]-species as minor components. ^{1}H-NMR. spectrometry indicates in each case the presence of single [$^2H_2$]species, [3,3-$^2H_2$]**2** and [3,3-$^2H_2$]**3**, as the main components. ^{2}H-NMR. spectrometry shows the same in the case of the {borneols} from run 32 (*Fig. 2*). The ^{1}H-NMR. spectra of the {borneols} show a weak signal due to 3-*exo* H-nuclei which is consistent with the presence of traces of [*endo*-3-^{2}H]**3** and the ^{2}H-NMR. spectrum of the {borneols} (*Fig. 2*) shows a weak signal due to 2-*exo* ^{2}H-nuclei which can be taken as evidence for the presence of traces of [2,3,3-$^2H_3$]**3**; the spectrum also establishes again that the {borneols} have the ^{2}H-atom at C(3) (almost exclusively) and C(2) (traces) and at none of the other C-atoms.

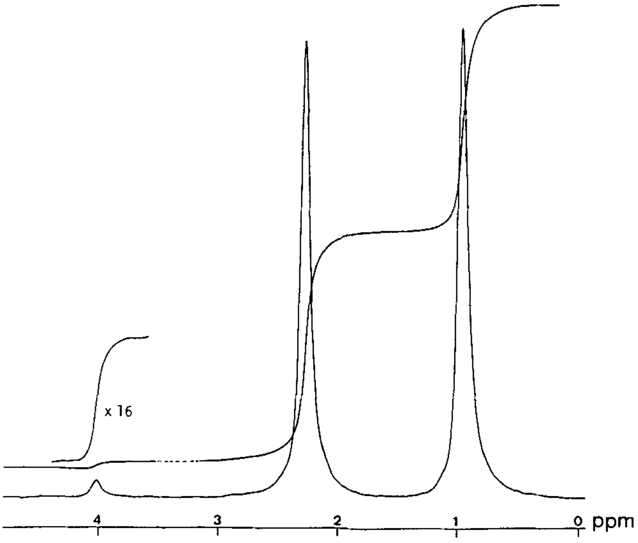

Fig. 2. *^1H-Noise decoupled 55.28-MHz-^2H-FT-NMR. spectrum of the {borneols} from run 32 [0.95 ppm (3-*endo-*^2H), 2.25 ppm (3-*exo-^{2}H), 4.00 ppm (2-exo-*^2H)]*

By inference from the structural assignments by NMR. spectrometry in the case of the trace components in the {borneols} ([2,3,3-$^2H_3$]**3** and [*endo*-3-^{2}H]**3**) and from the parallel experiments in the absence of ammonium chloride, we make the analogous assignments (correlation with MS.) in the case of the {isoborneols} ([2,3,3-$^2H_3$]**2** and [*endo*-3-^{2}H]**2**).

Since the samples of the substrate used contained traces of [*exo*-3-^{2}H]**1** (*ca.* 3%, see *2.1*), we conclude that the {isoborneols} and the {borneols} each contain traces of a second [^{2}H]species, namely [*exo*-3-^{2}H]**2** and [*exo*-3-^{2}H]**3**. *Table 6* lists the compositions of the {isoborneols} and {borneols} (mol fractions, in %) as obtained by MS.

The {isoborneol}/{borneol} ratios – 6:94 in every experiment (!) – determined initially by GC. of the crude isolates (weight % = mol fractions in % in this case) are indistinguishable from the ratios [3,3-$^2H_3$]**2**/[3,3-$^2H_2$]**3** that result when corrections for the presence of the minor components are made.

2.5.5. *A parallel run with unlabeled (+)-camphor.* A run exactly parallel to run 31 was carried out with **1**, and **2** and **3** were obtained in a 6:94 ratio.

2.5.6. *Summary and discussion.* In all runs (*Table 6,* see *2.5.2*), the disproportionations are still detectable – but they are almost completely suppressed. The best demonstration of this is the ^{2}H-NMR. spectrum (*Fig. 2*) of the resulting {borneols}. It should be contrasted with the spectra in *Fig. 1.* That it still occurs is indicated by the formation of the traces of [2,3,3-$^2H_3$]**2**, [2,3,3-$^2H_3$]**3**, and [*endo*-3-^{2}H]**1**. The latter is found together with unreacted substrate and is also recycled. Its reduction presumably (see *2.4.1*) proceeds like that of the [3,3-$^2H_2$]**1**, to give [*endo*-3-^{2}H]**2** and [*endo*-3-^{2}H]**3** in a 6:94 ratio.

Our ratios (**2**/**3** and [3,3-$^2H_2$]**2**/[3,3-$^2H_2$]**3**) are the same, 6:94, whether lithium, sodium or potassium is the reducing agent and whether **1** or [3,3-$^2H_2$]**1** is the substrate. They are identical with that found by *Murphy & Sullivan* in their reduction with lithium (see *2.5.1*) and distinctly smaller than that found by *Murphy & Sullivan* in their reductions with sodium and potassium (10:90).

Pinacol coupling is suppressed almost completely in the runs with lithium and completely in the runs with sodium. These findings also correspond to those of *Murphy & Sullivan* (see *2.5.1*).

Ketyl disproportionation and pinacol coupling are jointly suppressed in the presence of ammonium ion, as expected (see *1.3*). By inference, the abstraction of H-atoms from the medium by the ketyls can be taken to be also suppressed (see *1.8*).

Three mol-equiv. of lithium effected almost complete conversion in run 28 but much lower conversion in run 29. We assume that this is due to the rate of the reaction of the solvated electrons with ammonium ion varying somewhat from run to run. Using more lithium and more ammonium chloride (run 30) did not lead to high conversion but adding the ammonium chloride and the lithium or sodium batchwise (runs 31 and 34) did. The best procedure, however, is that of run 32 in which the solubility of the ammonium chloride was lowered by using more THF and in which an excess of partially undissolved ammonium chloride and an excess of metal was used (see *2.5.3*)[30]). Apparently, the suspended ammonium chloride dissolves rapidly enough to buffer the medium throughout the run but its concentration is low enough to favor reduction of the substrate over reduction of ammonium ion (to give eventually molecular hydrogen), and yet high enough to protonate the ketyl derived from [3,3-$^2H_2$]**1** rapidly.

2.5.7. *Mechanism.* It is likely that one of the variants of the general *Mechanism A* (see *1.1*) operates when, and only when, ammonium ion is the proton source. The variant which seems most likely to us was formulated as *Mechanism D* and we briefly discuss it.

The simplest explanation for the finding that the product ratios are the same whether the reductions are carried out with lithium, sodium or potassium, is that the free ketyls are protonated by ammonium ion. We next postulate that this protonation takes place on the O-atom rather than on the C-atom. This postulate is, *inter alia*, in line with the pK_A studies [10] referred to in the beginning (see *1.3*) and was already implicitly introduced at that stage. The ketyl radicals so formed are almost certainly pyramidal [1] [26a] [26c] while the ketyls are almost certainly planar [1] [26]. The hydroxycarbanions formed by reduction of the ketyl radicals are probably also pyramidal but must be extremely short-lived in the presence of ammonium ion. Equilibration *via* pyramidal inversion is therefore much more likely at the ketyl radical stage than at the carbanion stage [1]. The barriers for inversion of the ketyl radicals are not known but are probably small and our postulate requires them to be. This postulate also requires the subsequent reduction of the ketyl radicals to be slow enough to permit equilibration but fast enough to prevent dimerizations and disproportionations [7].

3. Concluding remarks. – This paper deals with the mechanism of the alkali metal/ammonia reductions of ketones but its conclusions are eminently practical. We have put into focus and linked with theory a mild procedure which suppresses ketyl dimerization and disproportionation[31]) and which we expect will always give pre-

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[30]) The ammonium chloride and the lithium can probably be added in single batches.

[31]) We established that ketyl disproportionation and dimerization are also suppressed in the case of four other substrates: [6,6-$^2H_2$]-2,2-dimethylcyclohexanone [6], the *cis*- and *trans*-[2,6-$^2H_2$]-2,6-dimethylcyclohexanones, and [3,3,5,5-$^2H_4$]-4-heptanone.

dominantly the thermodynamically more stable diastereoisomeric alcohol. The procedure should also permit reductions without racemization of optically active ketones that can racemize through formation of their enolates.

4. Appendix. Further experimental and analytical details. – 4.1. *NMR. and Mass spectrometry.* – The 360-MHz-^{1}H-FT-NMR. spectra and the ^{1}H-noise-decoupled-55.28-MHz-^{2}H-FT-NMR. spectra were recorded on *Bruker* WH 360 instruments, the former using C^2HCl_3 as the solvent and TMS as an internal standard, and the latter using $CHCl_3$ as the solvent and C^2HCl_3 (δ (ppm) 7.28) as an internal standard, by accumulation of 100–200 FID's of 90° pulses, using a repetition rate of 8 s, without field/frequency stabilization.

The low resolution MS. were recorded on an *Atlas* CH-4 mass spectrometer operating with an inlet temperature of *ca.* 150° and an electron energy of 70 eV.

4.2. *Gas Chromatography.* Analytical GC. was mainly[32]) performed on a *Hewlett-Packard* 5880 A instrument which is equipped with an electronic integrator/calculator. Small scale preparative GC. (see *4.10*) was performed on *Perkin-Elmer* 801 and 881 instruments. All three chromatographs were equipped with thermal conductivity detectors and regular glass columns packed with *Carbowax* on *Chromosorb* W, and were run with He as the carrier gas. Response factors were neglected[33]).

4.3. *Polarimetry and melting points.* Optical rotations were measured using a *Perkin-Elmer* 141 polarimeter. M.p. were determined in open capillaries using a *Büchi* apparatus and are not corrected.

4.4. *Alkali metals* (see [6][34])).

4.5. *Solvents.* THF and DEE were distilled from $LiAlH_4$ and stored over Na-wire in the dark. Ammonia (99.98%, 0.0087% H_2O[34])) was distilled from $NaNH_2$ or from KOH pellets[35]) into the reaction vessels.

4.6. *Substrates.* The **1** used as a substrate in reductions and for exchange had m.p. 175–176°, $[\alpha]_D^{20}$ +40.2° (c=0.84, EtOH), +40.6° (c=0.83, $CHCl_3$).

Exchange. To a stirred solution of 14 ml of dioxan in 30 g of ^2H_2O (99.98%)[34]) was added piecewise, at ambient temperature and under Ar, *ca.* 300 mg of Na-wire. After the Na had dissolved/reacted, 3.0 g of **1** was added and the resulting mixture (now two liquid phases) stirred at 50° for 7 days in a stoppered flask. After cooling, H_2O and DEE were added. Extraction with DEE, washing with H_2O, drying ($MgSO_4$), concentration and two bulb-to-bulb distillations afforded 2.6 g of a mixture consisting of *ca.* 97% of [3,3-$^2H_2$]**1** and *ca.* 3% of [3-^{2}H]**1** (see *4.11.1*), otherwise of high (>98%) purity as determined by GC.

4.7. *Metal/ammonia reductions.* The metal/ammonia reductions of **1** and [3,3-$^2H_2$]**1** were carried out in *Schlenk* tubes [6] under Ar[35]), with magnetic stirring using a *Teflon*-coated stirring bar. The dosage of the ammonia was by distillation into the graduated tubes and was not accurate. The temperatures of the reaction media was maintained as follows: *ca.* –75°; solid CO_2/acetone bath; *ca.* –35°; acetone bath maintained at *ca.* –35° by adding small pieces of CO_2; –33.5°; reflux, CO_2/acetone condenser. The procedures are given in *Sect. 2.2.1, 2.3.1, 2.3.2, 2.4,* and *2.5.3.*

Work-up. Ca. 15 ml of DEE was added to the reaction mixtures and the NH_3 evaporated through a *Vigreux* column. H_2O was added to the residues and the resulting mixtures were extracted three times with DEE. Drying ($MgSO_4$) and concentration using a spiral column afforded the crude isolates[36]).

4.8. *Distillation.* The mixtures of {camphors}, {isoborneols}, and {borneols} obtained after work-up were purified, without separation of any of the components (one fraction), by bulb-to-bulb distillation at

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[32]) Analyses by GC. in initial work and in some of the runs reported here were carried out on the *Perkin-Elmer* instruments, without electronic integration.

[33]) On injecting *ca.* 1:1 weighed mixtures, we found that the ratios **1**/**3** and **2**/**3** determined by analytical GC. needed to be corrected by multiplying with correction factors of 0.99 and 1.05, respectively. We neglect such corrections since these factors are small.

[34]) Specifications by the supplier.

[35]) We distilled the ammonia and carried out our experiments under Ar, but think that this does *not* critically affect the outcome of the experiments.

[36]) In one run, the crude isolate was put back into the aqueous phase and the isolation procedure was repeated. The composition of the first and the recycled isolates were identical according to analysis by GC.

ca. 200° (oven temp.)/12 Torr. This procedure was also used to roughly separate the above components from the pinacols and to purify the latter. After isolating the first fraction containing the above components, the pinacols in the residue were in turn purified, again without separation (one fraction), by bulb-to-bulb distillation at *ca.* 200° (oven temp.)/0.05 Torr.

4.9 *Column chromatography.* The components in the crude isolate from run 6 (starting from 3 mmol of [3,3-$^2H_2$]**1**) were also separated by column chromatography on silica gel (*Merck*, Kieselgel 60, 0.063–0.200 mm, 100 ml), using DEE/pentane 5:100 as eluant. The components were eluted in the order, 3,3,3′,3′-$^2H_4$]**5**, {camphors}, {isoborneols}, {borneols}.

4.10. *Analytical samples.* Analytical samples[37]) of the {camphors}, {isoborneols}, and {borneols} were obtained by small scale preparative GC.[38]) or by column chromatography (see *4.9*)[39]) followed by sublimation. Analytical samples of the pinacols were obtained using the same techniques except that column chromatographed **5**([3,3,3′,3′-$^2H_4$]**5**) was crystallized from EtOH. The purities of the purified samples were ⩾98% according to analyses by GC.

4.11. *Analysis by MS.* – 4.11.1. *Camphors.* The compositions of the various mixtures of [$^2H_2$]-, [^2H]-, and [$^2H_0$]-camphors were analyzed by measuring the $M^{+\cdot}$ intensities and correcting for the natural isotopic $(M+1)^+$ intensities (11% of $M^{+\cdot}$).

4.11.2. {*Isoborneols*} *and* {*borneols*}. The compositions of mixtures of [$^2H_3$]-, [$^2H_2$]-, and [^2H]-isoborneols and -borneols (see *2.2.2.2*) were carried out by measuring and correcting the $(M-CH_3)^+$ fragment intensities [27] because the $M^{+\cdot}$ intensities are too weak. The better method of preparing derivatives giving strong molecular ions was too elaborate for our purposes.

In most experiments, complete or near-complete structural assignments for the species detected by MS. could be made by NMR. spectrometry but in some, the structures of the [$^2H_2$]- and [^2H]-species could not be assigned in this way and had to be left unassigned; we know that the ^2H-atoms are at C(2) and C(3) and three [^2H]- and three [$^2H_2$]-species can therefore be formulated in each case.

The MS. of authentic samples of the species identified by NMR. spectrometry, namely [2,3,3-$^2H_3$]**2**, [2,3,3-$^2H_3$]**3**, [3,3-$^2H_2$]**2**, and [3,3-$^2H_2$]**3**, and as models for the unassigned [^2H]species, [*endo*-3-^2H]**2** and [*endo*-3-^2H]**3**, were measured for reference. This set of reference spectra is incomplete (see above, in each case two of the [$^2H_2$]-, and two of the [^2H]-species are missing) but sufficient. All of these reference spectra showed, as reported previously [27], no scrambling leading to loss of $CH_2{}^2H$, *i. e.*, the spectra showed $(M-CH_3)^+$ fragments only. Two known *ca.* 1:1 mixtures, of [2,3,3-$^2H_3$]**2** and [3,3-$^2H_2$]**2**, and of [3,3-$^2H_2$]**2** and [*endo*- 3-^2H]**2**, made by weighing and mixing (by dissolving in pentane and evaporating the pentane) the pure components, were analyzed by evaluating the $(M-CH_3)^+$fragment intensities as outlined below, and the compositions so determined corresponded within ± 1% to the weighed ratios.

The molecular ions of the isoborneols and borneols not only lose CH_3 but also H_2O and H^2HO, largely by an unusual 1,2-elimination [28]. In addition, with our spectrometer, the isoborneols and borneols underwent spurious elimination of H_2O and H^2HO in the inlet prior to ionization. *Table 7* lists the reference spectra in the region of the fragments of *m/z* 136 to 143. Determination of the compositions of mixtures {[2,3,3-$^2H_3$]**2**, [3,3-$^2H_2$]**2**, [^2H]**2**} and {[2,3,3-$^2H_3$]**3**, [3,3-$^2H_2$]**3**, [^2H]**3**} is complicated by the fact that the $(M-CH_3)^+$ fragments from {[^2H]**2**} and {[^2H]**3**} overlap with the isotopic fragments $(M+1-H_2O)^{+\cdot}$[40]) from [2,3,3-$^2H_3$]**2** and [2,3,3-$^2H_3$]**3**, respectively. Mixtures {[2,3,3-$^2H_3$]**2**, [$^2H_2$]**2**, [^2H]**2**, **2**]} and {[2,3,3-$^2H_3$]**3**, [$^2H_2$]**3**, [^2H]**3**, **3**} cannot be analyzed quantitatively because the $(M-CH_3)^+$ fragments from **2** and **3** overlap with the $(M-H_2O)^{+\cdot}$[40]) fragments from [2,3,3-$^2H_3$]**2** and [2,3,3-$^2H_3$]**3**, respectively. Such mixtures could, however, be analyzed qualitatively, and these qualitative analyses served to establish the conditions under which the simpler mixtures were formed. The presence or absence of **2** and **3** in the above

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[37]) We did not determine the $[\alpha]_D$ and m.p. of our samples.

[38]) Isomers differing in ^2H-content can be separated by GC. using capillary columns or packed columns developed for this purpose [22a]. We purposely used standard packed columns (see *4.2*) for analyzing (see *2.2.2.1*) and isolating unseparated mixtures of differently labeled isomers and obtained single peaks for each such mixture. In a control experiment, the first and the second halves of the peak corresponding to the {isoborneols} from run 6 were collected separately. Separate MS. analyses of the two halves gave, within the analytical error, identical compositions.

[39]) Analyses by MS. of samples from the same run purified either by GC. or by column chromatography had identical compositions, within the analytical error.

[40]) This formulation includes the elimination of H_2O prior to (inlet) and after ionization.

mixtures can be diagnosed by checking whether fragments of *m/z* 136, $[(M\text{-}H_2O)^{+}]$, are present or not. The quantitative compositions were calculated as described below for the case of mixtures {[2,3,3-$^2H_3$]**2**, [3,3-$^2H_2$]**2**, [$^2H_2$]**2**}; those of the corresponding mixtures {[2,3,3-$^2H_3$]**3**, [3,3-$^2H_2$]**3**, [^{2}H]**3**} were calculated analogously.

Table 7. *Mass spectra of isoborneols and borneols in the region of fragments of m/z 136 to 143* (fragments are given in % of the $(M\text{-}CH_3)^+$ fragment (= 100); observed and theoretical isotopic fragments (in brackets) are listed and the latter were used in our calculations)

m/z	**2**	[*endo*-3-^{2}H]**2**	[3,3-$^2H_2$]**2**	[2,3,3-$^2H_3$]**2**	**3**	[*endo*-3-^{2}H]**3**	[3,3-$^2H_2$]**3**	[2,3,3-$^2H_3$]**2**
136	110				66			
137	8 (12)	160	69		5 (7)	73	32	
138		19 (18)	60	69		7 (8)	38	22
139	100		7 (7)	60	100		6 (4)	35
140	7 (10)	100		6 (7)	7 (10)	100		3 (4)
141		10 (10)	100			8 (10)	100	
142			8 (10)	100			7 (10)	100
143				8 (10)				7 (10)

In a first approximation, the isotope fragment $(M+1\text{–}CH_3)^+$ due to {[^{2}H]**2**} at *m/z* 141 was neglected and the entire signal intensity at *m/z* 141 set equal to the $(M\text{-}CH_3)^+$fragment intensity due to [3,3-$^2H_2$]**2**. Correction for the corresponding isotopic fragment intensity $(M+1\text{-}CH_3)^+$ at *m/z* 142 (10%) gave the approximate intensity of the $(M\text{-}CH_3)^+$ fragment at *m/z* 142 from [2,3,3-$^2H_3$]**2**. The ratios of the approximate $(M\text{-}CH_3)^+$ fragment intensities due to [3,3-$^2H_2$]**2** and [2,3,3-$^2H_3$]**2** so obtained were next used to calculate approximate intensity ratios for the superimposed isotopic fragment $(M+1\text{-}H_2O)^{+}$ from [3,3-$^2H_2$]**2** and the $(M\text{-}H_2O)^{+}$ fragment from [2,3,3-$^2H_3$]**2** at *m/z* 139. If the reasonable assumption is made that spurious eliminations of H_2O and H^2HO from [3,3-$^2H_2$]**2** and [2,3,3-$^2H_3$]**2** take place at roughly similar rates, then this ratio is also a good approximation when such eliminations take place. From this ratio, the approximate intensity of the $(M\text{-}H_2O)^{+}$ fragment at *m/z* 139 from [2,3,3-$^2H_3$]**2** and that of the corresponding isotopic fragment $(M+1\text{-}H_2O)^{+}$ at *m/z* 140 (11%) can be calculated. Correction of the signal intensity at *m/z* 140 using this value gave the approximate intensity of the $(M\text{-}CH_3)^+$ fragment from {[^{2}H]**2**}. Starting with this peak and correcting successively for the isotopic fragments $(M+1\text{-}CH_3)^+$ gave, depending on the composition of the mixtures, the same or slightly improved second approximations of the $(M\text{-}CH_3)^+$ fragment intensities due to [3,3-$^2H_2$]**2** at *m/z* 141 and due to [2,3,3-$^2H_3$]**2** at *m/z* 142.

The size of the $(M\text{-}CH_3)^+$fragment intensities due to {[^{2}H]**2**} was thus obtained by corrections taking into account the first approximation of the ratios of the $(M\text{-}CH_3)^+$fragment intensities due to [3,3-$^2H_2$]**2** and [2,3,3-$^2H_3$]**2**, second, unchanged or slightly improved approximations of which then being obtained by taking into account the $(M\text{-}CH_3)^+$fragment intensities due to {[^{2}H]**2**}. Another reiteration had no effect.

The derived proportions of the $(M\text{-}CH_3)^+$fragment intensities of the three components so obtained correspond to the proportions of the components, as shown by the experiments described above.

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