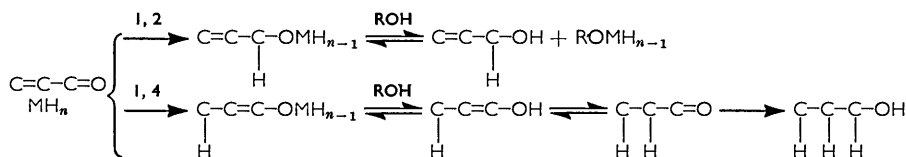


### 985. The Occurrence of 1,2- or 1,4-Addition in the Reduction of Some $\alpha\beta$ -Unsaturated Ketones with Metal Hydrides

By W. R. JACKSON and A. ZURQIYAH

3-Methylcyclohexenone, carvenone, and cholestenone have been reduced with sodium borohydride in three solvents. In "diglyme" and propan-2-ol the percentage of attack at the  $\beta$ -carbon atom (1,4-addition) decreased with increasing steric hindrance at this carbon atom. Reductions in pyridine gave only the products of 1,4-addition. When pyridine, other amines, and triphenylphosphine were present in small amounts during reductions in "diglyme," the amount of 1,4-addition was directly related to the boron basicity of the additive. The results are interpreted in terms of steric requirements of the reducing species, and relative steric hindrance to nucleophilic attack at the two possible sites in  $\alpha\beta$ -unsaturated ketones. Lithium aluminium hydride in ether or pyridine gave mainly the products of 1,2-addition, but lithium tetrakis(dihydro-*N*-pyridyl)aluminate paralleled other dihydropyridine derivatives in giving large amounts of saturated compounds.

$\alpha\beta$ -UNSATURATED ketones have two possible sites for nucleophilic attack by metal hydride ions. Addition at the carbonyl carbon atom leads to formation of allylic alcohol, and addition to the  $\beta$ -carbon atom gives the enol of the corresponding saturated ketone; this may be further reduced to a saturated alcohol.



Saturation of a double bond conjugated to a carbonyl-bearing substituent was first observed for borohydride reductions when saturated alcohols, together with the expected unsaturated alcohols, were obtained from reductions of some steroid unsaturated ketones.<sup>1</sup> Similar saturations had previously been recorded for several reductions with lithium aluminium hydride.<sup>2</sup> 1,4-Addition of hydride was shown not to be the exclusive mode of double-bond saturation in these cases, since allylic alcohols were reduced,<sup>3</sup> albeit more slowly than their carbonyl precursors, by this reagent. Evidence was obtained for an intermediate containing a carbon-metal bond in allylic alcohol reduction. Many more instances of double-bond saturation in borohydride reductions have been observed,<sup>4,5</sup> and it has been suggested<sup>6</sup> that diborane, liberated from excess borohydride by acid during product isolation, may be responsible for double-bond saturation.

The aim of this work has been to determine the factors which govern double-bond saturation in borohydride reduction of  $\alpha\beta$ -unsaturated ketones. Three ketones with  $\beta$ -substituents of different sizes were reduced by sodium borohydride in three solvents; the results are summarised in Table I. It was first essential to ensure that saturated products were formed by conjugate addition of hydride to unsaturated ketone. The possibility that diborane reactions were giving saturated products was excluded by keeping

<sup>1</sup> F. Sondheimer, M. Velasco, E. Batres, and G. Rosenkranz, *Chem. and Ind.*, 1954, 1482.

<sup>2</sup> R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 2548; R. W. Freedman and E. I. Becker, *ibid.*, 1951, **73**, 2366; A. Dornow, G. Messwarb, and H. H. Frey, *Chem. Ber.*, 1950, **83**, 445; A. Dornow and W. Bartsch, *ibid.*, 1954, **87**, 633.

<sup>3</sup> F. A. Hochstein and W. G. Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3484.

<sup>4</sup> N. A. Atwater, *J. Amer. Chem. Soc.*, 1961, **83**, 3071.

<sup>5</sup> T. L. Jacobs and R. B. Brownfield, *J. Amer. Chem. Soc.*, 1960, **82**, 4033.

<sup>6</sup> J. A. Marshall and W. S. Johnson, *J. Org. Chem.*, 1963, **28**, 595.

the mixture alkaline at all stages in product isolation. Acid conditions during isolation also led to loss of allylic alcohol as diene, especially with 3-methylcyclohex-2-en-1-ol which is particularly acid labile. Exclusion of moisture was attempted in all experiments but could not be guaranteed, and the formation of saturated alcohols, as opposed to saturated ketone, from reductions of 3-methylcyclohexenone in pyridine and "diglyme" indicates that a proton source is available to convert the metal hydride salt of the enolate into the enol which could then be reduced, probably through the keto-form (see above reaction sequence). Previous kinetic data indicated that saturated ketones are reduced more quickly than  $\alpha\beta$ -unsaturated ketones.<sup>7</sup> The possibility that further reduction of saturated ketone was occurring in aqueous medium during product isolation was eliminated after

TABLE 1

Reductions with sodium borohydride in (A) propan-2-ol, (B) "diglyme," (C) "triglyme," (D) pyridine

| Ketone                     | Molar ratio<br>NaBH <sub>4</sub> : ketone | Sol-<br>vent | Ratio 1,4-<br>to 1,2-<br>addition * | Ketone    | Molar ratio<br>NaBH <sub>4</sub> : ketone | Sol-<br>vent | Ratio 1,4-<br>to 1,2-<br>addition * |
|----------------------------|---|--------------|-------------------------------------|-----------|---|--------------|-------------------------------------|
| 3-Methylcyclo-<br>hexenone | 4 : 1                                     | A            | 45 : 55                             | Carvenone | 4 : 1                                     | A            | 39 : 61                             |
|                            | 1 : 1                                     |              | 45.5 : 54.5                         |           | 1 : 1                                     | B            | 38 : 62                             |
|                            | 1 : 4 †                                   |              | 43 : 57                             |           | 4 : 1                                     | B            | 64 : 36                             |
|                            | 4 : 1 ‡                                   |              | 40 : 60                             |           | 1 : 1                                     | D            | 63 : 37                             |
|                            | 4 : 1                                     | C            | 66 : 34                             |           | 4 : 1                                     | D            | 100 : 0                             |
|                            | 4 : 1 ‡                                   | C            | 64 : 36                             |           | Cholestenone                              | 4 : 1        | A                                   |
| 4 : 1                      | D   | 100 : 0      | 1 : 1                               | B         |   | 26 : 74      |                                     |
|                            |   |              | 4 : 1                               | B         |   | 22 : 78      |                                     |
|                            |   |              | 4 : 1                               | D         |   | 100 : 0      |                                     |

\* For methods of determining these ratios, see Experimental section. † Starting material (26%) was recovered in this experiment. ‡ Water (1% by volume) added prior to reaction.

an examination of the infrared spectrum of a reaction mixture, in pyridine prior to work-up, when strong hydroxyl absorption and complete absence of ketonic absorption was observed. The presence of a small amount of added water during reductions of 3-methylcyclohexenone in propan-2-ol and "triglyme" had little effect on the product ratio. The ratio of 1,4- to 1,2-addition was insensitive to the molar ratio of ketone to borohydride, which is consistent with the operation of a slow first hydride transfer from borohydride to ketone in "diglyme," "triglyme," and propan-2-ol.<sup>8,9</sup> This insensitivity contrasts with reported higher yields of saturated compounds obtained from reductions with large excesses of sodium borohydride.<sup>10</sup>

Double-bond saturation in the presence of excess hydride could be caused by a slower reduction of allylic alcohol competing with ketone reduction. The allylic alcohols from carvenone and cholestenone were treated with an excess of borohydride under the standard conditions for reduction in pyridine and "diglyme." Isolation followed by oxidation gave pure carvenone and cholestenone in good yield. Reduction of allylic alcohol by excess borohydride could thus be excluded.

The ratios of saturated to unsaturated products are interpreted as representing ratios of 1,2- to 1,4-attack of metal hydride ions. Reductions in "diglyme," "triglyme," and propan-2-ol gave increased amounts of 1,2-addition as the effective size of  $\beta$ -substituent was increased from 3-methylcyclohexenone and carvenone to cholestenone. Similar steric

<sup>7</sup> O. H. Wheeler and J. L. Mateos, *Canad. J. Chem.*, 1958, **36**, 1048.

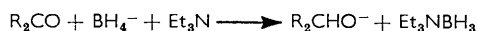
<sup>8</sup> L. W. Trevoy and W. G. Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 1675; E. R. Garrett and D. A. Lytle, *ibid.*, 1953, **75**, 6051; H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, 1957, **1**, 214; H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Amer. Chem. Soc.*, 1955, **77**, 6209.

<sup>9</sup> W. M. Jones and H. E. Wise, *J. Amer. Chem. Soc.*, 1962, **84**, 997.

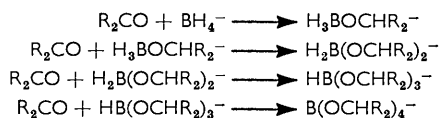
<sup>10</sup> D. Kupfer, *Tetrahedron*, 1961, **15**, 193.

control operates in 1,2- versus 1,4-addition of Grignard reagents to  $\alpha\beta$ -unsaturated carbonyl compounds.<sup>11</sup> No distinction could be made between 3-methylcyclohexenone and carvenone, since different analytical techniques were used to investigate the products from these compounds, and the differences in ratio lie within the combined analytical errors ( $\pm 3\%$ ). An increase in steric hindrance at the  $\beta$ -carbon atom by the isopropyl group of carvenone over the methyl group of 3-methylcyclohexenone may be partially compensated by the methyl group adjacent to the carbonyl carbon atom in carvenone. Reductions in propan-2-ol gave less 1,2-addition than reductions in ether solvents. This may be connected with the greater degree of ionisation of sodium borohydride in propan-2-ol,<sup>12</sup> or the possibility that isopropoxyborohydrides participate in reduction.

Reduction of the three ketones in pyridine gave exclusively products with saturated double bonds. This selective method of obtaining saturated alcohols from  $\alpha\beta$ -unsaturated ketones is known in the steroid field,<sup>10</sup> and borohydride reductions in pyridine are selective between keto-groups substituted in different positions in the steroid molecule.<sup>13</sup> The mechanism of reduction of saturated ketones by borohydride in the presence of amines has been investigated.<sup>9</sup> It was shown that addition of triethylamine to reductions in "diglyme" restricted the number of available hydrogens in sodium borohydride to one and led to formation of triethylamine-borine.



Evidence was also provided to show that the last three hydrogen atoms of a borohydride ion were involved in reduction as alkoxyborohydrides, and not as alkoxyborines, when ketones were reduced in "diglyme" in the absence of amines, *i.e.*, the following sequence of reactions normally occurs:



Pyridine in small amounts also partially stopped reduction at the borohydride stage,<sup>9</sup> and when used as solvent it could be expected to prevent reduction by any species other than the borohydride ion itself. From our reductions pyridine-borine could be isolated, indicating that reduction was restricted to the borohydride ion.

Nucleophilic attack by borohydride ion could be expected to be less susceptible to steric effects than attack by alkoxyborohydride ions, if indeed they are responsible for the subsequent steps in the reduction of conjugated ketones. The exclusive formation of saturated products from reductions in pyridine can thus be interpreted as exclusive 1,4-addition of borohydride ions. Reductions in "diglyme," "triglyme," and propan-2-ol give ratios representative of different degrees of reduction by borohydride ions and other species, probably alkoxyborohydride ions. The possibility that reduction is partially by pyridine-borine seemed unlikely because, although amine-borines are known to reduce ketones,<sup>14</sup> the rate of reduction has been shown to be much slower than by sodium borohydride in the presence of amines.<sup>9,15</sup> Pyridine-borine in pyridine was shown not to reduce carvenone or cholestenone under the standard conditions used for reduction.

<sup>11</sup> J. Klein, *Tetrahedron*, 1964, **20**, 465; for general discussion see G. F. Wright in Newman's "Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 406.

<sup>12</sup> H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.*, 1961, **83**, 4372.

<sup>13</sup> E. Elisberg, H. Vanderhaeghe, and T. F. Gallagher, *J. Amer. Chem. Soc.*, 1952, **74**, 2814; O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz, and C. Djerassi, *ibid.*, p. 3711; O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *ibid.*, 1953, **75**, 1286; A. F. Soloway, A. S. Deutsch, and T. F. Gallagher, *ibid.*, p. 2356; N. N. Suvorov, and Z. A. Varoslavtseva, *Zhur. obshchei Khim.*, 1959, **29**, 2889.

<sup>14</sup> R. P. Barnes, J. H. Graham, and M. D. Taylor, *J. Org. Chem.*, 1958, **23**, 1561.

<sup>15</sup> W. M. Jones, *J. Amer. Chem. Soc.*, 1960, **82**, 2528.

The effect of tertiary amines and other bases on reductions in "diglyme" gave the results in Table 2.

TABLE 2  
Reductions of methylcyclohexenone in "triglyme," and carvenone and cholestenone in "diglyme," in the presence of added bases\*

| Ketone              | Added base          | Ratio 1,4- to 1,2-addition † |
|---------------------|---------------------|------------------------------|
| Methylcyclohexenone | Triethylamine       | 98 : 2                       |
|                     | Piperidine          | 95 : 5                       |
| Carvenone           | Triethylamine       | 95 : 5                       |
|                     | Pyridine            | 100 : 0                      |
|                     | Collidine           | 100 : 0                      |
|                     | Triphenylphosphine  | 100 : 0                      |
|                     | Sodium isopropoxide | 59 : 41                      |
|                     | Diethylaniline      | 60 : 40                      |
| Cholestenone        | Pyridine-borine     | 66 : 34                      |
|                     | Triethylamine       | 86 : 14                      |
|                     | Pyridine            | 100 : 0                      |

\* Sodium borohydride, ketone, and additive were in molar ratio 4 : 1 : 4. † Ratios for methylcyclohexenone are for saturated : allylic alcohols; carvenone and cholestenone were reoxidised (see Experimental section).

Addition of triethylamine gave high yields of saturated compounds, again increasing from cholestenone to carvenone and methylcyclohexenone. This could indicate that, although reduction is mainly by the borohydride ion, the small amount of triethylamine is not sufficient to prevent some reduction by other subsequently formed reducing species which are much more susceptible to steric effects. Diethylaniline ( $pK_a$  6.6), a much weaker base than triethylamine ( $pK_a$  10.7), had no effect when present in small amounts during reduction in "diglyme." Pyridine ( $pK_a$  5.23), on the other hand, still gave more saturated compounds than triethylamine. It thus appears that pyridine, although a much weaker Brønsted base than triethylamine, is more effective in stopping reaction after the borohydride stage, *i.e.*, it more readily forms a stable amine-borine than does triethylamine. The strength of boron-nitrogen and boron-phosphorus bonds in amine- and phosphine-borines is not directly related to the Brønsted basicity of amines and phosphines. Triphenylphosphine, although almost non-basic, forms triphenylphosphine-borine with a boron-phosphorus bond of dissociation energy 37.6 kcal./mole in benzene,<sup>16</sup> while the gas-phase dissociation energy of trimethylamine-borine has been estimated as 31.5 kcal./mole<sup>17</sup> (33.8 kcal./mole using the new estimate of 34 kcal./mole for the dissociation energy of  $B_2H_6$ ,<sup>18</sup> as was used in the triphenylphosphine-borine calculation). Triphenylphosphine was added for a reduction of carvenone in "diglyme"; the stable triphenylphosphine-borine was precipitated, and removed during product isolation, and only the products of 1,4-addition were isolated. This work thus suggests that pyridine and triphenylphosphine are slightly stronger boron bases than triethylamine, which can be explained in terms of B-N and B-P bond strengthening, by some form of back-donation from boron to vacant *d*-orbitals in phosphorus and  $\pi$ -orbitals in the pyridine ring. Collidine ( $pK_a$  7.4) also appears to be a slightly stronger boron base than triethylamine in spite of the adverse steric effect of the 2,6-methyl groups which have a destabilising effect of *ca* 1.6 kcal./mole. in 2,6-lutidine-borine.<sup>19</sup> Piperidine ( $pK_a$  11.2), of comparative basicity to triethylamine, gave a similar result, small amounts of 1,2-addition products being detected. This result must be treated with some caution, since secondary-amine-borines are known to decompose at moderate temperatures<sup>20</sup> and some other mechanism of reduction may operate. Addition of the strong oxygen base,

<sup>16</sup> M. A. Frisch, H. G. Heal, H. Mackle, and I. O. Madden, *J.*, 1965, 899.

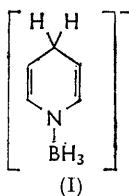
<sup>17</sup> F. G. A. Stone, *Chem. Rev.*, 1958, 58, 109.

<sup>18</sup> M. E. Garabedian and S. W. Benson, *J. Amer. Chem. Soc.*, 1964, 86, 176.

<sup>19</sup> H. C. Brown, D. Gintis, and L. Domash, *J. Amer. Chem. Soc.*, 1956, 78, 5387.

<sup>20</sup> H. C. Brown and E. J. Mead, *J. Amer. Chem. Soc.*, 1953, 75, 6263.

sodium isopropoxide, had no appreciable effect on the ratio of 1,2- to 1,4-addition. Reduction by sodium borohydride in the presence of pyridine-borane had no influence on the ratio, which eliminates the possibility that parts of the reduction in the presence of pyridine may be through a dihydropyridine-borane (I) or the corresponding *ortho*-isomer.



Nucleophilic attack of  $\text{BH}_4^-$  ions is considered to be exclusively at the conjugate position. The results in "diglyme" and propan-2-ol indicate that the other three hydride transfers must be predominantly to the carbonyl carbon atom, probably because the intermediate reducing species are more susceptible to adverse steric effects at the conjugate position. If the alkoxyborohydride mechanism<sup>9</sup> is tenable in the reduction of  $\alpha\beta$ -unsaturated ketones, it would be expected that a trialkoxyborohydride would be very susceptible to steric effects and attack would be almost exclusively at the carbonyl carbon atom. Sodium trimethoxyborohydride was prepared in tetrahydrofuran solution, and the results (Table 3) of re-

TABLE 3

| Reductions with sodium trimethoxyborohydride in tetrahydrofuran |   |
|---|---|
| Ketone  | Ratio of 1,4- to 1,2-addition *                       |
| 3-Methylcyclohexenone .....                                     | 13 : 87   |
| Carvenone .....   | 5 : 95  |
| Cholestenone .....  | 2 : 98  |
|   | 2 : 98 (in boiling tetrahydrofuran)                   |
|   | 26 : 74 ( $\text{NaBH}_4$ in boiling tetrahydrofuran) |

\* All reductions were carried out with a 4 : 1 ratio of reducing agent to ketone at 24°.

ductions by this solution show that attack at the carbonyl carbon atom was very much preferred. Sodium borohydride in tetrahydrofuran would only reduce cholestenone when the solution was refluxed, but gave a ratio very similar to the reduction in "diglyme" at 25°. Similarly, a reduction of cholestenone by sodium trimethoxyborohydride in boiling tetrahydrofuran still gave *ca.* 2% of 1,4-addition products.

The above results are compatible with the participation of alkoxyborohydride intermediates in reduction of  $\alpha\beta$ -unsaturated ketones, and agree with the reduction of cinnamaldehyde<sup>20</sup> with sodium trimethoxyborohydride, from which cinnamyl alcohol was obtained. Reduction may not be exclusively by sodium trimethoxyborohydride, as this can disproportionate in tetrahydrofuran to sodium dimethoxyborohydride and sodium tetramethoxyborate.<sup>21</sup>

The influence of pyridine on reductions with lithium aluminium hydride was briefly investigated. Reductions of carvenone in ether or pyridine gave large amounts of 1,2-addition (see Table 4) but, when lithium aluminium hydride was first allowed to react with

TABLE 4

| Reductions of carvenone with lithium aluminium hydride *  |                               |
|---|-------------------------------|
| Solvents  | Ratio of 1,4- to 1,2-addition |
| Ether .....   | 0 : 100                       |
| Pyridine ( $\text{LiAlH}_4$ added to a solution of ketone in pyridine) .....  | 8 : 92                        |
| Pyridine (ketone added to a solution of $\text{LiAlH}_4$ in pyridine which had been allowed to stand overnight) ..... | 73 : 33                       |

\* Ratio of  $\text{LiAlH}_4$  to carvenone, 4 : 1.

pyridine to form lithium tetrakis(dihydro-*N*-pyridyl)aluminate,<sup>22</sup> 1,4-addition became predominant.

<sup>21</sup> W. Gerrard, "The Organic Chemistry of Boron," Academic Press, London and New York, 1961, p. 140; H. C. Brown and E. J. Mead, *J. Amer. Chem. Soc.*, 1956, **78**, 3614.

<sup>22</sup> P. T. Lansbury and J. O. Peterson, *J. Amer. Chem. Soc.*, 1963, **85**, 2236; 1962, **84**, 1756; 1961, **83**, 3537.

Preferential 1,4-addition of hydrogen to  $\alpha\beta$ -unsaturated ketones thus parallels other *in vivo* and *in vitro* reductions by dihydropyridines.<sup>23</sup>

#### EXPERIMENTAL

*Materials.*—Sodium borohydride (Metal Hydrides Inc.) was estimated to be >98% pure by the well defined analytical procedure.<sup>24</sup> "Diglyme" (diethyleneglycol dimethyl ether) was purified by a previously described method.<sup>25</sup> "Triglyme" was redistilled from sodium. Propan-2-ol was allowed to stand over freshly heated barium oxide and redistilled from Drierite. The amine solvents were purified by conventional methods. 3-Methylcyclohex-2-en-1-one, b. p. 82—83°/14 mm.,  $n_D^{19}$  1.4940, was prepared by the method of Smith and Rouault,<sup>26</sup> who quote b. p. 96°/25 mm.,  $n_D^{20}$  1.4932. 3-Methylcyclohex-2-en-1-ol, prepared by lithium aluminum hydride reduction of the above ketone, had b. p. 35°/0.2 mm.,  $n_D^{20}$  1.4825 (lit.,<sup>27</sup> b. p. 56°/1 mm.). 3-Methylcyclohexanone, prepared by catalytic hydrogenation of the unsaturated ketone over a palladium-calcium carbonate catalyst, had b. p. 73—74°/28 mm.,  $n_D^{21}$  1.4455 (lit.,<sup>28</sup> b. p. 168—169°/760 mm.,  $n_D^{20}$  1.4463). The saturated ketone, on reduction with lithium aluminium hydride, gave a mixture of *cis*- and *trans*-3-methylcyclohexanol, b. p. 73—74°/28 mm.,  $n_D^{20}$  1.4554, in agreement with the constants quoted for the pure isomers.<sup>29</sup> Carvenone, b. p. 46°/0.2 mm.,  $n_D^{17}$  1.4845, was obtained from carvenone by reduction with zinc dust in alkali, followed by treatment with sulphuric acid;<sup>30</sup> it was necessary to contaminate the zinc dust with traces of a metallic impurity, *e.g.*, copper powder, before reduction could be achieved (lit.,<sup>30</sup> b. p. 232°/760 mm.,  $n_D^{19}$  1.4838). Catalytic hydrogenation of carvenone over palladium-calcium carbonate gave carvomenthones, b. p. 34°/0.3 mm.,  $n_D^{18}$  1.4553 (lit.,<sup>31</sup> b. p. 220—221°/760 mm.,  $n_D^{20}$  1.4554). Triphenylphosphine had m. p. 81.5—82°, and pyridine-borine, m. p. 9—11°, was prepared by the method of Taylor, Grant, and Sands,<sup>32</sup> who quote m. p. 10—11°.

*Reductions of 3-Methylcyclohex-2-en-1-one.*—Solutions of sodium borohydride in "triglyme" and pyridine were made up as described by Jones and Wise.<sup>9</sup> The hydride content of the solutions was estimated by withdrawing portions (1 ml.) and titrating with standard potassium iodate solution. Average values of *ca.* 0.53 mmole/ml. in pyridine and 0.6 mmole/ml. in "triglyme" were obtained. Saturated solutions of sodium borohydride in propan-2-ol were prepared as described by Brown *et al.*<sup>25</sup> The average hydride content of these solutions was significantly higher than that previously recorded (0.25 as opposed to 0.07 mmole/ml. at 20°) even after repeated drying and purification of the propan-2-ol. Equimolar solutions of the ketone were made up in a dry-box, as the ketone was hygroscopic.

Reactions in "triglyme" and pyridine were carried out by injecting appropriate amounts of solutions and solvents (up to 10 ml.) into glass tubes capped with self-sealing rubber stoppers. Reactions in propan-2-ol were performed in 50-ml. graduated flasks fitted with similar stoppers. All apparatus was baked dry, allowed to cool under anhydrous conditions, and flushed with nitrogen before use. The tubes or flasks were kept at 24° for 3 days with intermittent shaking.

The general procedure for the isolation of products in the absence of amines was to pour the reaction mixture into water (150 ml.) to which sodium hydrogen carbonate (10—15 ml. of a saturated solution) had been added. The mixture was shaken for a few minutes, left for a further 15 min., and extracted several times with pentane. The combined pentane extracts were washed with water (2  $\times$  50 ml.), dried (MgSO<sub>4</sub>), and the pentane removed through a 1-ft. column packed with glass helices.

Reaction mixtures containing amines were poured into water (150 ml.) containing potassium iodate (10 ml. of a 10% solution), and the mixture was allowed to stand for 15 min. to decompose the amine-borines formed in reaction. The products were isolated in pentane as above. The

<sup>23</sup> B. E. Norcross, P. E. Klinedinst, and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1962, **84**, 797; J. S. McGuire and G. M. Tompkins, *Fed. Proc.*, 1960, **19**, A29.

<sup>24</sup> D. A. Lyttle, E. H. Jensen, and W. H. Struck, *Analyt. Chem.*, 1952, **24**, 1843.

<sup>25</sup> H. C. Brown, E. J. Mead, and R. C. Subba Rao, *J. Amer. Chem. Soc.*, 1955, **77**, 6209.

<sup>26</sup> L. J. Smith and G. F. Rouault, *J. Amer. Chem. Soc.*, 1943, **65**, 634.

<sup>27</sup> M. I. Bowman, C. C. Ketterer, and C. Dinga, *J. Org. Chem.*, 1952, **17**, 563.

<sup>28</sup> F. K. Signaigo and P. L. Cramer, *J. Amer. Chem. Soc.*, 1933, **55**, 3326.

<sup>29</sup> A. K. McBeth and J. A. Mills, *J.*, 1945, 709.

<sup>30</sup> O. Wallach, *Annalen*, 1894, **279**, 377; 1895, **286**, 129.

<sup>31</sup> R. G. Johnston and J. Read, *J.*, 1935, 1139.

<sup>32</sup> M. D. Taylor, L. R. Grant, and G. A. Sands, *J. Amer. Chem. Soc.*, 1955, **77**, 1506.

absence of amine-borines was checked by infrared analysis (B-H stretch 4.2—4.3  $\mu$ ) as these compounds have been shown to be harmful to gas chromatography columns. All reactions in which amine-borines were formed developed colour which varied from light green with triethylamine and piperidine to yellow-red with pyridine and collidine. The colour remained in the aqueous phase during product isolation and soon faded.

3-Methylcyclohex-2-en-1-one, and the related saturated ketone, unsaturated alcohol, and saturated alcohols, were well separated on a 4-ft. column of 8% glycerol-propene oxide on 100—120 mesh Celite at 110°, using a Pye Argon Chromatograph. The geometrically isomeric saturated alcohols were not separated. Calibration of the detector with authentic mixtures showed an equal relative peak area response for all products.

Relative ratios of 1,2- to 1,4-addition products are summarised in the Tables. 1,4-Products occurred mainly as saturated alcohols (<2% saturated ketone) even when a 1 : 4-molar ratio of borohydride to ketone was used. A mixture of saturated ketone and saturated and unsaturated alcohols of known composition was subjected to the procedures for isolation and analysis. The resultant ratio was well within the  $\pm 3\%$  limits of accuracy which it was hoped to achieve. When a similar mixture was isolated by a procedure which involved acid washing ( $N-H_2SO_4$ ) a significant loss of unsaturated alcohol occurred.

A sample of 3-methylcyclohex-2-en-1-ol was recovered unchanged (by gas chromatography) after treatment with sodium borohydride in pyridine under the reaction conditions.

Reproducible results were difficult to obtain in propan-2-ol; the use of freshly made solutions of sodium borohydride appeared to be essential.

*Reductions of Carvenone.*—Reductions were carried out as for 3-methylcyclohexenone, but complete separation of the products by gas chromatography could not be achieved. Approximate values ( $\pm 5$ —10%) were obtained for the product ratios, and these agreed with results obtained by the general method outlined below. Carvenone (1.0 g.), in the appropriate amounts of solvent, was added under anhydrous conditions to solutions of sodium borohydride so that the total volume was 50 ml. The mixtures were stirred for 3 days at 24° under nitrogen, and the products isolated in ether by a similar procedure to that described previously. The complete absence of carvenone in the products was checked by infrared analysis. The products were dissolved in ether (15 ml.) and oxidised by stirring for 2 hr. at 20° with a solution of sodium dichromate dihydrate (1.32 g.) in sulphuric acid (1 ml.) and water (5 ml.).<sup>33</sup> The products were isolated in ether.

Carvenone and carvomethones were analysed on a 4-ft. column of poly(ethylene glycol) succinate (7%) on 100—120 mesh Celite at 75°. The detector was calibrated against authentic mixtures and showed a relative peak area response of 1 : 1.02 for carvenone to carvomethones. In some experiments a small sample of the reduction product was analysed by gas chromatography on the same column; the results always agreed qualitatively with those from the above procedure.

The ratios of carvone to carvomethones, summarised in the text, were reproducible to within  $\pm 3\%$  and were independent of the yields of crude products. A mixture of the unsaturated alcohols, obtained by lithium aluminium hydride reduction of carvenone in ether, was allowed to stand with sodium borohydride in pyridine and propan-2-ol under the reaction conditions. Carvenone was obtained on isolation and oxidation.

Carvenone (1.0 g.) was stirred for 3 days at 24° with pyridine-borine (2.46 g.) in pyridine (50 ml.). Isolation in ether gave starting material.

Triphenylphosphine (6.82 g.) was dissolved in "diglyme" (25 ml.), and sodium borohydride (1.01 g.) in "diglyme" (20 ml.) added. Carvenone (1.0 g.) in "diglyme" (5 ml.) was added immediately, and the mixture stirred for 3 days under the normal conditions. The colour of the solution became yellow and then red-brown. The mixture was poured into water, and a mixture of triphenylphosphine and triphenylphosphine-borine, m. p. and mixed m. p. 186—188° (lit.,<sup>16</sup> 188°) was filtered off. Oxidation gave carvenone.

*Reductions of Cholestenone.*—Cholestenone (0.5 or 1.0 g.) was reduced and re-oxidised under conditions similar to those described for carvenone.

The products were chromatographed on Spence Grade "H" alumina (60 g./1 g. oxidation products) which had been deactivated with dilute acetic acid (10%; 5% of wt. of alumina). Elution with pentane gave, in some experiments, small amounts of gummy material (<2%).

<sup>33</sup> H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, 1961, **83**, 2952.

Elution with benzene-pentane (1 : 3) gave mixtures of 5 $\alpha$ - and 5 $\beta$ -cholestanone. Further elution with this solvent followed by elution with benzene gave cholestenone.

The ratios were reproducible to within  $\pm 2\%$ , and again were independent of the overall yields of products. The yields were  $>92\%$  in all cases except for some reductions in the presence of triethylamine where recoveries as low as 72% were obtained. A mixture of 3 $\alpha$ - and 3 $\beta$ -hydroxycholest-4-ene (1 g.), obtained by reduction of cholestenone, in ether, was treated with sodium borohydride (1 g.) in "diglyme" (50 ml.) for 3 days at 24°. Oxidation gave cholestenone (0.94 g., 94%). In one reduction in pyridine, potassium iodate was not used in the work-up but the product was isolated in ether and chromatographed. Elution with pentane gave pyridine-borine, m. p. 9–11°.

*Reductions with Sodium Trimethoxyborohydride.*—A solution of sodium trimethoxyborohydride in tetrahydrofuran was prepared by the method of Brown and Mead<sup>20</sup> from sodium hydride (10.8 g. of a 50% dispersion in oil), methyl borate (30 g.), and tetrahydrofuran (400 ml.). The solution was filtered under nitrogen and used immediately.

(a) 3-Methylcyclohex-2-en-1-one (1.0 g.) was added to the sodium trimethoxyborohydride solution (64 ml.) and stirred for 2 days under nitrogen at 24°. The mixture was poured into warm water (300 ml.), set aside for 15 min., and the product isolated in pentane.

(b) Carvenone (1.0 g.) was similarly treated with the sodium trimethoxyborohydride solution (43 ml.) and the product isolated in ether.

(c) Cholestenone (1.0 g.), after reduction with the solution (20 ml.) and oxidation, gave, on chromatography, saturated ketones (20 mg.) followed by cholestenone (0.81 g.). When the experiment was repeated at reflux temperature for 12 hr., saturated ketones (16 mg.) and cholestenone (0.8 mg.) were obtained. When cholestenone (0.5 g.) was heated with sodium borohydride (0.2 g.) in tetrahydrofuran (200 ml.) for 3 days under reflux, isolation and oxidation gave saturated ketones (0.105 g.) and cholestenone (0.296 g.).

*Reductions of Carvenone with Lithium Aluminium Hydride.*—(a) Lithium aluminium hydride (1.0 g.) in ether (20 ml.) was added to carvenone (1.0 g.) at 24° in ether (20 ml.), and the mixture stirred overnight under nitrogen. Excess hydride was decomposed with aqueous ether and the product isolated in ether. Oxidation gave carvenone. A larger scale experiment was used to prepare the carvenols (5.75 g.; 82% after distillation), b. p. 46–48°/0.3 mm.,  $n_D^{19}$  1.4773 (lit.,<sup>34</sup> b. p. 99–102°/14 mm), from carvenone (7 g.).

(b) Lithium aluminium hydride (1.0 g.) was added to a solution of carvenone (1.0 g.) in pyridine (50 ml.), and the mixture stirred and analysed as above.

(c) Lithium aluminium hydride (1.0 g.) was dissolved in pyridine (45 ml.), and the solution allowed to age for 2 days.<sup>22</sup> Carvenone (1.0 g.) in pyridine (5 ml.) was added to the orange solution, the mixture was stirred overnight at 24° under nitrogen, and the products were isolated, oxidised, and analysed as before.

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<sup>34</sup> R. J. Johnston and J. Read, *J.*, 1934, 233.