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# Synthesis and reactions of some 2,7-disubstituted norbornanes

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SYNTHESIS AND REACTIONS OF  
SOME 2,7-DISUBSTITUTED NORBORNANES

by

Paul Richard Story

A Dissertation Submitted to the  
Graduate Faculty in Partial Fulfillment of  
The Requirements for the Degree of  
DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

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Ames, Iowa

1959

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## INTRODUCTION

Because of the unique orientation of the carbon skeleton, the bicyclo- $/2,2,1/-$ heptane (norbornane) nucleus, shown in Figure 1, presents an interesting model for the perpetration of a wide variety of experiments. Probably the most important single investigation of this nature was the demonstration of the neighboring carbon (anchimeric assistance) effect in the solvolyses of 2-substituted-bicyclo- $/2,2,1/-$ heptanes by Winstein.<sup>1</sup>

Since then, the norbornane and related unsaturated systems have been investigated relatively intensively, especially with regard to the preparation and reactions of compounds substituted on the six membered ring. In contrast, the investigation of simple molecules substituted in the 7-position, because of preparative difficulties, has been somewhat limited.

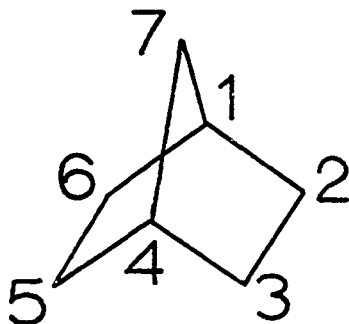


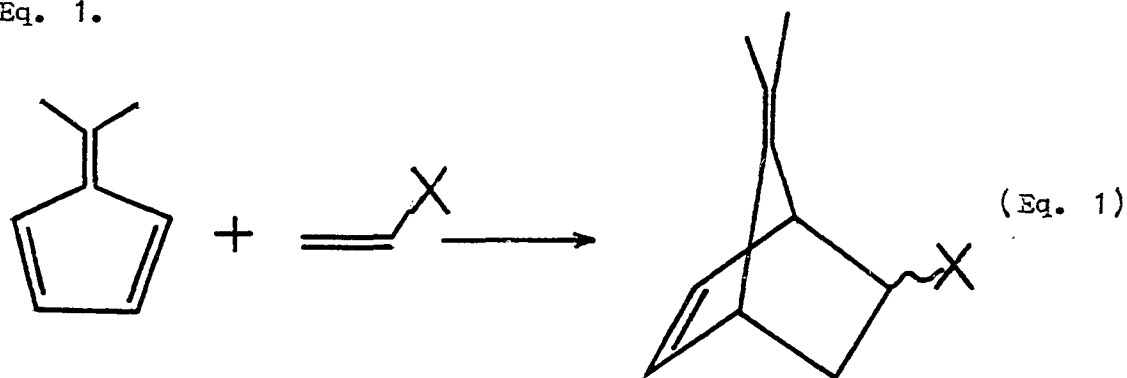
Figure 1. Bicyclo- $/2,2,1/-$ heptane

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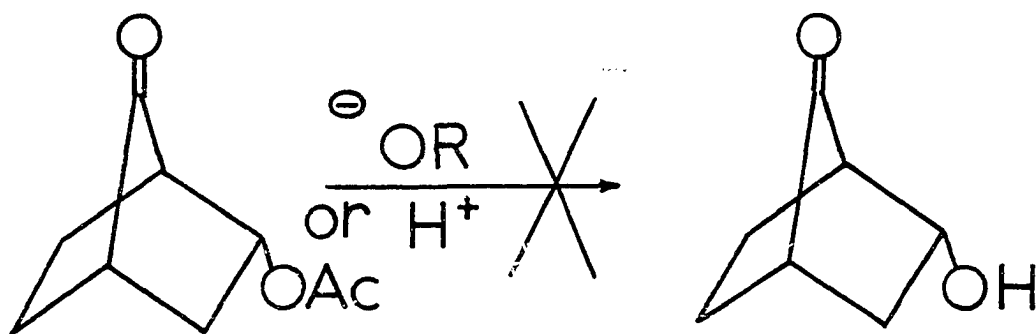
<sup>1</sup>S. Winstein and D.S. Trifan, J. Amer. Chem. Soc., 71, 2953 (1949)

It is the purpose of this work to overcome, at least in some degree, this difficulty and provide a facile entry into the 2,7-disubstituted-bicyclo- $/2,2,1/$ -heptane system and, further, to investigate the reactions of some of the resultant compounds.

The greatest obstacle lay in the initial step, i.e., to find a dienophile which would at the same time be sufficiently reactive to give a good yield of adduct with dimethylfulvene and allow, in a simple manner, substitution of a hetero atom, preferably oxygen, at carbon 2 as shown in Eq. 1.



As is the custom of the best laid plans, the most interesting chemistry turned up in the most unexpected places. For example, the selective hydrogenation of some of the adduct derivatives furnished some very interesting and surprising results. Along in the same vein, the keto-acetate (IX) could not be hydrolyzed under any conceivable conditions to the corresponding ketol, but apparently suffered a retro-aldol

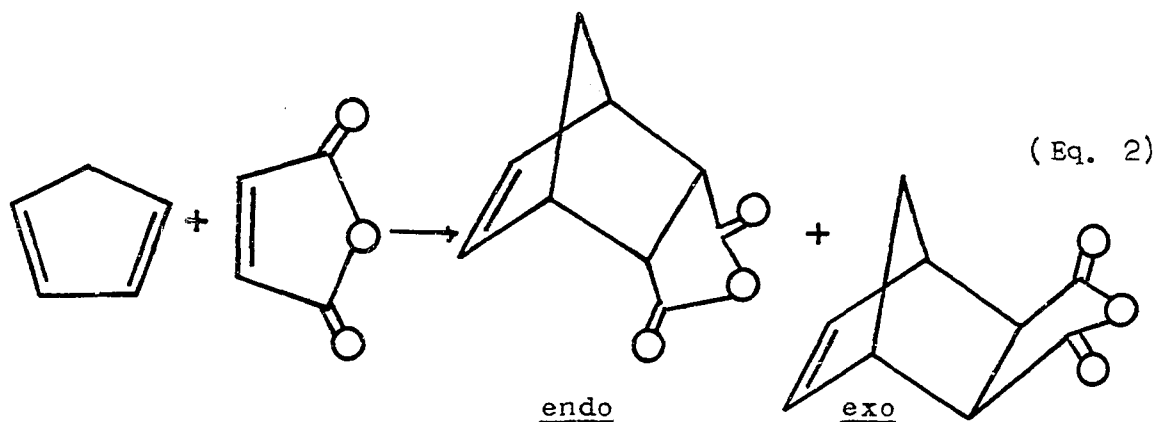


These points, along with others of equal interest, shall be elaborated further in the ensuing discussion.



## HISTORICAL

With the advent of the Diels-Alder reaction, entry into the bicyclo- $/2,2,1/$ -heptane system has become commonplace.<sup>2</sup> For example, the adduct derived from cyclopentadiene used as the diene and maleic anhydride as the dienophile has probably received more attention, synthetically and mechanistically, than any other Diels-Alder reaction.<sup>3</sup> The endo iso-



mer is the major product, frequently exclusively so, at lower temperatures where the reaction is rate controlled. At higher temperatures, or under equilibrating conditions, considerable exo isomer may be formed since the exo isomer is

<sup>2</sup> (a) J.A. Norton, Chem. Revs., 31, 319 (1942); (b) M.C. Kloetzel, Organic Reactions, Vol. 4, p. 1, John Wiley & Sons, New York 1948; (c) H.L. Holmes, ibid., Vol. 4, p. 60; (d) L.W. Butz and A.W. Rytina, ibid., Vol. 5, p. 136 1949; (e) K. Alder, Newer Methods of Preparative Organic Chemistry, p. 381, Interscience, New York 1948

<sup>3</sup> K. Alder, G. Stein and E. Rolland, Ann., 525, 247 (1936)

usually the thermodynamically more stable.

The bicyclo- $/2,2,1/$ -heptane molecule is of particular interest because of the fixed stereochemical relationship of substituent groups and has received much attention along these lines. In order to better visualize the subsequently discussed effects and reactions, a model of the ring system as calculated by Krieger<sup>4</sup> is presented in Figure 2.

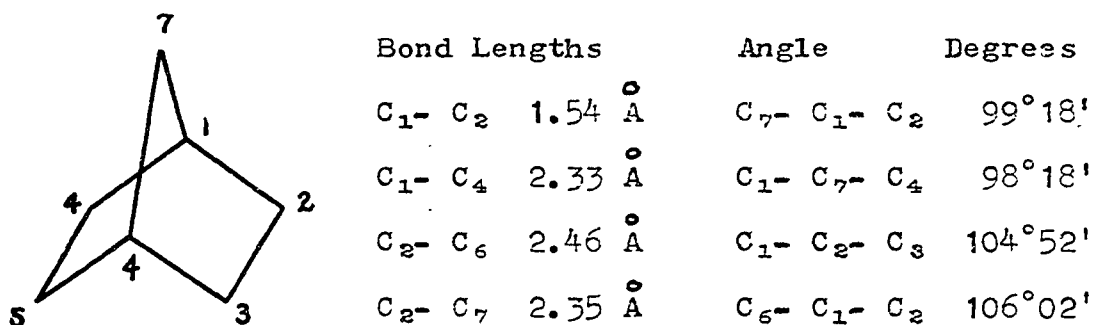
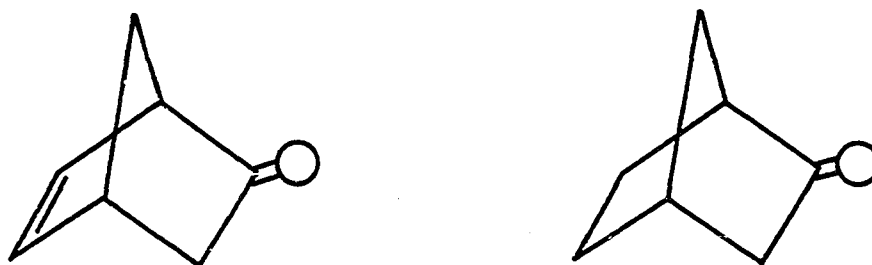


Figure 2. Krieger's model of norbornane

A ramification of this unusual stereochemical relationship is the interaction of the double bond and the carbonyl in dehydronorcamphor (bicyclo- $/2,2,1/$ -5-heptenone-2) as evidenced



<sup>4</sup>H. Krieger, Suomen Kem., 31B, 348 (1958)

by its ultraviolet spectrum. Bartlett and Tate<sup>5</sup> have shown that dehydronorcamphor has a maximum at 300.5 m $\mu$  in ethanol, with an extinction coefficient of 292. Considerably different is the corresponding maximum of norcamphor which lies at 287 m $\mu$ , with an extinction coefficient of 29.

In a paper which appeared the following month, Cookson and Wariyar<sup>6</sup> showed, in a very extensive survey, the stereochemistry necessary to obtain spectroscopic interactions in unsaturated ketones. According to Cookson and Wariyar, the p-orbital of the carbonyl carbon and the p-orbital of the second carbon (from the carbonyl) of the double bond must be pointed at one another in order to obtain an interaction. Dehydronorcamphor, for which Cookson and Wariyar obtained a maximum at 295 ( $\epsilon = 315$ ) in ethanol, is consistent with this picture. The observed absorption, according to these workers, is most likely due to the normal  $n \rightarrow \pi$  transition of the isolated carbonyl<sup>7</sup> influenced by the adjacent  $\pi$  electrons, as opposed to a charge transfer absorption<sup>8</sup>, on the basis of the insensitivity of the maximum

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<sup>5</sup> P.D. Bartlett and B.E. Tate, J. Amer. Chem. Soc., 78, 2473 (1956)

<sup>6</sup> R.C. Cookson and N.S. Wariyar, J. Chem. Soc., 2302 (1956)

<sup>7</sup> H.L. McMurray, J. Chem. Phys., 9, 231 (1941)

<sup>8</sup> R.S. Mulliken, J. Amer. Chem. Soc., 74, 811 (1952)

wavelength to substitution on the double bond and the known sensitivity of  $n \rightarrow \pi$  transitions to solvent.<sup>9</sup>

To date, 2-substituted-bicyclo- $/2,2,1/$ -heptanes, both saturated and unsaturated, have received most attention. 7-substituted molecules have been investigated to a lesser extent, chiefly because of preparative difficulties, although a few have been prepared and graphically illustrate chemical consequences of the special fixed stereochemistry inherent in the bicyclic system. The tremendously greater reactivity of I tosylate ( $10^7 \times$ ) as compared to the syn isomer, II tosylate, in solvolysis reactions is a striking example of such a consequence.<sup>10</sup> The  $\pi$  orbital of the double bond is oriented so as to stabilize the 7-norbornenyl cation as it is

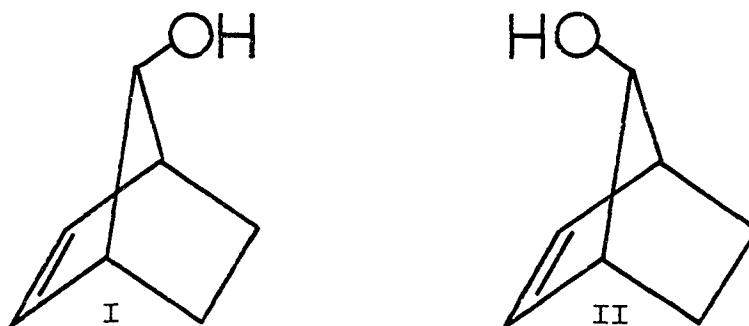


Figure 3. Anti- and syn-norborneols

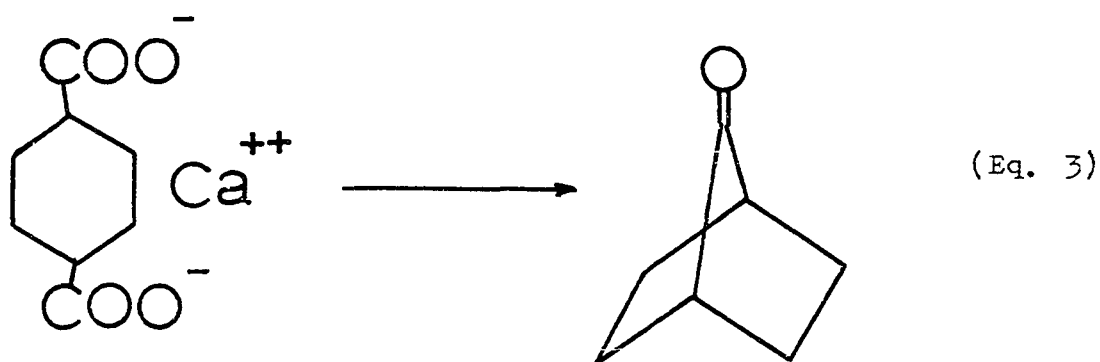
being formed. The dimensions of this cation have been cal-

<sup>9</sup> L. Goodman and H. Shull, J. Chem. Phys., 22, 1138 (1954)

<sup>10</sup> S. Winstein and E. T. Stafford, J. Amer. Chem. Soc., 79, 505 (1957)

culated<sup>11</sup> by Roberts and coworkers

One of the earliest attempts to prepare a 7-substituted-bicyclo-/2,2,1/-heptane was recorded by Zelinski<sup>12</sup> in his attempt to prepare bicyclo-/2,2,1/-7-heptanone by fusion of the alkaline earth salts of trans-hexahydroterephthalic acid. It is very unlikely, however, that the desired ketone was obtained as claimed by Zelinski. Stark<sup>13</sup> has reported, probably erroneously also since later workers have not been able to duplicate either result, the preparation of bicyclo-/3,1,1/-7-heptanone in like fashion.



Probably one of the first authentic preparations of a bridged carbonyl was that of Japp and Meldrum<sup>14</sup> who prepared diphenylcyclopentadieneone which could be isolated only as

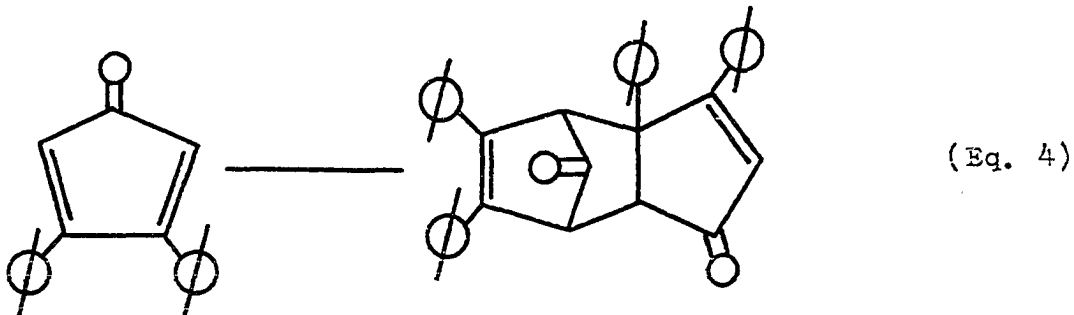
<sup>11</sup> W.G. Woods, R.A. Carboni and J.D. Roberts, J. Amer. Chem. Soc., 78, 5653 (1956)

<sup>12</sup> N. Zelinski, Ber., 34, 3798 (1901)

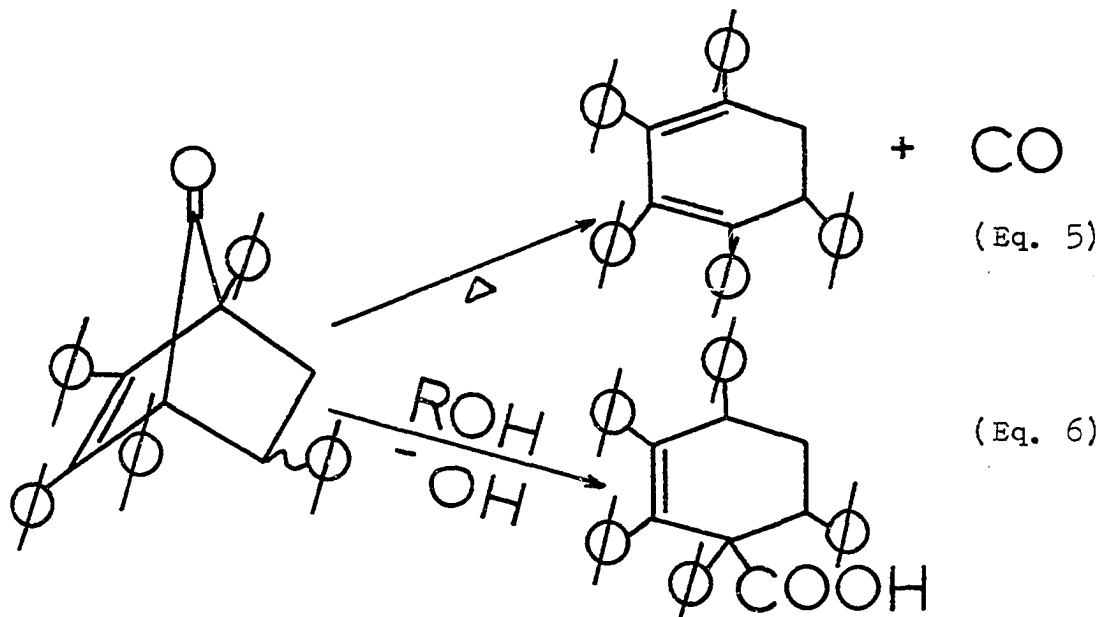
<sup>13</sup> O. Stark, Ber., 45, 2369 (1912)

<sup>14</sup> F.R. Japp and A.N. Meldrum, J. Chem. Soc., 79, 1024 (1901)

the dimer, Allen<sup>15</sup> has probably contributed more to the



chemistry of bridged carbonyls, especially in the /2,2,1/-system, than any other single investigator. Allen has found that bridged carbonyls, unsaturated in the 6-membered ring, lose CO quantitatively and quite rapidly on heating at 200-220° or even at lower temperatures, if favorably substituted.



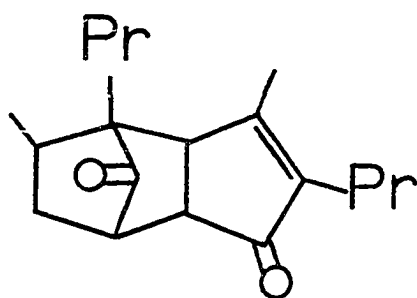
This presents a difficulty, then, in the preparation of such compounds via reactions which require temperatures of this order. An interesting and novel reaction of bridged carbo-

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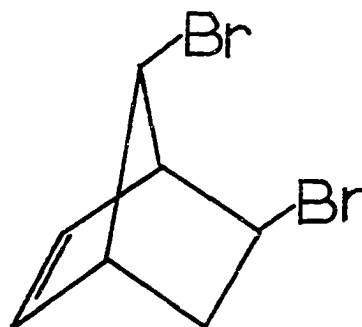
<sup>15</sup> C.F.H. Allen, Chem. Revs., 37, 209 (1945)

nyls is their hydrolytic ring opening which has been elaborated by Allen and Van Allan.<sup>16</sup> III, incidently, was prepared by the Diels-Alder condensation of tetracyclone (tetraphenylcyclopentadienone) and styrene. Tetracyclone, unlike the diphenyl derivative or cyclopentadienone, itself, is monomeric. For this reason, most cyclopentadienones cannot be used to prepare bridged carbonyls directly.

Until recently, only polyarylated or polyhalogenated bicyclo- $/2,2,1/-7$ -heptanones, which for the most part were unsaturated in the six membered ring, had been prepared. Allen and Van Allan<sup>17</sup> introduced one of the first bicyclo- $/2,2,1/-7$ -heptanones which is not so substituted nor unsaturated with their preparation of IV by catalytic hydrogenation of the dimer of allethrolone.<sup>18</sup>



IV



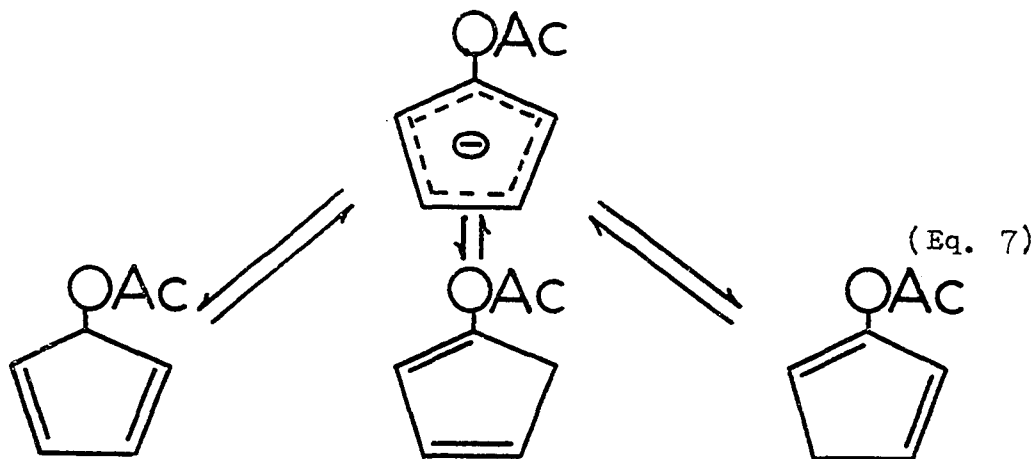
V

<sup>16</sup> C.F.H. Allen and J.A. Van Allan, J. Org. Chem., **10**, 333 (1945)

<sup>17</sup> C.F.H. Allen and J.A. Van Allan, ibid., **20**, 323 (1955)

<sup>18</sup> F.B. LaForge, N. Greene, and M.S. Schechter, J. Amer. Chem. Soc., **74**, 5392 (1952)

Since then, several even simpler 7-substituted-bicyclo-  
/2,2,1/-heptanes, including some bicyclo-/2,2,1/-7-hepta-  
nones, have been prepared. Winstein and Shatavsky<sup>19</sup> and Winstein et al<sup>20</sup> (Woodward's method) have prepared I in two ways. Woodward's method involves reacting ethylene with acetoxy-cyclopentadiene, which was produced in situ from acetoxydi-cyclopentadiene at 190°. The other consisted of the selective hydrolysis of V, obtained by bromination of bicycloheptadiene, followed by zinc debromination of the bromohydrin. II was prepared by bromination of bicycloheptadiene oxide.<sup>10</sup> These reactions, however, generally lead to mixtures with no useful substituents in the six membered ring. The use of substituted cyclopentadienes presents even greater problems. Substituted cyclopentadienes, such as acetoxy-cyclopentadiene,



<sup>19</sup> S. Winstein and M. Shatavsky, J. Amer. Chem. Soc., **78**, 592 (1956)

<sup>20</sup> S. Winstein, M. Shatavsky, C. Norton and R.B. Woodward, ibid., **77**, 4183 (1955)



dimerize quite readily so that they must be reacted at cracking temperatures. These stringent conditions will decompose many dienophiles. Further, acetylcyclopentadiene readily isomerizes<sup>21</sup> as shown in Eq. 7 and gives a mixture of products which are difficultly separable.

Certain 7-keto compounds have been prepared via the use of dimethylfulvene, which reacts similarly to cyclopentadiene

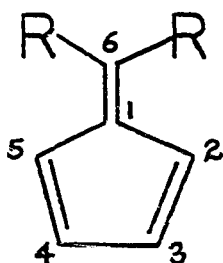


Figure 4. Fulvene nucleus

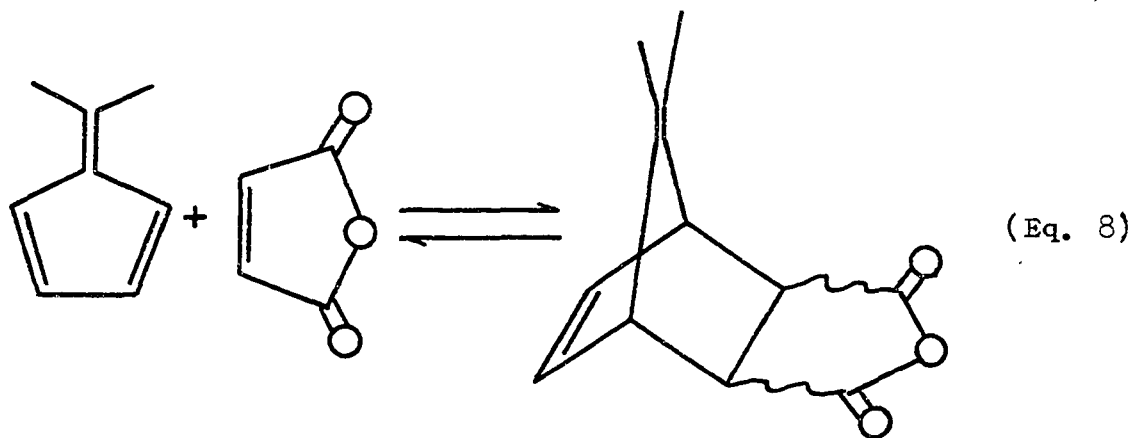
in the Diels-Alder reaction. Dimethylfulvene is the simplest fulvene homologue to receive much investigation, and that chiefly in the field of its Diels-Alder reactions. Fulvene, itself, has been prepared only recently<sup>22</sup> and, as a consequence, its reactions have received relatively little attention. The use of fulvenes as dienes is complicated by several factors, paramount among them being the ready thermal reversibility of the reaction, especially in solution. Di-

<sup>21</sup> M. Rosenblum, J. Amer. Chem. Soc., 79, 3179 (1957)

<sup>22</sup> J. Thiec and J. Wiemann, Bull. soc. chim. France, 177 (1956)

methylfulvene also quickly absorbs two molecules of oxygen from air to form a diperoxide of undetermined structure. For a full discussion of fulvenes, one should refer to the excellent reviews by Bergmann,<sup>23</sup> Day<sup>24</sup> and Thiec and Wiemann.<sup>22</sup>

The condensation of dimethylfulvene and maleic anhydride, as shown in Eq. 8, has been thoroughly explored by Alder and Ruhmann<sup>25</sup> and others.<sup>26, 27, 28</sup> Wilder and Winston<sup>29</sup> have converted adduct VI into several bicyclo-/2,2,1/-7-heptanones by selective hydrogenation of the endocyclic double bond fol-



<sup>23</sup> E.D. Bergmann, Progr. Org. Chem., 3, 81 (1955)

<sup>24</sup> J.H. Day, Chem. Rev., 53, 167 (1953)

<sup>25</sup> K. Alder and R. Ruhmann, Ann., 566, 1 (1950)

<sup>26</sup> E.P. Kohler and J. Kable, J. Amer. Chem. Soc., 57, 917 (1935)

<sup>27</sup> D. Craig, J.J. Shipman, J. Kiehl, F. Widmer, R. Fowler and A. Hawthorne, ibid., 76, 4573 (1954)

<sup>28</sup> P. Wilder and A. Winston, ibid., 77, 5598 (1955)

<sup>29</sup> P. Wilder and A. Winston, ibid., 78, 868 (1956)

lowed by ozonolysis of the exocyclic double bond. Alder and Ruhmann<sup>25</sup> and Kohler and Kable<sup>26</sup> had previously ozonized this very adduct but did not attempt the isolation of any bridged ketone. Wilder and Winston<sup>29</sup> realized rather poor yields (30%) in the ozonolysis and further failed to obtain compounds substituted with a hetero atom on the six membered ring. Yields for selective hydrogenation of the endocyclic double bond were given by none of the above investigators and, in the case of Alder and Ruhmann, the procedure used was not described, except to the extent of the catalyst and solvent. It would be remarkable, indeed, if the hydrogenations were completely selective with both the endo and exo isomers.

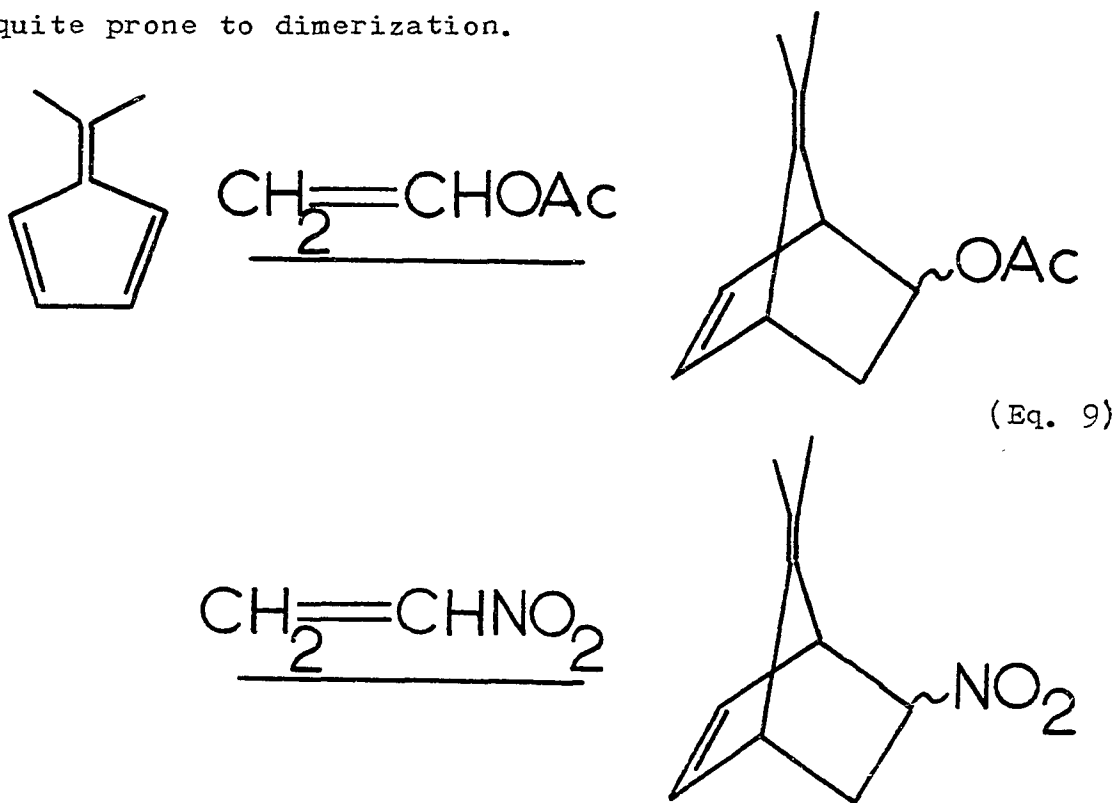
## DISCUSSION

To be useful as a general synthetic scheme the first few reactions of the scheme, at least, should be of moderately high yield. In this particular case, the first step was the crucial one, i.e., the Diels-Alder condensation of dimethylfulvene with a suitable dienophile. Dimethylfulvene was chosen as the diene because it is readily attainable and its adducts will have a substituent in the 7-position which should be convertible to a carbonyl. Diphenylfulvene was considered less favorable because its reactions are even more reversible and because of anticipated difficulty in later conversion to the 7-carbonyl. Cyclopentadieneone would be more ideal but, of course, has not been isolated for it exists as a dimer.

Three dienophiles presented themselves as possibilities, namely, vinyl acetate, nitroethylene and  $\alpha$ -acetoxyacrylonitrile. Vinyl acetate was tried with justified apprehension since it is only a moderately reactive dienophile. Diphenylfulvene, but not dimethylfulvene, has been reacted with a variety of dienophiles.<sup>25</sup> With most moderately reactive dienophiles, e.g., methyl acrylate, reaction times were several months and yields were generally poor. This, of course, involves certain obvious disadvantages.

The first attempt to condense dimethylfulvene and

vinyl acetate was made under the conditions used by Roberts et al<sup>30</sup> in the condensation of cyclopentadiene and vinyl acetate. Slightly lower temperatures and free radical inhibitors, however, did not prevent the formation of polymeric materials, which were the only products. It is possible that the reaction might succeed at room temperature and a reaction time of several months, although this is doubtful since dimethylfulvene, unlike diphenylfulvene, is quite prone to dimerization.



Nitroethylene has been reacted with cyclopentadiene to

<sup>30</sup>  
J.D. Roberts, C.C. Lee and W.H. Saunders, J. Amer. Chem. Soc., 76, 4501 (1954)

give good yields of 2-nitronorbornene<sup>31, 32, 33</sup> and, on general principles, should be more reactive than vinyl acetate.

The nitroethylene-dimethylfulvene adduct would be quite useful, for it could conceivably be a succinct route to 2-amino-7-ketones, or the 2-nitro group of the dihydro adduct might be converted to the corresponding ketone via the Nef reaction. This will have to remain conjecture for the present, since 2-nitronorbornenes do not give the corresponding ketone in the Nef reaction,<sup>34, 35</sup> but rearrange exclusively as shown by Noland et al.<sup>36</sup> The dihydro adduct may be less prone to rearrangement, although it, too, could rearrange by the same mechanism.

Unfortunately, dimethylfulvene and nitroethylene reacted with explosive force on warming to room temperature after mixing (neat) at 0°. The reactants, after being allowed to stand in solution at room temperature for two weeks, exploded

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<sup>31</sup> K. Alder, H.F. Rickert and E. Windemuth, Ber., 71B, 2451 (1938)

<sup>32</sup> W.C. Wildman and C.H. Hemminger, J. Org. Chem., 17, 1641 (1952)

<sup>33</sup> E.E. van Tamelen and R.J. Thiede, J. Amer. Chem. Soc., 74, 2615 (1952)

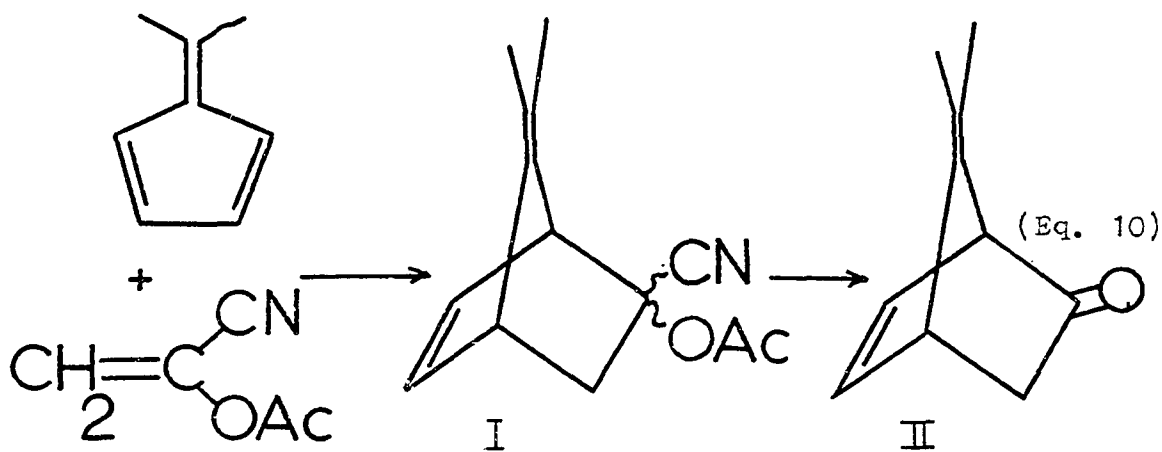
<sup>34</sup> W.E. Noland, Chem. Revs., 55, 137 (1955)

<sup>35</sup> M.F. Hawthorne, J. Amer. Chem. Soc., 79, 2510 (1957)

<sup>36</sup> (a) W.E. Noland, J.H. Cooley and P.A. McVeigh, ibid., 79, 2976 (1957); (b) Ibid., 81, 1209 (1959)

again on removal of the solvent. The explosion is very possibly caused by a reaction other than the Diels-Alder condensation, perhaps a polymerization.

The third dienophile,  $\alpha$ -acetoxyacrylonitrile, looked the most promising for it has several obvious advantages. First, the olefinic double bond is sufficiently negatively substituted to hold promise of fair reactivity. Secondly, the adduct should easily hydrolyze directly to the dieneone (II), so as to essentially introduce the elements of ketene into the molecule. The utility of the dienophile has already been demonstrated with cyclopentadiene in the preparation of dehydronorcamphor by Bartlett and Tate.<sup>37</sup> Its chief disadvantage lies in its unavailability, since it is extremely difficult, although possible, to prepare<sup>38</sup> in an ordinary labora-



<sup>37</sup> P.D. Bartlett and B.E. Tate, J. Amer. Chem. Soc., **78**, 2473 (1956)

<sup>38</sup> F. Johnston and L.W. Newton, U.S. Patent 2,395,930 (1946)

tory. It is available, however, on occasion from industry such as Eastman Chemical Products, Inc., Kingsport, Tennessee, who so generously supplied this laboratory with 1000 g.

The condensation, as shown in Eq. 10, was first carried out under the conditions described by Bartlett and Tate<sup>37</sup> for cyclopentadiene, i. e., 100°. Poor yields were realized, however. Best yields of a mixture of adducts, whose individual stereochemistry is unknown, were obtained at 55-60° and a reaction time of 30 days, although quite good yields were obtainable after two weeks, the most frequently used reaction period. It was not possible to determine the exact amount of adduct formed because one epimer seemed to be a liquid, refusing to crystallize from the mother liquor after the solid isomer had been removed. This liquid, which could not be completely freed of dimethylfulvene, etc., generally produced 30-40% of the total ketone (II) on hydrolysis.

It generally sufficed merely to wash the solid isomer with pentane before hydrolysis. The optimum time of hydrolysis was found to be 2.5-3 hours. Any deviation from this time invariably resulted in lower yields.

The dieneone (II) was unfortunately an oil and as a result was extremely difficult to free from dimethylfulvene even though the boiling points are widely separated. The ketone is fairly heat stable, but the color of dimethylfulvene begins to appear if the ketone is heated much above 100°



at 760 mm.

Spectra of dieneone (II)

The infra-red spectrum (neat) of the dieneone (II) was found to have major absorptions at 5.69, 5.77 and 5.85 $\mu$  in the carbonyl range, a peak at 6.40 $\mu$  corresponding to the endocyclic double bond<sup>39,40</sup> and a peak at 6.13 $\mu$  corresponding to the exocyclic double bond.

The ultra-violet spectrum in ethanol exhibited the type of interaction described by Cookson and Wariyar,<sup>41</sup> giving a maximum at 308 m $\mu$  and  $\epsilon = 423$ . Comparison with the ultra-violet of norcamphor, which has a maximum at 295 m $\mu$ <sup>41</sup> or 300 m $\mu$ <sup>37</sup> and  $\epsilon = 290-315$ , indicates that the exocyclic double bond is interacting with the carbonyl either directly or indirectly, probably influencing the normal  $n \rightarrow \pi$  transition as supposed by Cookson and Wariyar. The interaction must be comparatively large, since the shift in maximum is from 8 to 13 m .

An increase in  $\epsilon$  may depend more on a change in symmetry than an increase in transannular interaction, for the sym-

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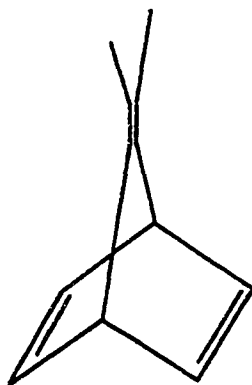
<sup>39</sup> E.R.H. Jones, G.H. Mansfield and M.C. Whiting, J. Chem. Soc., 4073 (1956)

<sup>40</sup> P.v.R. Schleyer, J. Amer. Chem. Soc., 80, 1700 (1958)

<sup>41</sup> R.C. Cookson and N.S. Wariyar, J. Chem. Soc., 2302 (1956)

metry change may make certain forbidden transitions more allowed.  $\epsilon$ , then, is not necessarily as reliable a criterion of the extent of transannular interaction as  $\lambda$ .<sup>42</sup>

It is this same type of interaction which focuses theoretical interest on the triene (XII). Theoretically the



XII

triene should have no aromatic character. The  $\pi$  orbital of each double bond is certainly capable of overlapping with its neighbor, however. The dieneone (II) seemed like a good starting point for the preparation of the molecule. A base catalyzed elimination was not attempted at first because of the lack of a completely trans hydrogen and anticipated difficulty on this score. Another worker is investigating this possibility with indefinite results to date.

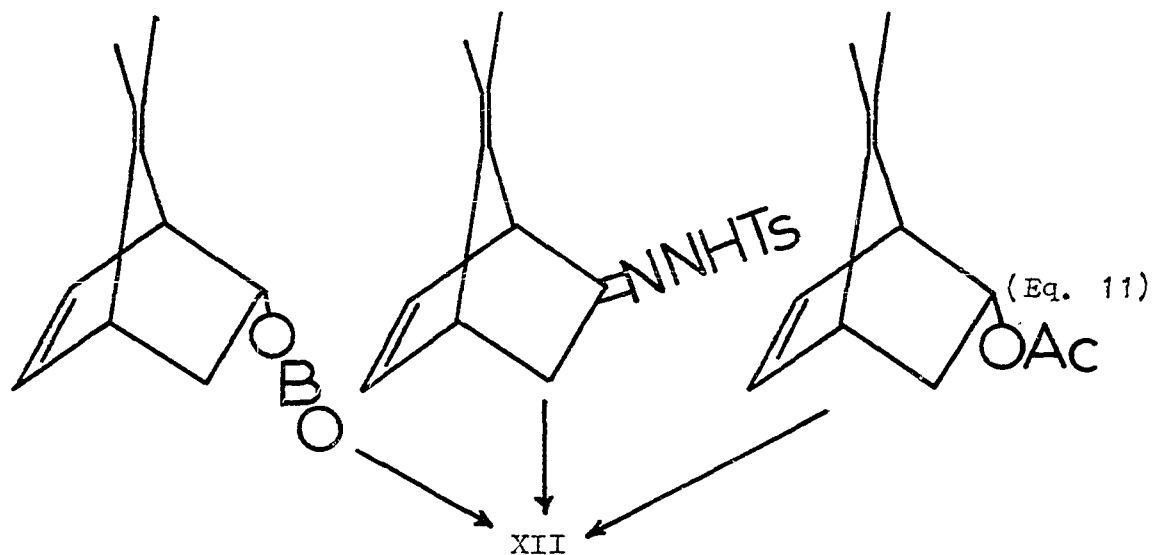
The molecule is beautifully set up for a cis elimination, prompting an attempt at acetate pyrolysis. Unfortu-

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<sup>42</sup>

H.L. McMurray, J. Chem. Phys., 9, 231 (1941)

nately the high temperatures (400-500°) necessary for such



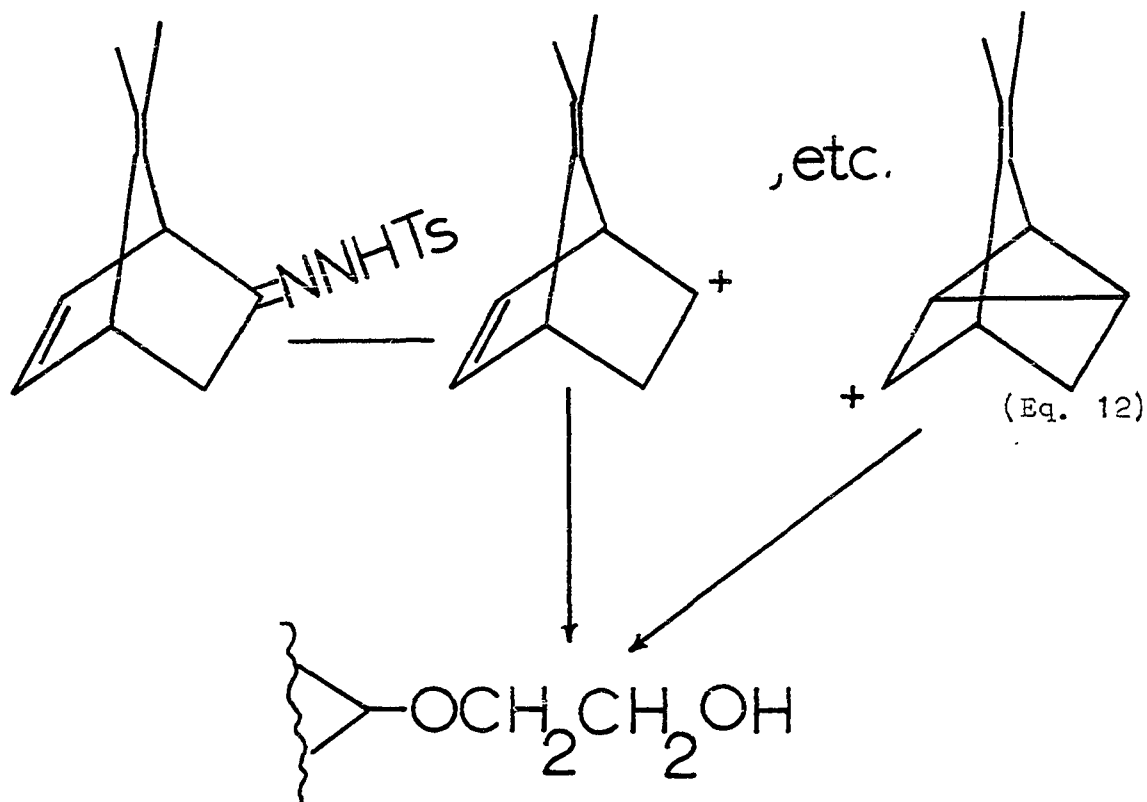
eliminations are also more than enough to reverse the Diels-Alder adduct. Apparently the latter process occurred to the exclusion of the former judging from GPC analysis and the color of the product. Borate ester eliminations are also cis and have an added attraction in that the pyrolysis usually proceeds at about 200°. The procedures outlined by O'Connor and Nace<sup>43</sup> and Dev<sup>44</sup> were tried to no avail.

The elimination of p-toluenesulfonylhydrazones, as shown in Eq. 11, looked most promising. For one thing, the reaction temperature of 160-170° was possibly in a range to avoid extensive reversal of the adduct. Judging from the IR and the boiling point, the product was most likely the mono-

<sup>43</sup> G.L. O'Connor and H.R. Nace, J. Amer. Chem. Soc., 77, 1578 (1955)

<sup>44</sup> S. Dev, J. Indian Chem. Soc., 33, 769 (1956)

(ethylene glycol) ether derived from the 2-carbonium ion or



a corresponding rearranged product. None of the triene could be isolated.

#### Hydrogenation of dieneone (II)

The next step in the general synthetic scheme, the hydrogenation of the dieneone (II), was anticipated to be a simple clean-cut reaction for it should be a simple matter to selectively hydrogenate the endocyclic double bond, which is disubstituted, over the tetrasubstituted exocyclic double bond, according to the principles set forth by Linstead

et al.<sup>45</sup> As mentioned earlier, various workers have hydrogenated the dimethylfulvene-maleic anhydride adduct without reporting yields, intimating that the reaction proceeds smoothly. Woodward and Baer<sup>46</sup> have successfully reduced the corresponding pentamethylenefulvene-maleic anhydride adduct with platinum oxide/ethyl acetate.

By GPC analysis it was found that hydrogenation of the dieneone in 95% ethanol with 5% Pd/C (150 mg catalyst/80-90 ml ethanol) proceeded to give only 50% hydrogenation of the endocyclic bond unless the amount of catalyst were reduced to 30-35 mg in 80-90 ml of a mixture of 50% ether. Under the latter conditions the endocyclic bond was hydrogenated to the extent of 70%, thus increasing the selectivity of the reaction somewhat. Because of the extreme difficulty in separating the three isomeric ketonic products, the reaction would have to proceed in at least 90% yield, or better, to find synthetic utility. Consequently, this path was abandoned in favor of hydrogenation of certain derivatives. It was reasoned that a bulkier group in exo conformation would serve to inhibit hydrogenation of the exocyclic bond.

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<sup>45</sup> R.P. Linstead, W.E. Doering, S.B. Davis, P. Levine and R.R. Whetstone, J. Amer. Chem. Soc., 64, 1985 (1942)

<sup>46</sup> R.B. Woodward and H. Baer, ibid., 66, 645 (1944)

### Hydride reductions

$\text{LiAlH}_4$  reduction of the dieneone (II) gave, according to GPC analysis and proof of structure of the keto-acetate (IX), 88-90% endo-diene-ol (III), a slightly surprising result since the 2-position does not appear to be exceptionally more hindered from the endo side than the exo side. Presumably, this may be explained using the arguments of Dauben et al<sup>47</sup> and others. According to Dauben, ketones which are only slightly sterically hindered from one side, or from neither, will yield the most stable alcohol as the predominant product, i. e., the reduction is under product development control. With bulkier reducing agents, such as  $\text{NaBH}_4$  in methanol, the reduction may become more steric approach control, i. e., it may become more important for the reducing agent to approach from the less sterically hindered side to donate the hydride ion. The reductions of menthone, 4-methyl and 2-methylcyclohexanones were compared by Dauben et al.<sup>47</sup>

The very small quantity of exo-diene-ol produced by  $\text{LiAlH}_4$  reduction of dieneone (II) and the ambiguity of hydride reductions in general prompted an investigation of the stereochemistry of such reductions using the norbornyl nucleus. The results of this investigation are summarized accordingly in Table 1.

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<sup>47</sup> W.G. Dauben, G.J. Fonken and D.S. Noyce, J. Amer. Chem. Soc., 78, 2579 (1956)

Table 1. Distribution of epimers in reductions of ketones and equilibration of alcohols (% endo)

Ketone	Hydride		
	LiAlH <sub>4</sub>	LiAl(OC(CH <sub>3</sub> ) <sub>3</sub> ) <sub>3</sub> H	Al(OC(CH <sub>3</sub> ) <sub>2</sub> ) <sub>3</sub> Equilibration
Dieneone (II)	88-90	94	56
Monoeneone (XI)	92-94	98	52-53
Dehydronorcamphor	90-91	77	65
Norcamphor	92.5 <sup>a</sup>	92.5	(about 50)
Camphor	10 <sup>b</sup>	75 <sup>c</sup>	90

<sup>a</sup>Obtained by Hirsjarvi (Footnote 51)

<sup>b</sup>Reduced by Noyce and Denny (Footnote 50)

<sup>c</sup>Reduced by Wheeler and Mateos (Footnote 48)

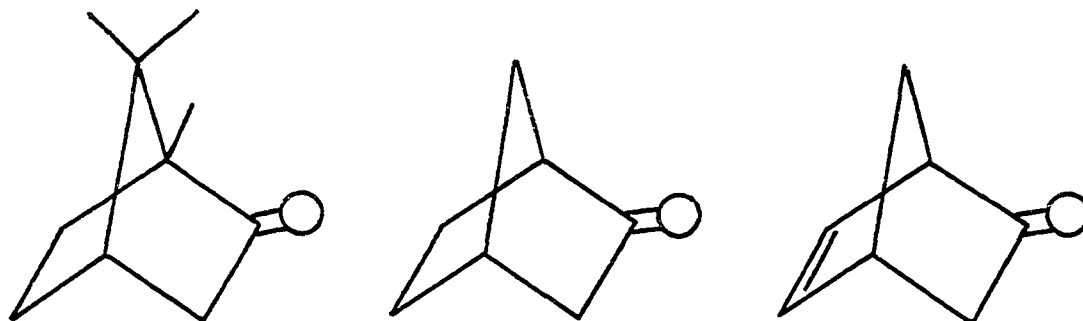
It may be seen from Table 1 that LiAlH<sub>4</sub> is remarkably stereospecific, especially considering the equilibration figures, and further that, except in the case of camphor and dehydronorcamphor, lithium tri-*t*-butoxyalumino hydride is even more stereospecific.

Wheeler and Mateos<sup>48</sup> first used LiAl(OC(CH<sub>3</sub>)<sub>3</sub>)<sub>3</sub>H<sup>49</sup> in

<sup>48</sup> O.H. Wheeler and J.L. Mateos, Can. J. Chem., **36**, 1431 (1958)

<sup>49</sup> H.C. Brown and R.F. McFarlin, J. Amer. Chem. Soc., **80**, 5372 (1958)

the investigation of the stereochemistry of hydride reductions. Camphor is known<sup>50</sup> to give 90% exo isomer on reduction with  $\text{LiAlH}_4$ . This, using Dauben's explanation, is an



Camphor

Norcamphor

Dehydronorcamphor

example of steric approach control, since obviously the exo side is much more sterically hindered. Wheeler and Mateos<sup>48</sup> reduced camphor with  $\text{LiAl}(\text{OC}(\text{CH}_3)_3)_3\text{H}$  and obtained 25% exo isomer. This is explained as product development control overcoming steric approach control. Even though the endo side is more favorable for approach, such approach would give an exo salt which would be highly hindered in the transition state of formation. As a result, the reducing agent has a greater tendency to donate a hydride ion from the less favorable side to give the more stable product.

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<sup>50</sup> D. S. Noyce and D. B. Denny, J. Amer. Chem. Soc., **72**, 5743 (1950)



Hirsjarvi<sup>51</sup> has also reduced several ketones, including norcamphor, which gave 92.5% endo-norborneol with  $\text{LiAlH}_4$ . Hirsjarvi feels previous workers have formulated theories concerning hydride reductions on meager evidence and further, feels the only conclusion one may draw at this stage is that  $\text{LiAlH}_4$  always gives chiefly the endo alcohol except where the carbonyl is effectively sterically hindered.

Beckman and Mezger<sup>52</sup> have reduced several ketones, also including norcamphor, and obtained the same results as Hirsjarvi. These workers feel that the high stereospecificity of  $\text{LiAlH}_4$  reductions may be explained in the following way. The relatively large  $\text{AlH}_4^-$  anion will attempt to approach the more positive carbonyl carbon from the opposite side of the carbonyl oxygen and, indeed, from the side of the number 7 carbon atom because less steric hindrance is found there. Consequently, the hydride will bond from the exo side and the  $-\text{OH}$  will be directed to the endo position.

Cram and Greene<sup>53</sup> have suggested that  $\text{LiAlH}_4$  coordinates first with the carbonyl oxygen, since  $\text{LiAlH}_4$  and Grignard

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<sup>51</sup> P. Hirsjarvi, Ann. Acad. Sci. Fennicae A II, 81 (1957)

<sup>52</sup> S. Beckmann and R. Mezger, Ber., 89, 2738 (1956)

<sup>53</sup> D.J. Cram and F.D. Greene, J. Amer. Chem. Soc., 75, 6005 (1953)

reagents have been shown to do so,<sup>54</sup> resulting in the oxygen becoming a very bulky group and seeking a position, then, of least hindrance. Cram has also suggested that his results could indicate that the second, third and fourth hydrogens of  $\text{LiAlH}_4$  are more reactive than the first. Electronically, at least, the alkoxy substituted hydrides should be able to donate a hydride ion more readily.

Dehydronorcamphor gave interesting results as seen in Table 1. All ketones, except camphor, gave roughly the same percent endo isomer with  $\text{LiAlH}_4$ . With lithium tri-*t*-butoxy-alumino hydride, these same four ketones gave similar results again, except for dehydronorcamphor which gave considerably more exo isomer.

What effects are controlling the reductions of these four ketones? Is steric hindrance to approach or product stability more important? The results of Kooyman and Vegter<sup>55</sup> would seem to indicate that, at least in the case of norcamphor, the exo side is less sterically hindered. These investigators chlorinated norbornane with various halogenating agents and found that  $\text{Cl}_2$ , under free radical conditions, gave 70% exo, whereas  $\text{SO}_2\text{Cl}_2$ , a bulkier reagent, gave 95% exo.

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<sup>54</sup> H.L. Cohen and G.F. Wright, J. Org. Chem., 18, 432 (1953)

<sup>55</sup> E.C. Kooyman and G.C. Vegter, Tetrahedron, 4, 382 (1958)

This was interpreted to mean that the *exo* side is less sterically hindered. These results parallel those in the reduction of norcamphor or of dieneone (II), i.e., the bulkier reducing agent is more stereospecific because the greater hindrance to the *endo* side becomes more important with the bulkier reagent. The simplest conclusion, then, is that the reductions with both reagents, in the case of dieneone (II), monoeneone (XI) and norcamphor, are probably steric approach controlled, since close evaluation of the relative steric factors in these three ketones indicates them to be about equal. In dehydronorcamphor, because of the absence of the axial hydrogens, the steric balance is undoubtedly shifted in the direction of that of camphor, leaving two alternatives.

One, that the *exo* side in dehydronorcamphor is very slightly more sterically hindered, resulting in no steric influence on  $\text{LiAlH}_4$ , i.e., product development control. The bulkier  $\text{LiAl}(\text{OC}(\text{CH}_3)_3)_3\text{H}$  is affected, however, to give more *exo* isomer. Examination of models indicates the contrary of this assumption, showing that the *exo* side is probably more open to approach.

The second alternative is the following. It does not seem possible to definitely establish the controlling influence in the  $\text{LiAlH}_4$  reduction of dehydronorcamphor even though the *exo* side appears to be less sterically hindered. Reduction by lithium tri-*t*-butoxyalumino hydride, however, is

very likely steric approach controlled as indicated by a comparison with dieneone (II). In both dieneone (II) and dehydronorcamphor, approach to the endo side is equally hindered, so that the rates of reduction from this side will be equal. The exo side, however, is more hindered in the case of dehydronorcamphor, thereby slowing the rate of reduction from the exo side by bulky reducing agents.  $\text{LiAlH}_4$  is probably sufficiently small to escape the effect of the 7-hydrogen. Dehydronorcamphor, thus, seems to be a borderline case between camphor and norcamphor.

All of this, unfortunately, does not explain the specificity of  $\text{LiAlH}_4$ , which will probably not be understood until the mechanism of the reaction is elucidated. An understanding is further complicated by the fact that it is entirely possible that no one has ever carried out a complete reduction with  $\text{LiAlH}_4$ . Aside from the results of Cram and Greene<sup>53</sup> which could be interpreted to mean that alkoxy hydrides are much more reactive, Hirsjarvi,<sup>51</sup> for example, reduced one equivalent of norcamphor with only three equivalents of  $\text{LiAlH}_4$ . This means that at least part of the norcamphor was reduced by an alkoxy substituted hydride, hence a bulkier reducing agent. Beckman and Mezger,<sup>52</sup> who offer an explanation of the specificity of  $\text{LiAlH}_4$ , used only 2 equivalents of  $\text{LiAlH}_4$  per equivalent of ketone. Further investigation may reveal that true  $\text{LiAlH}_4$  reductions, if possible,

are not so stereospecific. The standpoint of Hirsjarvi<sup>51</sup> is probably safest at this time.

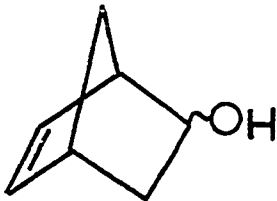
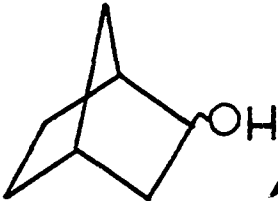
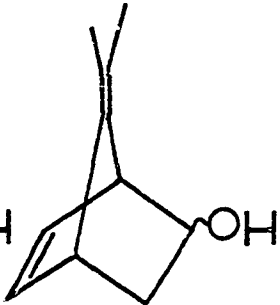
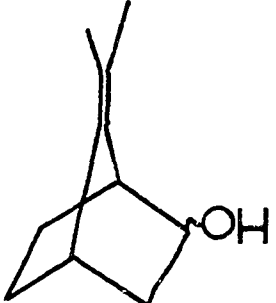
This investigation has shown that, for the preparation of pure epimers, lithium tri-*t*-butoxyaluminum hydride may be more useful than  $\text{LiAlH}_4$ . It has also been shown that exo-diene-ol, needed for future work, may be obtained by equilibrating the endo isomer. These seem to be the only worthwhile conclusions.

#### Intramolecular hydrogen bonding

GPC analysis of the mixtures of alcohols obtained as

Table 2. Retention times (min.) of some bicyclic alcohols in gas-phase chromatography

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	I	II	III	IV
<u>endo</u>	79 <sup>a</sup>	104 <sup>a</sup>	30 <sup>b</sup>	38 <sup>b</sup>
<u>exo</u>	94	96	33	28

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<sup>a</sup>Determined at 160° at a flow rate of 30 ml of He/min.

<sup>b</sup>Determined at 210° at a flow rate of 41 ml of He/min.

discussed above, gave some very startling results as shown in Table 2.

Infra-red spectroscopic evidence<sup>56</sup> has recently appeared indicating intramolecular hydrogen bonding between the hydroxyl group and the double bond of endo-norborneol, but not of the exo isomer. The data of Table 2 show that alcohols, capable of internal hydrogen bonding, show strikingly lower retention times.

From the table it may be seen that endo-I, which has been shown to hydrogen bond internally, elutes from the polar Ucon column (see Experimental) much more rapidly than its exo isomer. Under the same conditions, exo-II is eluted very slightly more rapidly than its endo isomer, giving an incomplete resolution of peaks. The most significant difference is pointed up in the following way. Hydrogenation of I has no appreciable effect on the exo isomer, but serves to increase the retention time of the endo isomer by 25 minutes.

Both the endo and exo isomers of compound III are capable of intramolecular hydrogen bonding. Hydrogenation of III serves to decrease the retention time of the exo isomer, but increases that of the endo isomer. Consequently, an endo-exo mixture of III is barely resolved, while an endo-exo mixture of IV is very cleanly resolved and the order of ap-

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<sup>56</sup> P.v.R. Schleyer, D.S. Trifan and R. Bacskai, J. Amer. Chem. Soc., 80, 6681 (1958)

pearance of the peaks is reversed.

These findings constitute the first evidence, other than spectra, of such hydrogen bonding and suggest that GPC may become an important supplement to infra-red in assigning configuration to compounds of unknown stereochemistry.

#### Hydrogenation of endo-diene-ol (III) and derivatives

Since the hydrogenation of the dieneone (II), as described earlier, was insufficiently selective for synthetic purposes, recourse was taken to the hydrogenation of certain derivatives of the dieneone (II).

Before proof of structure of the endo-keto-acetate (IX), it was tentatively assumed, on the basis of certain solvolysis data of the diene-tosylate (V), that the major product of the  $\text{LiAlH}_4$  reduction of dieneone (II) was the exo isomer. It was assumed, then, that hydrogenation of the exo-acetate or exo-alcohol should be much more selective in favor of the endocyclic double bond. This is exactly what happened in the case of the acetate, but it was learned later, of course, that the acetate was actually endo. The only possible explanation seems to be that the endo-diene-acetate (IV) was selectively adsorbed to the surface of the catalyst (Pd/charcoal) on the side of the acetoxy substituent. The endo-diene-tosylate (V), a very bulky substituent, likewise gave good selectivity in hydrogenation of the endocyclic double bond.

In the endo-diene-acetate and the tosylate, this assumed preferential adsorption to the catalyst surface appears to outweigh the increased steric hindrance to the endocyclic double bond. The results are summarized in Table 3.

Table 3. Percentage of hydrogenation at  $\Delta^5$  in various dienes

Substance hydrogenated	$\Delta^5$	$\Delta^7$	
		$\alpha^a$	$\beta^a$
Dieneone (II)	70	(	30 )
<u>endo</u> -Diene-ol (III)	61 <sup>b</sup>	15	24
<u>endo</u> -Diene-acetate (IV)	95.4	3.3	1.3
<u>endo</u> -Diene-tosylate (V)	95	--	--

<sup>a</sup>Hydrogenation at  $\Delta^7$  gives a mixture of anti and syn isomers which are called  $\alpha$  and  $\beta$  here, since the conformation of these products is not known

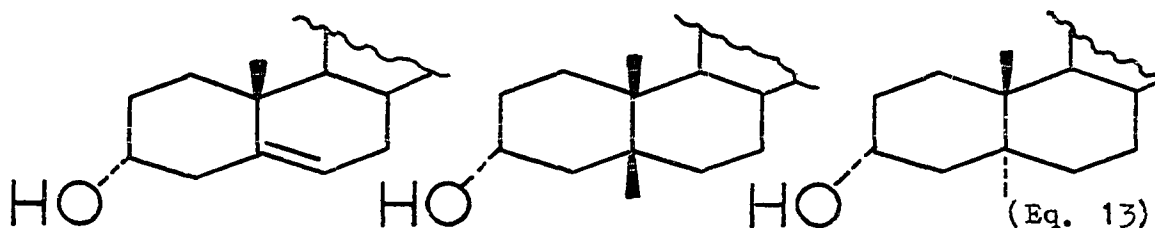
<sup>b</sup>Conditions may be improved to give a better yield

Other possible examples of this type of selective adsorption in hydrogenations are available. Hadler,<sup>57</sup> for example, points out that "electronically polarizable groups may either assist or oppose the primary steric factor." Marker et al have obtained a quantitative yield of A/B trans

<sup>57</sup>H.I. Hadler, Experientia, 11, 175 (1955)



ring juncture from hydrogenation of 3- $\alpha$ -hydroxy- $\Delta^5$ -sterols in neutral media.<sup>58</sup> As shown in Eq. 13, to obtain the A/B



3- $\alpha$ -hydroxy  $\Delta^5$

A/B cis

A/B trans

trans compound, it would be necessary for hydrogenation to occur from the same side as the hydroxyl, hence in direct steric conflict. Lewis and Shoppee,<sup>59</sup> in contrast, found only steric effects operative in the hydrogenation of several 3- $\alpha$ - $\Delta^5$ -compounds, including the 3- $\alpha$ - $\Delta^5$ -sterol described above. These workers, who promoted hydrogenation with strong mineral acids, obtained mainly A/B cis and further found that the percentage of A/B cis increased as the size of the 3- $\alpha$ -substituent increased (e.g. methoxy, acetoxy). Since the oxygen of these substituents would be highly protonated under

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<sup>58</sup> R.E. Marker, T.S. Oakwood and H.M. Crooks, J. Amer. Chem. Soc., 58, 481 (1936)

<sup>59</sup> J.R. Lewis and C.W. Shoppee, J. Chem. Soc., 1365 (1955)

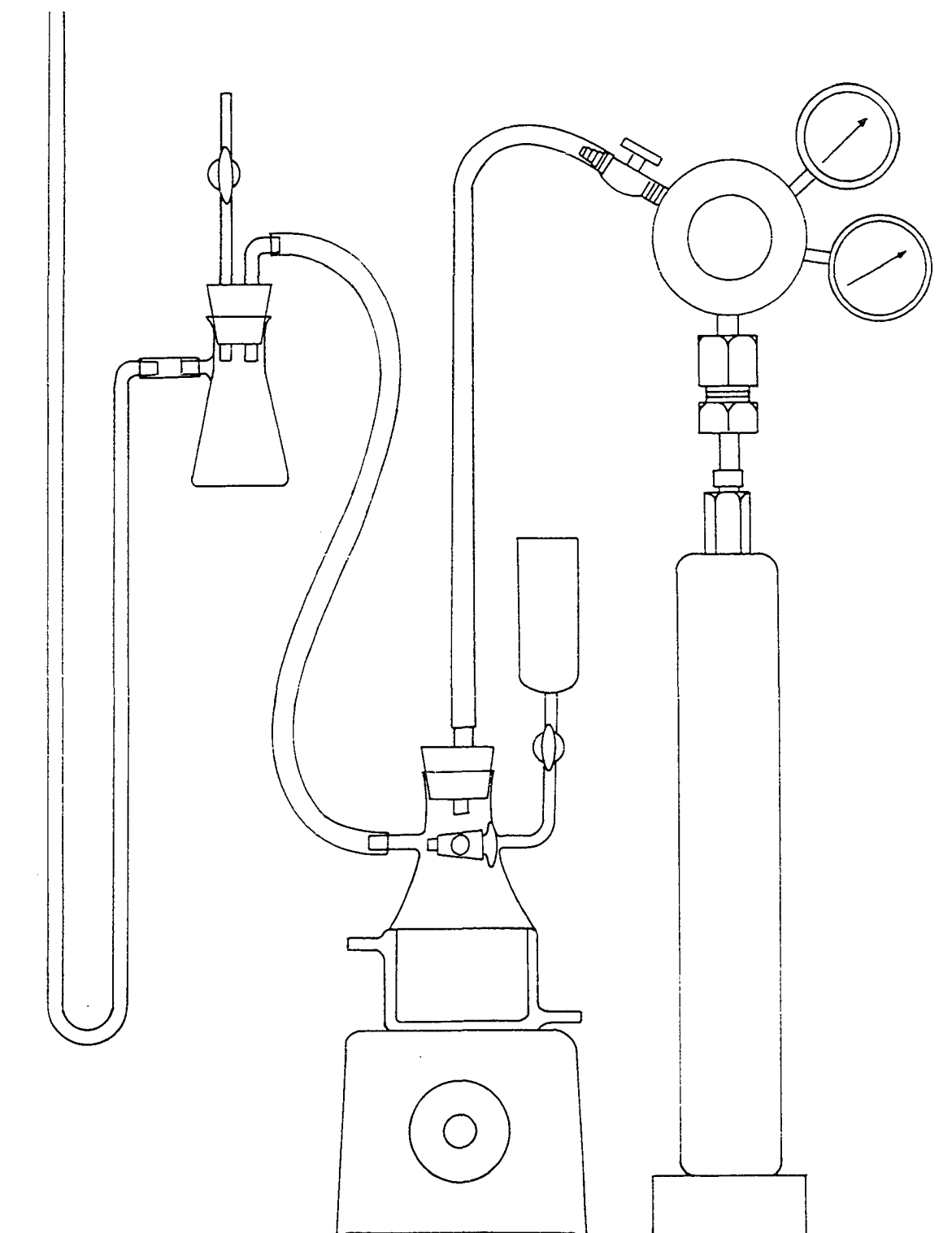
these circumstances, it is very possible the molecule would no longer be selectively adsorbed on the surface of the catalyst.

It should be very interesting to investigate the hydrogenation of the exo isomers of this series in both acid and neutral media along with the endo isomers in acid media. Projects along these lines have been planned.

For this reaction scheme to be successful, it became necessary to selectively hydrogenate rather large quantities of dienes. The only method available at the time for atmospheric pressure hydrogenations was by the upward displacement of hydrogen from a large burette by mercury or by oil. This is, of course, a tedious process, requiring constant attention, and is awkward and expensive on all but a small scale.

The outgrowth of this need for a larger, more versatile apparatus is the apparatus shown in Figure 5, whose construction is described in the Experimental. The basis of the apparatus is the use of an ordinary pressure regulator to regulate pressure and hydrogen flow into the reaction vessel. If hydrogen uptake is stopped, the flow of hydrogen from the tank is stopped by the regulator. Consequently, the apparatus needs no attention and merely shuts itself off when the hydrogenation is complete. In the case of a selective hydrogenation, the rate of hydrogen uptake can be very accurately followed by closing the lecture bottle and noting the time

Figure 5. A convenient atmospheric pressure hydrogenation apparatus



HYDROGENATION APPARATUS

for a given fall in the manometer.

To increase the sensitivity of the primary pressure gauge, the lecture bottle was partially filled with paraffin to leave a volume of 180 ml (including primary gauge). With a tank of this size, 0.05 moles of an olefin would require 100 psi of hydrogen at 25°. The apparatus is of limitless versatility for, by changing the size of the tank and/or the primary gauge, it would be possible to operate in the range of moles or in the realm of the 500 ml burette at 0.01 mole.

### Ozonolyses

As pointed out earlier, few workers have ozonized the  $\Delta^7$  double bond in norbornane derivatives and in all cases but one, no attempt was made to isolate a 7-norbornone. Wilder and Winston<sup>60</sup> realized poor yields (30%) of 7-ketones in all cases, except for that of a hydrocarbon.

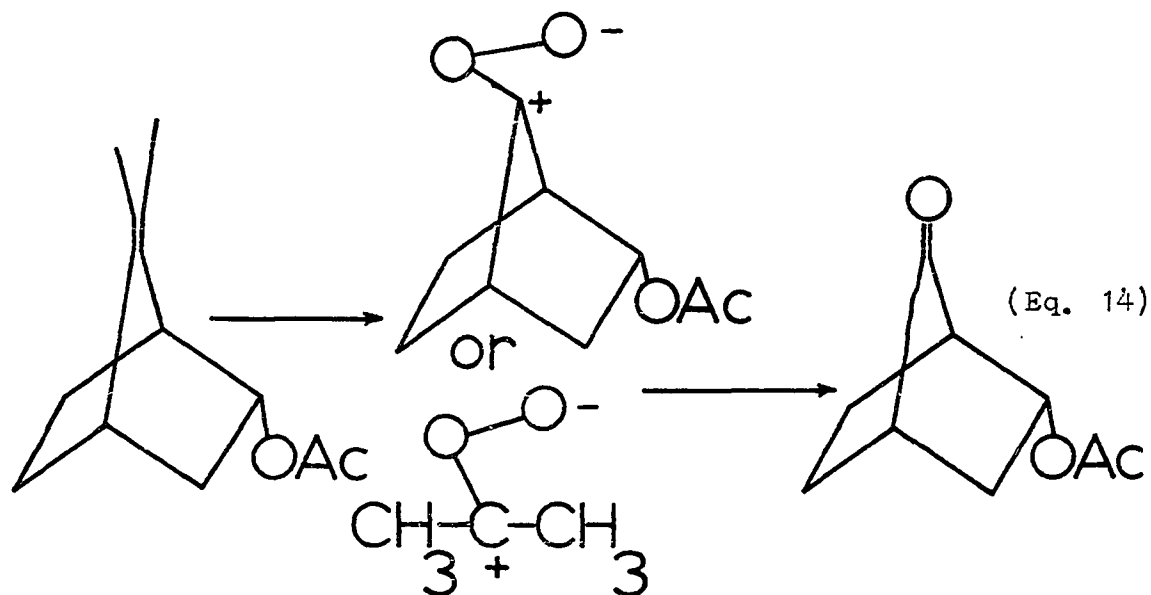
Ozonolysis of the endo-monoene-acetate (VII) proceeded equally well in all three solvents tried.  $\text{CH}_2\text{Cl}_2$  is superior to methanol or acetic acid, however, because of tedious extractive procedures involved with the latter two. It was hoped the 45% yield obtained in  $\text{CH}_2\text{Cl}_2$  could be improved in a solvent which would trap the intermediate zwitterion,<sup>61</sup>

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<sup>60</sup> P. Wilder and A. Winston, J. Amer. Chem. Soc., **78**, 868 (1956)

<sup>61</sup> P.S. Bailey, Chem. Revs., **58**, 925 (1958)

as proposed by Criegee, before it has a chance to rearrange or, recombine to form the ozonide and then rearrange. Many



such zwitterions have been trapped in methanol as the methoxy hydroperoxide to increase yields by preventing rearrangement. In this particular case, if the bicyclic moiety forms the zwitterion, it cannot add to the acetone formed to give the ozonide. Criegee has shown that acetone will not undergo such addition by zwitterions.<sup>61</sup> Determination of the other product obtained in the ozonolysis would, no doubt, shed much light on the course of the ozonolysis. The other 55% of the total yield seems to be a single high boiling (120°/0.35 mm) oil, whose infra-red spectrum has key absorptions at 5.75, 5.85, 8.05 and a broad weak absorption at 3.1, very possibly an acetoxy acid.

Structure of the endo-keto-acetate (IX) was proved by its conversion, in good yield, via the ethylene thioketal to

endo-norborneol, after the fashion of van Tamelen and Judd<sup>62</sup> in the proof of structure of  $\beta$ -isocamphor, which contains a bridge carbonyl.

Preparation of the endo-keto-tosylate (X) was attempted, for this molecule should provide an interesting and unique study of the displacement reactions of  $\beta$ -tosyl ketones. It has recently been shown by Bartlett and Trachtenberg<sup>63</sup> that the activating influence of the carbonyl in displacement reactions of  $\alpha$ -substituted ketones, most likely, arises from either the  $\pi$  orbital system of the carbonyl partially overlapping with the incoming iodide ion so as to lower the transition state energy, as proposed by Dewar<sup>64</sup> and by Winstein et al.,<sup>65</sup> or from the electrostatic effect of the carbonyl, as favored by Pearson et al.<sup>66</sup>

This keto-tosylate (X) is not an  $\alpha$ -tosyl ketone, but it has already been shown, from UV data of the dieneone (II), that the  $\pi$  orbital of the bridge double bond interacts with

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<sup>62</sup> E. E. van Tamelen and C. I. Judd, J. Amer. Chem. Soc., **80**, 6305 (1958)

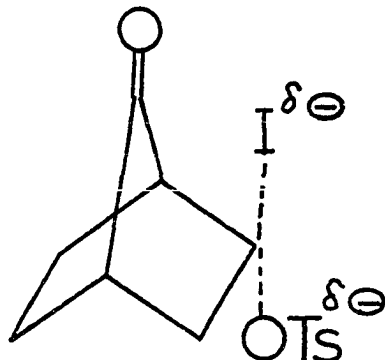
<sup>63</sup> P. D. Bartlett and E. N. Trachtenberg, J. Amer. Chem. Soc., **80**, 5808 (1958)

<sup>64</sup> M. J. S. Dewar, The Electronic Theory of Organic Chemistry, p. 73, Clarendon Press, Oxford 1949

<sup>65</sup> S. Winstein, E. Grunwald and H. W. Jones, J. Amer. Chem. Soc., **73**, 2700 (1951)

<sup>66</sup> R. G. Pearson, S. H. Langer, F. V. Williams and W. J. McGuire, J. Amer. Chem. Soc., **74**, 5130 (1952)

the 2-carbonyl. It is possible, then, because of the transannular influence of the bridge carbonyl, that the keto-tos-



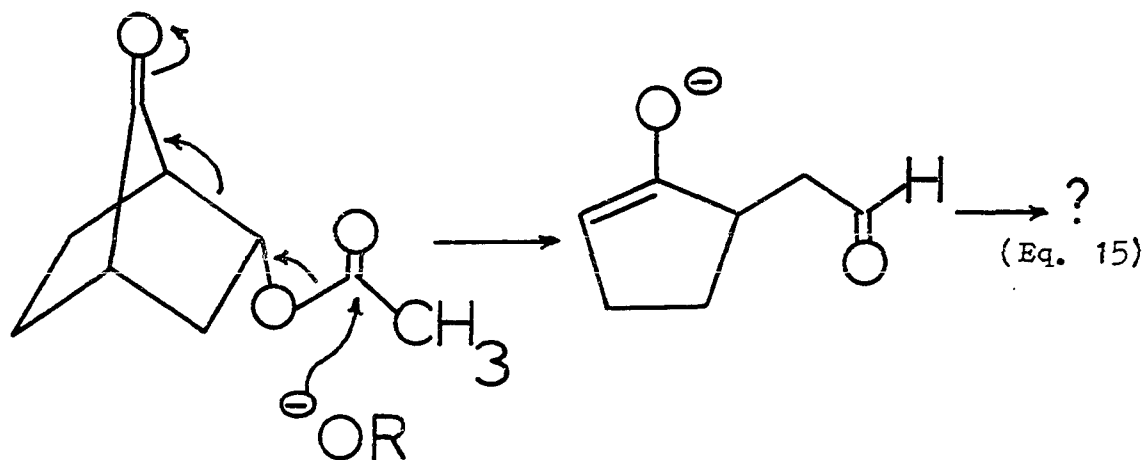
ylate (X) would enjoy a reactivity, in  $S_N2$  displacement reactions, associated with  $\alpha$ -tosyl ketones.

The ketol (XIII), a possible route to the keto-tosylate (X), was not obtained on ozonolysis of the monoene-ol (VI) in ethyl acetate,  $CH_2Cl_2$  or acetic acid.

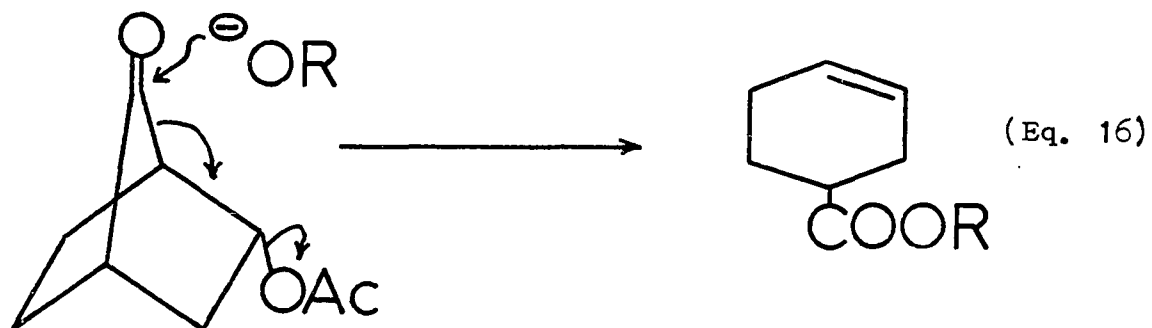
Attempted hydrolysis of the endo-keto-acetate (IX) to the corresponding ketol (XIII) gave some very interesting results. In bases, such as  $NaOCH_3$  in methanol, the keto-acetate (IX) yielded an uncharacterizable amorphous solid in just a few seconds. If the reaction were neutralized after two or three minutes, neither starting material nor ketol could be isolated. Hydrolysis in aqueous base proceeded more slowly, because of low solubility, to give the same amorphous solid. This product exhibits key absorptions in the infrared at 5.75, 6.1 and 3.0 in  $CHCl_3$ . It is very likely that



the hydrolysis proceeds via a retroaldol, as shown in Eq. 15.



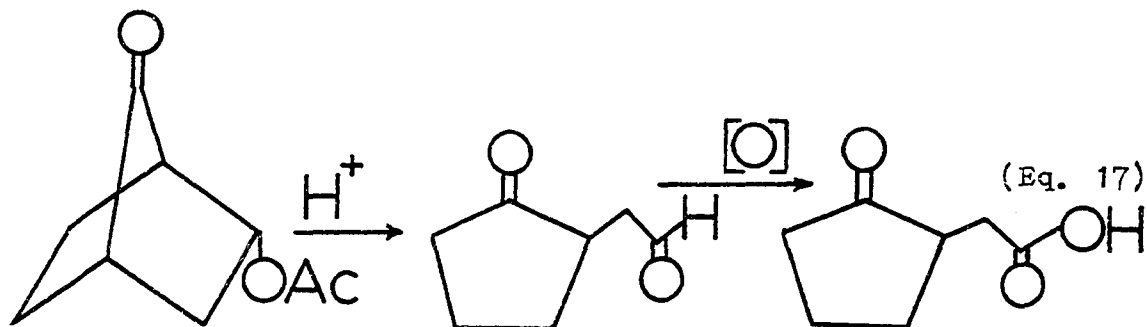
The rapidity of this hydrolysis may be accounted for by considering that, conformationally, the molecule is perfect for the suggested ring opening. In addition, considerable strain is relieved. It is also possible, but less likely, that the



ring opening occurs as shown in Eq. 16. If this is the mode of reaction, the tosylate should be considerably faster than

the acetate, provided addition to the carbonyl is not the rate determining step.

Acid hydrolysis, which proceeded considerably slower, gave an oil in good yield, whose IR (3.75, 5.75, 5.81) supports the keto-aldehyde shown in Eq. 17.



$KMnO_4$  oxidation of the product gave a keto-acid, whose IR (5.75, 5.83, 3.0(broad)) was compatible with the molecule shown in Eq. 17.

Because of the failure to obtain the ketol (XIII), the only recourse to the endo-keto-tosylate (X) appeared to be by ozonolysis of the endo-monoene-tosylate (VIII). Ozonolysis in  $CH_2Cl_2$  gave only a 14% yield of a substance whose IR, at least, appeared to be that of the expected keto-tosylate. Ozonolysis in acetic acid increased the yield to greater than 23%. The recrystallized and dried product consistently exhibited a weak absorption in its IR at 2.80. Further, the

elemental analysis did not check for the expected keto-tosylate. The analysis did check repeatedly, however, for an oxygenated keto-tosylate (X). It is also very possible that the material crystallizes as a mono-hydrate. The product of ozonolysis of the monoene-tosylate (VIII), thus, remains uncertain at this time.

## EXPERIMENTAL

GPC analyses

All acetates and ketones were determined on a 10 or 12.5 ft. x 1/4 in. copper coil packed with 27% by weight of a mixture composed of 2/3 Apiezon-M and 1/3 Dow Corning Silicone 702 fluid on firebrick, using an apparatus constructed from a Gow-Mac thermal conductivity cell.

Alcohols were determined on a 12 ft. x 1/4 in. coil packed with 23% by weight Union Carbide Ucon polar No. 50-HB-2000, described as a mono alkyl ether of a mixed polyoxyethylene-cxypropylene diol, on Celite.

Construction and use of the hydrogenation apparatus

An ordinary hydrogen lecture bottle was partially filled with paraffin to leave a volume of 178 ml and fitted with a pressure regulator, by means of a special adapter, to serve as the hydrogen source, as shown in Figure 5. The pressure regulator serves to maintain a constant hydrogen pressure, generally 10-20 mm, in the reaction vessel, which consists of a 250 ml Erlenmeyer flask, with added water jacket and sidearms. The catalyst may be pre-reduced, in which case, the sample is drawn into the reaction vessel by application of a slight vacuum to the sidearm which is fitted with a stopcock.

The rate of hydrogenation may be followed by closing the

lecture bottle and recording the time required for the manometer to fall a given distance, usually +10 mm to -10 mm, to check against the occurrence of a leak. The amount of hydrogen absorbed can be determined by noting the primary pressure gauge which is fairly sensitive since the volume of the tank is small (180 ml, tank + gauge). Sensitivity can be increased by reducing the volume of the tank further, and/or by using a more sensitive primary gauge. Frequently, completion of the reaction or a change in the rate of hydrogenation may be detected even more simply, for the manometer will usually indicate a slight increase in pressure.

#### Dimethylfulvene

Dimethylfulvene was prepared from cyclopentadiene, acetone and potassium hydroxide according to the procedure of Crane et al.<sup>67</sup>

#### $\alpha$ -Acetoxyacrylonitrile

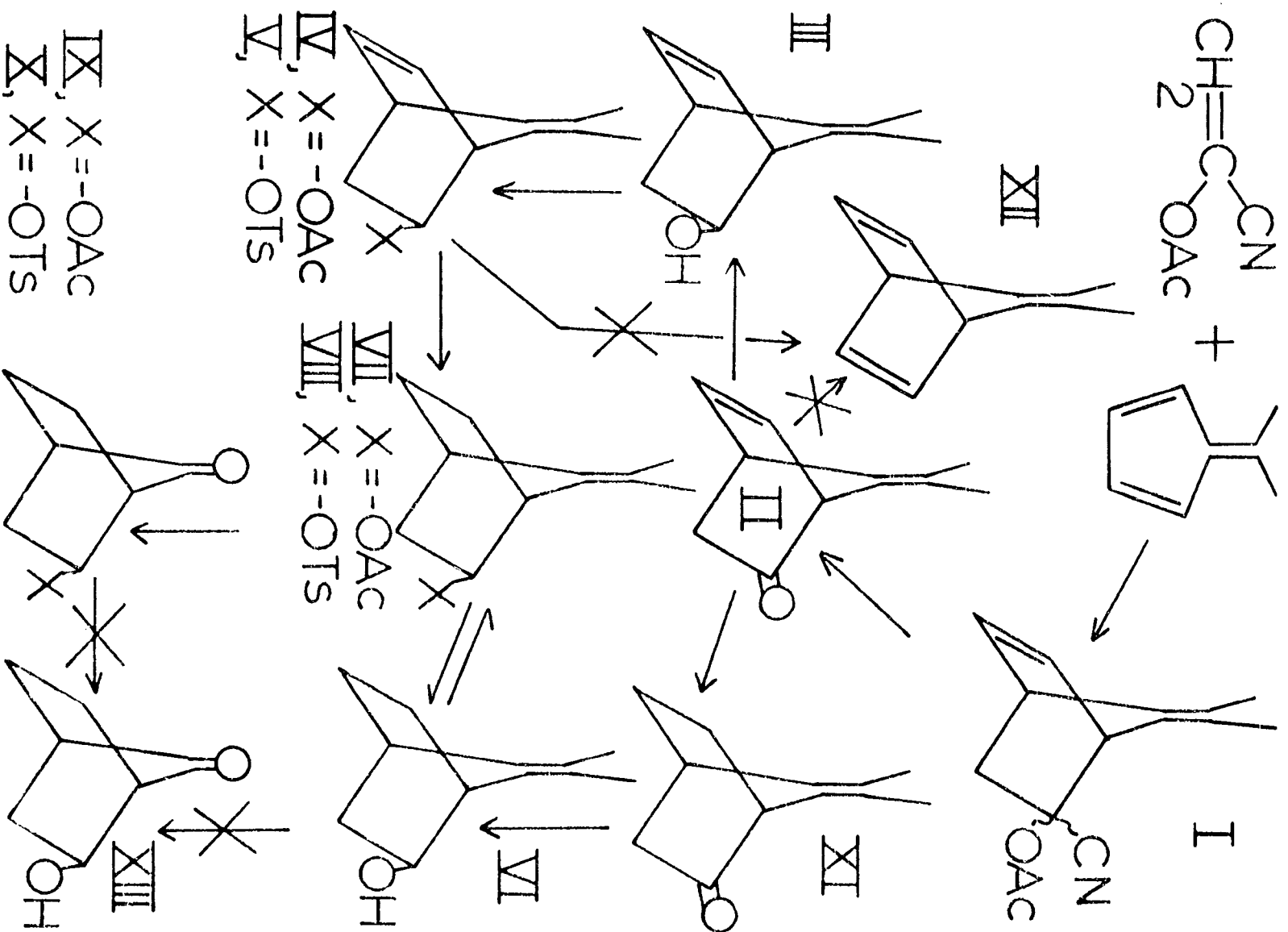
$\alpha$ -Acetoxyacrylonitrile was generously supplied, in part, by Eastman Chemical Products, Inc., Kingsport, Tennessee and, in part, was prepared from the reaction of ketene and hydrogen cyanide catalyzed by potassium acetate, according to

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<sup>67</sup> G. Crane, C.E. Boord and A.L. Henne, J. Amer. Chem. Soc., 67, 1237 (1945)

<sup>68</sup> F. Johnston and L.W. Newton, U.S. Patent, 2,395,930 (1946)

Figure 6. Synthetic scheme



Johnston and Newton, using the ketene generator described by Williams and Hurd.<sup>69</sup>

### Nitroethylene

Nitroethylene was prepared by phthalic anhydride dehydration of 2-nitroethanol<sup>70</sup> as described by Buckley and Scaife.<sup>71</sup>

### Attempted preparation of 2-acetoxy-7-isopropylidene-bicyclo- /2,2,1/-5-heptene

After the method used by Roberts et al<sup>72</sup> to prepare dehydronorbornyl acetate, 22.5 g (0.21 mole) of dimethylfulvene and 21 g (0.24 mole) of vinyl acetate were heated at 200° in a sealed tube for 10 hours. Careful distillation of the product yielded only starting materials and considerable polymeric material.

The above procedure was duplicated except that 0.1 g of N-phenyl- $\beta$ -naphthylamine, as a polymerization inhibitor, was added. Again, chiefly polymeric material was obtained.

The addition of 0.1 g of chloranil, as polymerization

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<sup>69</sup>J.W. Williams and C.D. Hurd, J. Org. Chem., 5, 122 (1940)

<sup>70</sup>H.T. Roy, Jr., U.S. Patent, 2,710,830 (1955)

<sup>71</sup>G.D. Buckley and C.W. Scaife, J. Chem. Soc., 1471(1947)

<sup>72</sup>J.D. Roberts, C.C. Lee and W.H. Saunders, J. Amer. Chem. Soc., 76, 4501 (1954)



inhibitor, gave the same negative results.

11 g (0.104 mole) of dimethylfulvene and 16 g (0.186 mole) of vinyl acetate were heated at 150° for 10 hours but resulted, again, in only polymeric products.

Attempted preparation of 2-nitro-7-isopropylidene-bicyclo-  
/2,2,1/-5-heptene

To 40 g (0.377 mole) of dimethylfulvene was added 13 g (0.178 mole) of nitroethylene at 0°. The flask was stoppered and allowed to warm to room temperature. On reaching room temperature, the reaction mixture exploded violently and burst into flames, sending the contents of the flask to the ceiling and leaving behind a mass of carbon.

In an attempt to avoid such a violent reaction, 5 g (0.069 mole) of nitroethylene and 7 g (0.066 mole) of dimethylfulvene were dissolved in 50 ml of benzene and allowed to stand at room temperature for two weeks. After most of the solvent was removed by slow distillation, an explosion, similar to the previous one, occurred. According to Buckley and Scaife,<sup>71</sup> nitroethylene polymerizes violently in the presence of a trace of base.

2-Acetoxy-2-cyano-7-isopropylidene-bicyclo-/2,2,1/-5-heptene

(I) Cyano-acetate

100 g (0.94 mole) dimethylfulvene and 50 g (0.45 mole)

of  $\alpha$ -acetoxyacrylonitrile were heated at 55-60° for 30 days in a stoppered flask which had been flushed with nitrogen. After this period, part of the excess fulvene was removed under vacuum from the resultant mushy solid. The product was then washed by stirring with 200 ml of pentane and filtering to yield 60 g (61%) of a slightly yellow solid. Generally, the cyanoacetate (I) is not purified any further, but used in this form. An analytical sample was recrystallized three times from pentane to give white needles which melted at 122.5-123.5°.

Anal. Calcd. for  $C_{13}H_{15}O_2N$ : C, 71.86; H, 6.96; N, 6.45.  
Found: C, 71.92; H, 6.79; N, 6.50.

The wash pentane, on removal of solvent, was found to contain 76 g of a heavy oil, which appeared to consist of dimethylfulvene, polymer and some cyanoacetate (I).

7-Isopropylidene-bicyclo-/2,2,1/-5-hepteneone-2 (II) Dieneone

60 g (0.28 mole) of the slightly impure cyanoacetate (I) was dissolved in 530 ml of 1 N  $NaOCH_3$  in methanol and allowed to stand at room temperature for three hours, after which 1700 ml of ice and water were added and the resultant oil extracted thrice with methylene chloride. In some cases, it may be necessary to extract with ether to avoid emulsions. The extracts were combined and washed twice with water, once with saturated NaCl solution and finally dried over anhydrous

$\text{Na}_2\text{SO}_4$ . After removal of the solvent at atmospheric pressure, the product was distilled to yield 24 g (59%) of the dieneone (II), b.p.  $46^\circ/0.30$  mm.

76 g of the heavy oil, obtained from the pentane wash of the cyanoacetate (I), was hydrolyzed in like fashion to yield 16 g of the dieneone (II). The combined yields of dieneone (II) represent an overall yield, based on  $\alpha$ -acetoxyacrylonitrile, of 60%. Generally, however, most cyanoacetate (I) preparations were run for 14 days, rather than 30 days, because of the time involved, resulting in 45-50% yields of dieneone (II).

Semicarbazone derivative The semicarbazone was prepared according to Shriner and Fuson<sup>73</sup> and recrystallized from 95% ethanol, m.p.  $209-210^\circ$ , dec.

Anal. Calcd. for  $\text{C}_{11}\text{H}_{15}\text{ON}_3$ : C, 64.36; H, 7.37; N, 20.47. Found: C, 64.32; H, 7.19; N, 20.40.

7-Isopropylidene-bicyclo-2,2,1/-5-heptene-2,3-dione

Selenium dioxide oxidation 200 mg (0.0013 mole) of dieneone (II), 240 mg of  $\text{SeO}_2$  and 3 ml of acetic anhydride were heated at  $140^\circ$  for 3 hours, according to the method<sup>74</sup> of

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<sup>73</sup> R.L. Shriner and R.C. Fuson, The Systematic Identification of Organic Compounds, 3rd ed., p. 170, John Wiley & Sons, Inc., New York 1948

<sup>74</sup> W.C. Evans, J.M. Ridgion and J.L. Simpson, J. Chem. Soc., 137 (1934)

Evans et al in the preparation of camphorquinone. The reaction mixture, which became very black, was neutralized with dilute KOH and extracted with ether. No product could be isolated. Reaction time was shortened to one-half hour with the same results.

Via the  $\alpha$ -oxime<sup>75</sup> 0.6 g (0.004 mole) of dieneone (II), 0.412 g (0.004 mole) of n-butyl nitrite, 4 ml of ether, 4 ml t-butyl alcohol and 4 ml of potassium t-butoxide solution (1.6 g K/40 ml t-butyl alcohol) were stirred for 7 hours at 3°. After removal of the ether and most of the t-butyl alcohol under reduced pressure, 20 ml of water was added and the resultant solution was extracted with 3 portions of benzene. Saturation of the solution with CO<sub>2</sub> caused precipitation of a dark brown polymeric material, from which no recognizable product could be obtained.

7-Isopropylidene-bicyclo-2,2,1-5-heptene-2-(p-toluenesulfonylhydrazone)

9 g (0.061 mole) of dieneone (II) and 11.5 g (0.062 mole) of p-toluenesulfonylhydrazide<sup>76</sup> were dissolved in 200 ml of 1% ethanolic HCl and refluxed for 30 minutes according to the general method for preparation of sulfonylhydrazones described

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<sup>75</sup> H. Rapoport and J.Z. Pasky, J. Amer. Chem. Soc., **78**, 3788 (1956)

<sup>76</sup> K. Freudenberg and F. Blummel, Ann., **440**, 45 (1924)

by Bamford and Stevens.<sup>77</sup> Scratching the reaction vessel initiated crystallization of the product which on filtration afforded 17 g (88%) of the hydrazone, m.p. 155-157°.

Attempted preparation of 7-isopropylidene-bicyclo-/2,2,1/-  
2,5-heptadiene (XII)

From the sulfonylhydrazone 6 g (0.019 mole) of the above sulfonylhydrazone was dissolved in 75 ml of 1.5 N Na/CH<sub>2</sub>OHCH<sub>2</sub>OH and heated at 160-170° until N<sub>2</sub> ceased to be evolved. H<sub>2</sub>O was added to the solution and the product was extracted with pentane. The combined extracts were washed with water and dried. Distillation, after concentration of the extract, gave about 3-4 g of a yellow oil, b.p. 92-98°/1 mm. The infra-red spectrum indicated the product to be an unsaturated hydroxy-ether. None of the expected triene (XII) could be isolated.

Acetate pyrolysis 0.5 g of the endo-diene-acetate (IV) was pyrolyzed in a 6 in. column packed with 3/16 in. glass helices at 500°. GPC and IR data failed to show the presence of the triene (XII).

Borate ester pyrolysis The meta-borate ester of the endo-diene-ol (III) was prepared by the method of O'Connor and Nace<sup>43</sup> and pyrolyzed accordingly. Analysis of the prod-

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<sup>77</sup> W.R. Bamford and T.S. Stevens, J. Chem. Soc., 4735 (1952)

ucts, however, failed to indicate the presence of the triene (XII).

endo-7-Isopropylidene-bicyclo- $\{2,2,1\}$ -5-heptenol-2 (III) Diene-ol

To 2.6 g (0.068 mole) of  $\text{LiAlH}_4$ , covered with 250 ml of anhydrous ether in a flask equipped with a stirrer, was added 10 g (0.067 mole) of dieneone (II), dissolved in 250 ml of ether. The rate of addition was adjusted so as to maintain constant refluxing of the ether. After addition was complete, the reaction mixture was stirred at room temperature for one hour. To effect hydrolysis, about 3 ml of water was slowly added to remove excess  $\text{LiAlH}_4$ . Hydrolysis was completed by the addition of about 75-100 ml of wet  $\text{Na}_2\text{SO}_4$ , which also served to coagulate the hydroxides formed. The ether solution was decanted and the solid material washed twice with ether. The ether extracts were combined and dried over anhydrous  $\text{Na}_2\text{SO}_4$ .

After removal of the ether through a 1 ft Vigreux column by slow, atmospheric pressure distillation, the semi-solid crude product was recrystallized from pentane. Two crops were taken from the pentane mother liquor, combined and recrystallized again from pentane to yield 8 g (80%) of endo-diene-ol (III), m.p. 74-75°, b.p. 59°/0.6 mm. The alcohol sublimes readily at 70° and 760 mm pressure to give long thin

needles, m.p. 74-75°.

Anal. Calcd. for  $C_{10}H_{14}O$ : C, 79.95; H, 9.39. Found: C, 80.06; H, 9.48.

GPC analysis of the crude alcohol (and of its acetate) indicated 88-90% endo alcohol present in the mixture. The exo isomer, which comprised approximately half of the recombined mother liquors, could not be crystallized.

All ketones were reduced by  $LiAlH_4$  in exactly this manner.

$LiAl(OC(CH_3)_3)_3H$  reduction of the dieneone (II)

To a solution of 400 mg (0.01 mole) of  $LiAlH_4$  in 30 ml of tetrahydrofuran (fractionated from  $LiAlH_4$ ) was slowly added 2 ml of t-butanol at 0°. Subsequently, 1.0 g of dieneone (II) (0.0067 mole) in 30 ml of tetrahydrofuran was slowly added, after which the reaction mixture was allowed to stand at 0° for 30 minutes and at room temperature for 1 hour. This was the procedure used by Wheeler and Mateos<sup>48</sup> in the reduction of camphor. The solution was extracted with ether, after being neutralized with 1 N HCl. The combined extracts were washed with water,  $NaHCO_3$  solution, water and saturated NaCl solution, in that order, and finally dried over anhydrous  $Na_2SO_4$ . GPC analysis of the crude alcohol (and acetate) after removal of the ether, as before, indicated a composition of 94% endo isomer.

Since  $\text{LiAlH}_4$  will react with only 3 molecules of *t*-butanol, a slight excess of the alcohol is allowable, in fact, even desirable to assure uniformity of reducing agent.

All reductions with  $\text{LiAl}(\text{OC}(\text{CH}_3)_3)_3\text{H}$  were carried out in exactly this fashion.

#### Equilibration of *endo*-diene-ol (III)

The equilibration was conducted in two separate runs, for 72 hours and for 120 hours. Identical results were obtained.

5 g (0.033 mole) of *endo*-diene-ol (III), 6.8 g (0.033 mole) of aluminum isopropoxide and 5 drops (1/8 ml) of acetone were dissolved in 100 ml of fractionated and dried (refluxed over aluminum isopropoxide) isopropyl alcohol. This mixture was refluxed for the times given above. At the end of the reflux period, about 150 ml of water, along with sufficient 2 N HCl, was added to neutralize the solution. The combined ether extracts were washed with water followed by saturated NaCl solution and dried further over anhydrous  $\text{Na}_2\text{SO}_4$ . One gram of the crude product was acetylated, after removal of the ether in the usual manner, in the fashion described herein, for purposes of GPC analysis. GPC analysis of both the crude acetate and crude alcohol indicated 56% *endo* isomer.

All equilibrations were conducted in this manner.



endo-7-Isopropylidene-bicyclo-/2,2,1/-5-heptene-2-(p-toluene-sulfonate) (V) Diene-tosylate

All tosylates were prepared according to Tipson's<sup>78</sup> method, except that the resultant tosylate was extracted with  $\text{CH}_2\text{Cl}_2$  rather than  $\text{CHCl}_3$  and the reaction mixture was allowed to stand in the refrigerator ( $5^\circ$ ) for 36-48 hours.

10 g (0.067 mole) of endo-diene-ol (III) and 14 g (0.074 mole) of tosyl chloride in 100 ml of pyridine yielded 19 g (94%) of the endo-diene-tosylate (V), m.p. 65.5-66.5, from pentane.

Anal. Calcd. for  $\text{C}_{17}\text{H}_{20}\text{O}_3\text{S}$ : C, 67.09; H, 6.62; S, 10.52. Found: C, 67.06; H, 6.64; S, 10.61.

endo-2-Acetoxy-7-isopropylidene-bicyclo-/2,2,1/-5-heptene (IV) Diene-acetate

3.4 g (0.023 mole) of endo-diene-ol (III) was dissolved in 14 g (0.147 mole) of acetic anhydride and 35 ml of anhydrous pyridine (Fisher AR) and refluxed for 1 hour. The reaction mixture was poured into about 40 g of ice and extracted with methylene chloride. The combined extracts were washed three times with ice cold 2 N sulfuric acid to free the solution of excess pyridine. The solution was subsequently washed with ice water, saturated  $\text{NaHCO}_3$ , ice water,

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<sup>78</sup> R.S. Tipson, J. Org. Chem., 9, 235 (1944)

saturated NaCl and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, in that order. Distillation yielded 4.0 g (92%) of the endo-diene-acetate (IV), b.p. 66-68°/0.4 mm.

All acetates were prepared in exactly this fashion.

endo-2-Acetoxy-7-isopropylidene-bicyclo-/2,2,1/-heptane (VII)

Monoene-acetate

32 mg of 5% Pd/C was placed in the hydrogenation apparatus<sup>79</sup> shown in Figure 5 and covered with 4 g (0.021 mole) of diene-acetate (IV), dissolved in a mixture of 45 ml of 95% ethanol and 45 ml of ether. The amount of catalyst and solvent was held constant in all reductions, regardless of the quantity or nature of the substance being hydrogenated.

After allowing the solution to come to the temperature of the cooling jacket ( 13°), the system was flushed with hydrogen and hydrogen uptake started at 10-20 mm pressure. The rate of hydrogenation was followed as described (vide supra) and found to stop completely, even on increase in pressure, after the uptake of one mole-equivalent (42 psi). Actual uptake invariably agreed with the calculated uptake within ±2 psi in every case.

The solution was filtered and the catalyst washed well with ether. The ether solution was washed free of ethanol

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<sup>79</sup> P.R. Story and C.H. DePuy, J. Chem. Ed., in press, (1959)

with water, then dried in the usual way. GPC and IR analysis of the crude product, after careful removal of the ether, indicated 95% of the endo-monoene-acetate (VII). Distillation of the product yielded 3.65 g (91%), b.p. 48-50°/0.2 mm.

endo-7-Isopropylidene-bicyclo-/2,2,1/-heptane-2-(p-toluene-sulfonate) (VIII) Monoene-tosylate

From the diene-tosylate      The endo-diene-tosylate (V) was hydrogenated in exactly the same manner as the diene-acetate.

5 g (0.016 mole) of endo-diene-tosylate (V) yielded 4.35 g (86%) of endo-monoene-tosylate (VIII), m.p. 72.3-72.8°, on recrystallization from pentane.

Anal. Calcd. for  $C_{17}H_{22}O_3S$ : C, 66.65; H, 7.24; S, 10.44. Found: C, 66.37; H, 7.39; S, 10.24.

From endo-monoene-ol (VI)      2 g (0.013 mole) of monoene-ol (VI) and 2.8 g (0.015 mole) of tosyl chloride gave 3.9 g of crude endo-monoene-tosylate (VIII), m.p. 68-70°. Recrystallization from pentane gave 2.3 g (57%), m.p. 72.3-72.8°.

7-Isopropylidene-bicyclo-/2,2,1/-2-heptanone (XI) Monoeneone

The dieneone (II) was hydrogenated in the usual manner to give a product, which was shown by GPC and IR analysis to consist of 70% of the desired monoeneone (XI). This hydro-

genation differed from that of the diene-acetate, in that hydrogen uptake did not completely stop upon absorption of one mole-equivalent of hydrogen.

endo-7-Isopropylidene-bicyclo-/2,2,1/-2-heptanol (VI) Mono-ene-ol

From monoeneone (XI)  $\text{LiAlH}_4$  reduction of the impure monoeneone (XI), in the usual manner, gave, according to GPC analysis, 92:94% endo-monoene-ol (VI), which could be purified by recrystallization from pentane, m.p. 81.5-82.5°.

Anal. Calcd. for  $\text{C}_{10}\text{H}_{16}\text{O}$ : C, 78.89; H, 10.59. Found: C, 78.66; H, 10.31.

From monoene-acetate (VII) Hydrolysis of the endo-monoene-acetate (VII) in KOH in ethanol gave the endo-monoene-ol (VI) described above, according to GPC and mixed melting point data.

From diene-ol (III) Hydrogenation of the endo-diene-ol (III), in the usual manner, yielded 61% of the endo-monoene-ol (VI), according to GPC analysis. Here, again, uptake of hydrogen did not cease completely after the absorption of one mole-equivalent of hydrogen.

endo-2-Acetoxy-bicyclo-/2,2,1/-7-heptanone (IX) Keto-acetate

Ozonolysis in methylene chloride 7.2 g (0.037 mole) of endo-monoene-acetate (VII) was dissolved in 200 ml of

methylene chloride and cooled to  $-35^{\circ}$  in a dry ice-ethanol bath. Ozone was obtained from pure dried oxygen by the use of a Welsbach Ozonator, Model T-23. In every case, ozone was used at a rate of  $3.1 \times 10^{-4}$  moles/min. in oxygen at a flow rate of approximately  $0.0125 \text{ ft}^3/\text{min.}$  through a fritted glass tube. The end-point was determined by a trap of aqueous NaI immediately following the reaction vessel. The visible end-point invariably agreed with the calculated end-point, which was determined by ozonolysis of a NaI solution and titrating the liberated iodine with  $\text{Na}_2\text{S}_2\text{O}_3$ . Hydrolysis was effected by washing the  $\text{CH}_2\text{Cl}_2$  solution with two 100 ml portions of  $\text{H}_2\text{O}$ . This solution was dried by washing with a saturated solution of NaCl and standing over anhydrous sodium sulfate. After removal of  $\text{CH}_2\text{Cl}_2$ , the product was distilled under vacuum to yield two fractions. The first fraction, which distilled at  $57^{\circ}$  at 0.45 mm, constituted 2.8 g (45%) and was shown to be the endo-keto-acetate (IX) by its characteristic infra-red spectrum at 5.62 in the carbonyl region and by its conversion to endo-norborneol (vide infra). The second fraction, whose main peaks in the infra-red were at 2.9, 5.75 and 5.83, distilled at  $120^{\circ}/0.45 \text{ mm}$  and accounted for the remainder of the product.

Anal. Calcd. for  $\text{C}_9\text{H}_{12}\text{O}_3$ : C, 64.27; H, 7.19. Found: C, 64.40; H, 7.46.

2,4-Dinitrophenylhydrazone of the keto-acetate (IX)

The derivative, prepared in the conventional manner, yielded orange-red plates from benzene-hexane, which melted sharply at 150-151°.

Anal. Calcd. for  $C_{15}H_{16}O_6N_4$ : C, 51.72; H, 4.63. Found: C, 51.52; H, 4.83.

Ozonolysis in methanol 1.1 g (0.0052 mole) of monoene-acetate (VII) was dissolved in 150 ml of methanol and ozonized as described above. After ozone uptake was complete, 300 ml of water was added and the solution was extracted with 2 portions of  $CH_2Cl_2$ . The combined extracts were washed with water and dried with saturated NaCl and by standing over anhydrous  $Na_2SO_4$ . The infra-red spectrum of the crude product was identical with that of the product obtained by ozonolysis in  $CH_2Cl_2$ , thus indicating no worthwhile increase in yield.

Ozonolysis in acetic acid To 1 g of monoene-acetate (VII) in 100 ml of glacial acetic acid was added 1 ml of  $H_2O$ . The solution was then ozonized under the same ozonator conditions as before at 20°. Uptake of  $O_3$  was slow, so that ozone continually passed into the NaI trap. The reaction was stopped when the solution turned blue, indicating an accumulation of ozone. Acetic acid, itself, was shown to absorb no ozone by ozonizing a blank of acetic acid. The product was extracted as above. The infra-red spectrum, again, was identical with that of the product obtained by ozonolysis in methylene chloride.

Oxidation by OsO<sub>4</sub>-HIO<sub>4</sub> Using the method of Wieland et al,<sup>80</sup> 2 g (0.01 mole) of monoene-acetate (VII) along with 30 mg of OsO<sub>4</sub> and 2.5 g of HIO<sub>4</sub> were dissolved in a mixture of 125 ml of dioxane (purified according to Fieser<sup>81</sup> and distilled through a 40 plate column), 1.74 ml of anhydrous pyridine (Fisher AR) and 26 ml of H<sub>2</sub>O and stirred at 0° for 5.5 hours. At the end of this period, 1.5 g of HIO<sub>4</sub> and 30 mg of OsO<sub>4</sub> were added and the solution stirred 5 hours longer, after which 1.0 g of HIO<sub>4</sub> and 30 mg of OsO<sub>4</sub> were added. Stirring was continued for 9 hours at room temperature.

The reaction mixture was poured into 200 ml of water, extracted with CH<sub>2</sub>Cl<sub>2</sub> in three portions and washed twice with H<sub>2</sub>O, once with saturated NaCl and dried further over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Distillation, after removal of the CH<sub>2</sub>Cl<sub>2</sub>, yielded 0.9 g, b.p. 57°/0.45 mm, which was shown by IR and GPC analysis, to consist, chiefly, of starting material, although a small amount of keto-acetate (IX) was present.

Proof of structure of keto-acetate (IX)

Preparation of the ethylene thioketal 1 g (0.0059 mole) of keto-acetate (IX) was dissolved in a mixture of 25 ml of BF<sub>3</sub> etherate and 2.5 ml of ethanedithiol and allowed to

<sup>80</sup>P. Wieland, K. Heusler, H. Ueberwasser and A. Wettstein, Helv. Chim. Acta, 41, 74 (1958)

<sup>81</sup>L.F. Fieser, Experiments in Organic Chemistry, 3rd ed., p. 284, D.C. Heath and Co., Boston 1957

stand at room temperature overnight, after the fashion of van Tamelen and Judd<sup>62</sup> and of Fieser<sup>82</sup> with slight modification. The reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed twice with 2 N NaOH, followed by water. After drying with saturated NaCl solution and anhydrous sodium sulfate, the ether was removed by distillation, as usual.

Raney nickel reduction of the thioketal      The thioketal was dissolved in 50 ml of absolute ethanol, to which was added about 18 g of W-7 Raney nickel.<sup>83</sup> This mixture was refluxed for one hour. The solution was filtered free of nickel, which was washed with several portions of 95% ethanol. In an earlier trial run, infra-red analysis indicated that the base present in W-7 Raney nickel was not sufficient to hydrolyze the resultant acetate to norborneol. As a result, 2 g of KOH was added, at this point, to the ethanol solution and allowed to stand at room temperature overnight. Subsequently, the reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed with water and dried by washing with saturated NaCl solution and standing over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After removal of ether, 0.45 g (68%) of a solid product was obtained, which melted at

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<sup>82</sup> L.F. Fieser, J. Amer. Chem. Soc., 76, 1945 (1954)

<sup>83</sup> H.R. Billica and H. Adkins, Organic Syntheses, Coll. Vol. 3, p. 176, John Wiley & Sons, New York 1955



130-142°. One recrystallization from pentane gave a melting point of 148-149.5°. One further recrystallization yielded 0.34 g (51%), which melted at 149-150°. endo-Norborneol is reported to melt at 149-150°<sup>84</sup> and to give a melting point depression<sup>85</sup> in a mixed melting point with exo-norborneol, which melts at 127-128°<sup>84</sup>. Mixed melting point with an authentic sample of endo-norborneol gave no depression. The IR of the product, also, was identical to that of an authentic sample.

#### Hydrolysis of the keto-acetate (IX)

1 N NaOCH<sub>3</sub> in methanol 100 mg of the keto-acetate (IX) was dissolved in 1.5 ml of 1 N NaOCH<sub>3</sub> in methanol and allowed to stand at room temperature for 4 minutes. Water was added and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The solution, before extraction, immediately darkened on addition of the keto-acetate but became almost colorless on neutralization with dilute HCl. The colored material was apparently a minor product, since the isolable material was unchanged, regardless of whether it was extracted from a basic, neutral or acidic solution. Removal of the CH<sub>2</sub>Cl<sub>2</sub> gave a good yield

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<sup>84</sup> Elsevier's Encyclopaedia of Organic Chemistry, Vol. 12A, p. 628, Elsevier Publishing Co., Inc., New York 1948

<sup>85</sup>

H. Toivonen, Ann. Acad. Sci. Fennicae AII, 72 (1956)

of an amorphous solid which defied crystallization. The product was only slightly soluble in ether, but was very soluble in  $\text{CH}_2\text{Cl}_2$  and chloroform. The material, whose infrared spectrum exhibited major peaks at 2.8, 5.75 and 6.1 in chloroform, absorbed bromine in  $\text{CH}_2\text{Cl}_2$  with no evolution of  $\text{HBr}$ . A blank of  $\text{CH}_2\text{Cl}_2$  did not absorb bromine.

2 N KOH in ethanol Hydrolysis in ethanolic KOH produced the same product as above, but required a slightly longer reaction time.

1 N aqueous NaOH 150 mg of keto-acetate (IX) was slowly titrated with an equivalent amount of 1 N NaOH over a period of about 5 minutes. At the end of this reaction period the pH of the solution was about 9. Upon neutralization with dilute HCl, the dark yellow color, which had developed, was reduced considerably. A very small quantity of unreacted keto-acetate was extracted with ether. The product, which was identical with the products obtained in the two previous hydrolyses, was extracted with methylene chloride and amounted to about 75 mg.

2 N HCl 200 mg of keto-acetate (IX) was refluxed with 5 ml of 2 N HCl for 1.5 hours. Extraction with  $\text{CH}_2\text{Cl}_2$  gave a good yield (about 150 mg) of an oil whose infra-red spectrum in  $\text{CHCl}_3$  exhibited major peaks at 3.75, 5.75 and 5.81. This product was allowed to stand overnight with an aqueous  $\text{KMnO}_4$  solution. After the  $\text{MnO}_2$  was filtered off, the

solution was acidified, saturated with NaCl and extracted with ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The acidic product of this oxidation was molecularly distilled to yield 100 mg of a semi-solid material whose IR gave major peaks at 5.75, 5.83 and a broad peak at about 3.0.

#### Dehydronorcamphor

Dehydronorcamphor was prepared according to the directions of Bartlett and Tate.<sup>87</sup>

#### Norcamphor

Norcamphor was obtained from dehydronorcamphor by hydrogenation in the usual manner.

#### endo-Norborneol

endo-Norborneol was prepared by  $\text{LiAlH}_4$  reduction of norcamphor by the general procedure described herein, m.p. 148.5-150°, after four recrystallizations from pentane. The reported melting point is 149-150°.<sup>84</sup>

#### Attempted preparation of endo-bicyclo-2,2,1/-7-heptanone-2-ol (XIII) Ketol

Ozonolysis in ethyl acetate 0.5 g (0.0033 mole) of endo-monoene-ol (VI) was dissolved in 50 ml of ethyl acetate

and ozonized as usual. After ozone uptake was complete, 10 ml of water was added and the heterogeneous mixture was shaken and warmed slightly. The water layer was then saturated with NaCl and the ethyl acetate solution decanted and dried over anhydrous sodium sulfate. An IR spectrum of the oil obtained, after removal of the ethyl acetate in vacuo, failed to reveal any of the expected ketol (XIII). The spectrum gave major peaks at 3.0 (broad) and several in the carbonyl region, the lowest at 5.75  $\mu$ .

Ozonolysis in methylene chloride      0.5 g (0.0033 mole)  
of endo-monoene-ol (VI) was dissolved in 50 ml of  $\text{CH}_2\text{Cl}_2$  and ozonized according to general procedure. The resultant reaction solution was washed twice with water, dried in the usual way and distilled free of  $\text{CH}_2\text{Cl}_2$  to yield 0.4 g of an oil whose IR was essentially the same as that obtained by ozonolysis in ethyl acetate.

Ozonolysis in acetic acid      0.5 g (0.0033 mole) of  
endo-monoene-ol (VI) was dissolved in 100 ml of acetic acid and ozonized by general procedure. 150 ml of water was added and the solution extracted with  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  extracts were washed with water, saturated  $\text{NaHCO}_3$  solution and dried as before. Distillation of the  $\text{CH}_2\text{Cl}_2$  yielded an oil whose infra-red spectrum disclosed a weak absorption at 2.85 and probably two incompletely resolved strong absorptions in the carbonyl region, the lower at 5.73  $\mu$ . This product and

that obtained from ozonolysis in methylene chloride were acetylated, but did not yield any keto-acetate (IX).

endo-Bicyclo-2,2,1-7-heptanone-2-(p-toluenesulfonate) (X)

Keto-tosylate

Ozonolysis in methylene chloride 4 g (0.013 mole) of endo-monoene-tosylate (VIII) was dissolved in 200 ml of  $\text{CH}_2\text{Cl}_2$ , cooled to  $-35^\circ$  and ozonized under the same conditions described for the keto-acetate (IX). About ten minutes after completion of the reaction, as evidenced by the NaI trap, the ozonized solution was washed twice with 300 ml of water. The solution was then washed with saturated  $\text{NaHCO}_3$ , saturated  $\text{NaCl}$  and dried further over anhydrous  $\text{Na}_2\text{SO}_4$ . The IR spectrum of the crude reaction product, which amounted to 4.5 g of a viscous oil after removal of  $\text{CH}_2\text{Cl}_2$ , indicated the presence of a carboxylic acid. Consequently, the product was dissolved in 60 ml of  $\text{CH}_2\text{Cl}_2$  and extracted twice with 2 N  $\text{NaOH}$ . Previous tests had shown the product to be only slowly affected by aqueous base. The unknown acid was extracted by this procedure, leaving 0.9 g of crude product whose IR indicated it to be the desired keto-tosylate (X). The product was recrystallized, with much difficulty, from ether-pentane to yield 0.5 g (14%), after drying at  $78^\circ/0.40$  mm for 2 hours, m.p.  $88-89^\circ$ . The infra-red spectrum of the recrystallized product invariably gave a weak absorption at 2.85.

Ozonolysis in acetic acid      26 g (0.085 mole) of endo-monoene-tosylate (VIII) was dissolved in 550 ml of glacial acetic acid, to which had been added 3 ml of water, and ozonized as described above, in three separate runs. In contrast to the ozonolysis of the monoene-acetate (VII) at lower concentrations in acetic acid, uptake of ozone was sufficiently rapid that the end point could be determined rather accurately from the NaI solution and agreed to within  $\pm 2$  minutes with the calculated time. Ice water was added to precipitate the product which was extracted with methylene chloride. The  $\text{CH}_2\text{Cl}_2$  solution was extracted with ice cold 2 N NaOH, water and dried in the usual way. At this point, the  $\text{CH}_2\text{Cl}_2$  extracts from the three runs were combined. Removal of  $\text{CH}_2\text{Cl}_2$  gave 10-11 g of a viscous oil which appeared to be chiefly keto-tosylate (X) from its IR. Crystallization from tetrahydrofuran-hexane gave 5.5 g (23%) of a material whose IR indicated fairly pure keto-tosylate (X), exhibiting peaks at 5.65, in the carbonyl region, 6.25, 7.30 and a doublet at 8.37 and 8.45, m.p. 84-86°. The remaining mother liquor still contained considerable product which could not be crystallized out. Recrystallization of the product from tetrahydrofuran-hexane gave white platelets, m.p. 87.5-89°, after drying as before.

Anal. Calcd. for  $\text{C}_{14}\text{H}_{16}\text{O}_4\text{S}$ : C, 59.99; H, 5.75; S, 11.41.  
Found: I: C, 56.67; H, 5.52; S, 10.87. II: C, 57.30;

H, 5.70; S, 10.50.

The elemental analysis seems to be consistently incorrect for the expected keto-tosylate (X). It does check, however, quite accurately, for an oxygenated keto-tosylate molecule. The analysis checks less accurately for a monohydrate of the keto-tosylate (X)

Attempted preparation of the semi-carbazone of endo-keto-tosylate (X)

The preparation was carried out according to the directions of Shriner and Fuson.<sup>73</sup> However, only starting material, which crystallized very nicely from ethanol-water or from ethanol, could be recovered.

## SUMMARY

An investigation of three dienophiles, vinyl acetate, nitroethylene and  $\alpha$ -acetoxyacrylonitrile, has shown that  $\alpha$ -acetoxyacrylonitrile and dimethylfulvene provide an excellent route to 2,7-disubstituted norbornanes, which have, hitherto received limited study because of preparative difficulties.

Hydrolysis of the  $\alpha$ -acetoxyacrylonitrile-dimethylfulvene adduct, cyanoacetate (I), yielded the dieneone (II), whose hydrogenation to the monoeneone (XI) proved insufficiently selective for the purposes of this scheme. Further experimentation showed that certain endo derivatives of the dieneone (II) gave excellent selective hydrogenation of the endocyclic double bond, even though substituents in the endo position increase steric hindrance to the endocyclic bond. These results force one to the conclusion that the oxygen containing substituents serve as points of adsorption on the catalyst surface. The generality of this observation is to be further investigated. A large scale hydrogenation apparatus, necessary to make the selective hydrogenation a feasible part of the synthetic scheme, was developed.

Since future work will require compounds in the system with exo substituents and  $\text{LiAlH}_4$  reduction of dieneone (II) gave only 10% exo alcohol, an investigation of hydride reduc-



tions in this and related systems was undertaken. The only worthwhile conclusions seem to be that  $\text{LiAl}(\text{OC}(\text{CH}_3)_3)_3\text{H}$  is more selective than  $\text{LiAlH}_4$  and that exo-diene-ol may be obtained by equilibration of the endo alcohol with aluminum isopropoxide.

Ozonolysis of the monoene-acetate (VII) proceeded in good yield to give the keto-acetate (IX). The corresponding ketol (XIII) could not be obtained, however, by hydrolysis of the keto-acetate (IX) or by ozonolysis of the monoene-ol (VI). For this reason, to prepare the keto-tosylate (X), ozonolysis of the monoene-tosylate (VIII) was attempted, giving indefinite results to date. The keto-acetate (IX) proved quite sensitive to base, apparently suffering a retroaldol in a very rapid reaction. Acid hydrolysis was slower and gave a keto-aldehyde corresponding, in IR, to that expected from a retroaldol.

These results show that further elaboration in this system is hindered by the inability to obtain the 'parent compound', the ketol (XIII), from which many derivatives may be prepared. Investigations in progress at present will undoubtedly resolve this problem.

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