

# FUNCTIONALIZATION OF NON-ACTIVATED CARBON ATOMS

YEHUDA MAZUR

*Department of Organic Chemistry, The Weizmann Institute of Science,  
Rehovot, Israel*

## ABSTRACT

Chemical methods are described for regio- and stereospecific reactions at saturated C atoms unactivated by neighbouring groups. These reactions include epimerizations at tertiary C atoms and introduction of oxygen atoms into C—H bonds.

The epimerizations used free radical chain reaction induced by photolysis of  $\text{HgBr}_2$  in hydrocarbon solvents. Hydroxylation at tertiary C atoms was done either with irradiated peracetic acid or with ozone, the former reaction operating by a free radical chain and the latter by an insertion mechanism. It was also possible to introduce oxygen preferentially into secondary C-atoms by *t*-dibutyl peroxide. Attempts were made to use oxygen atoms as reagent for functionalizing unreactive C atoms.

---

For many years the functionalization of unactivated carbon atoms has been performed with the aid of enzymes. Some of the enzymatic reactions, such as the specific microbiological oxidation of steroids, are used to this day as important industrial processes<sup>1</sup>. Only during the last 15 years have intramolecular reactions been found by which unactivated carbon atoms could be attacked. The best-known are those of oxy-radicals and of irradiated carbonyl chromophore<sup>2</sup>. These reactive intermediates are created in specific positions of the molecule and their reaction will be restricted to their neighbourhood. Lately a novel approach was described by Breslow *et al.* in which a reagent is chemically attached to a molecule in a sterically accessible position<sup>3</sup>. This approach permits creation of a reactive position in the vicinity of almost any part of the molecule.

We have used another approach to functionalize non-active positions, mainly in the steroid molecule. We have looked for specific reagents capable of distinguishing between apparently similar 'inactive' carbon atoms. I shall restrict myself to reactions leading both to epimerization at tertiary C atoms and to introduction of oxygen into the C—H bonds.

Our interest in the selective reactions of unactivated C atoms arose from an incidental observation. Attempting to photolyse a saturated steroidal ester in the presence of mercuric salts, we observed an unusual epimerization at one of the tertiary C atoms of the molecule. We have irradiated cyclohexane solution of 17 $\beta$ -acetoxy androstane in the presence of  $\text{HgBr}_2$  with 254 nm light, and isolated in almost quantitative yield the 17 $\beta$ -acetoxy-14 $\beta$ -androstane<sup>4</sup> (Figure 1). The unexpected epimerization at C14 interested us for two

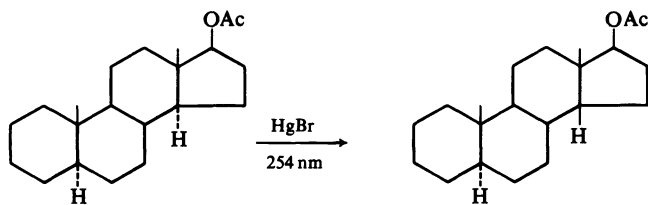


Figure 1

reasons: we saw in it a new method for attacking an apparently 'inactive' site in the presence of an 'activating' substituent located in a different position in the molecule. The second reason was a new and simple synthesis of 14 $\beta$ -steroids, the alternative ways being long and cumbersome.

Two questions arose: what is the function of the irradiated HgBr<sub>2</sub> and how can this method be used as a general route for epimerization of 'inactive' C atoms.

HgBr<sub>2</sub>, which is slightly soluble in cyclohexane and other hydrocarbons (the solvents used in the epimerization studies), has  $\lambda_{\text{max}}$  at 236 and 198 nm ( $\epsilon$ , 2400 and 15000). When irradiated at 253.7 nm, it decomposes to HgBr and subsequently to metallic Hg<sup>4</sup>. Since the epimerization could be performed in very pure hydrocarbons only and was suppressed by O<sub>2</sub>, olefins and phenols, it became obvious that it was a free radical reaction. It also became apparent that both the bromine atom and HBr are necessary for these reactions to take place; we could replace HgBr<sub>2</sub> by NBS, CBrCl<sub>3</sub> or Br<sub>2</sub> (the yields when the latter two reagents were used were small), and we were able to use light of higher wavelength (330 nm) when employing HBr gas in cyclohexane, and AIBN as an initiator.

The question is why the epimerization occurred preferentially at the hydrindane junction. Is this a specific property of this steroid or is it the general behaviour of five-membered rings? We therefore irradiated separately under identical conditions (+)3-methylcyclopentanone and (+)3-methylcyclohexanone, both in the presence of HgBr<sub>2</sub>, and observed almost complete racemization in the five-membered ring and a slight racemization in the six-membered ring (Figure 2). Thus tertiary C atoms in the five-membered ring are more reactive than those in the six-membered ring. This difference in the rate is clearly shown by comparing epimerization of *trans*- and *cis*-hydrindane with that of *trans*- and *cis*-decalin, the former being completely equilibrated after 12 h and the latter after 90 h (Figure 2)<sup>5</sup>.

The advantage of this equilibration method over others previously described, such as use of Lewis acids, hydrogenation and elevated temperature<sup>6</sup>, is the ambient temperature and the avoidance of carbonium ion rearrangements. Even more important is the fact that tertiary C atoms in compounds possessing other substituents may also be epimerized, as shown

FUNCTIONALIZATION OF NON-ACTIVATED CARBON ATOMS

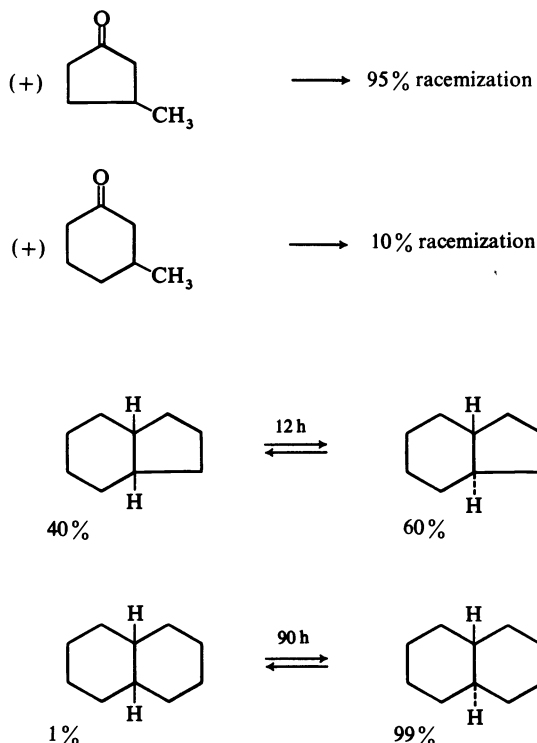


Figure 2

in Figure 3<sup>5</sup>. The four compounds resulted in the same mixture of epimers I and II.

We have applied the isomerization method to different ring systems bearing various functional groups<sup>4,5</sup> (Figure 4). A further example of the use of epimerization is shown in Figure 5<sup>7</sup>. An exceptional result was obtained in the case of cyclic ethers<sup>7</sup>. Although it is well known that the H atoms  $\alpha$  to oxygen in ethers are easily detached, we have observed in the case of the two steroidal isomers possessing six-membered pyrane rings preferential epimerization at C14 (Figure 6).

It is apparent that the rate of H abstraction depends strongly on the steric compression in the vicinity of the reacting C atom. Thus, an axial methyl group in androstane derivative will be isomerized before the H atom at C14<sup>5</sup> (Figure 7). On the other hand, the stability of the free radical formed is also an important factor contributing to the ease of isomerization. The phenyl group thus isomerizes very fast from the axial to the equatorial conformation (Figure 8)<sup>5</sup>.

In a classical series of papers published between 1942 and 1950 Linstead described the establishment of the configuration of keto-perhydrophenanthrenes which constituted one of the bases of conformational analysis<sup>8</sup>.

YEHUDA MAZUR

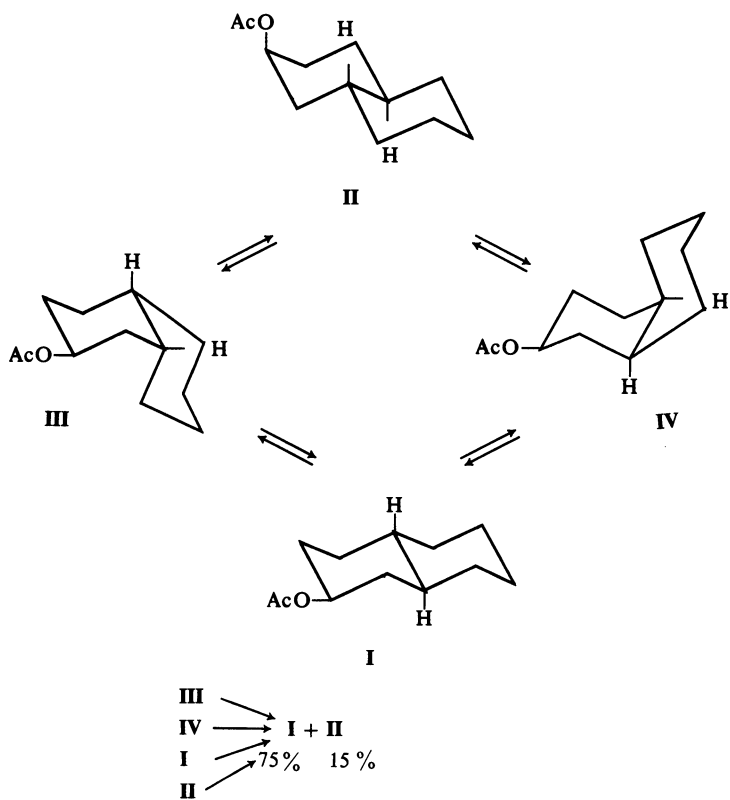


Figure 3

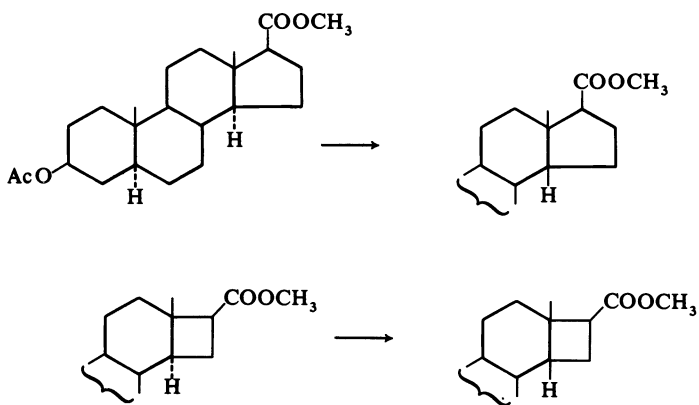


Figure 4

FUNCTIONALIZATION OF NON-ACTIVATED CARBON ATOMS

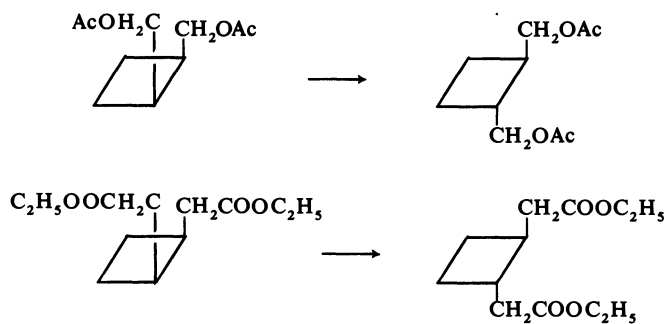


Figure 5

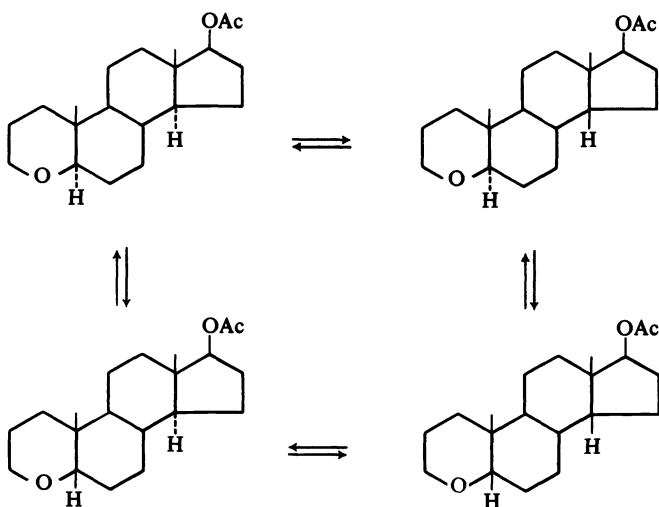


Figure 6

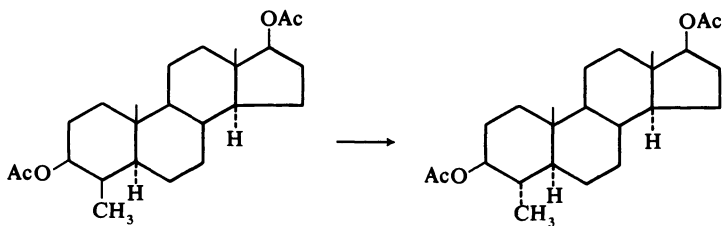


Figure 7

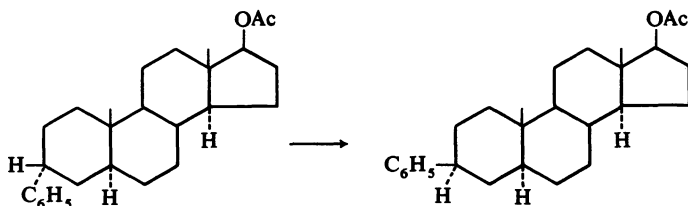
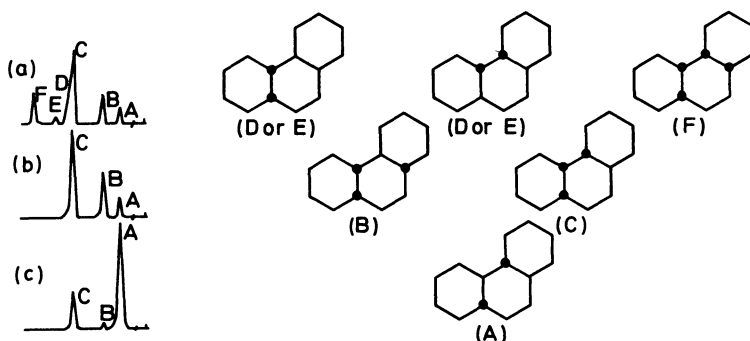


Figure 8

In these studies keto-perhydrophenanthrenes were converted to perhydrodiphenic acids whose configurations have been established unequivocally by degradation. However, no experimental correlations of the stabilities of perhydrophenanthrenes were known, since no equilibration techniques could be applied to such systems owing to extensive skeletal rearrangements. This problem, which was also treated recently by Allinger *et al.*<sup>9</sup>, who synthesized some of the perhydrophenanthrene isomers, was dealt with by us in a simple way<sup>10</sup>. A mixture of six epimers obtained by Raney nickel hydrogenation of phenanthrene was irradiated in cyclohexane in the presence of HgBr<sub>2</sub>. Figure 9 shows that three of the epimers disappeared after a comparatively short reaction time.

Since the epimerization occurs in a stepwise manner through a series of inversions at a single C atom, the compounds may be classified in three groups. The one with the most stable configuration is the all-*trans* hydrocarbon (Figure 9).



Glc chromatogram of: (a) the mixture of six perhydrophenanthrenes obtained by hydrogenation of phenanthrene over Raney nickel; (b) the same mixture after 18 h irradiation in the presence of HgBr<sub>2</sub>; (c) the same mixture after 40 h irradiation in the presence of HgBr<sub>2</sub>

Figure 9

## FUNCTIONALIZATION OF NON-ACTIVATED CARBON ATOMS

In order to decide between the alternative structures we have synthesized the all-*cis* ketone, using the Linstead procedure, and epimerized it. The respective hydrocarbons were correlated with compounds F and C (Figure 10): irradiation with  $\text{HbBr}_2$  of F resulted in B and C, which then equilibrated to A.

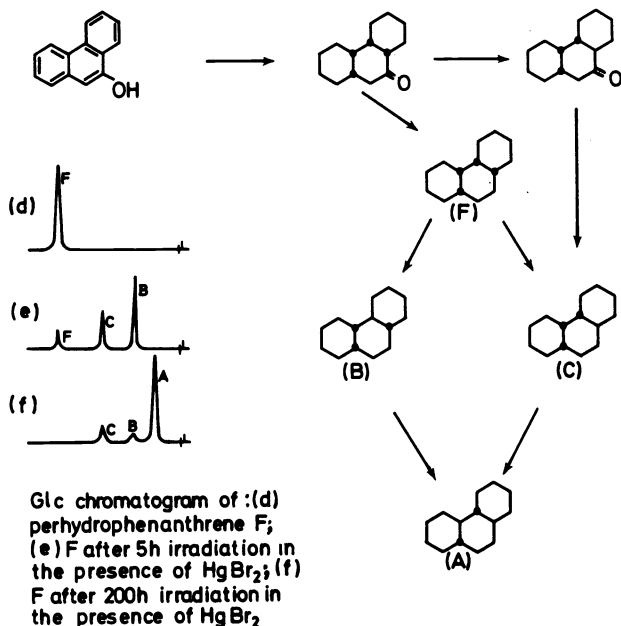


Figure 10

Thus, by a simple experimental procedure we could establish the configuration of five out of the six perhydrophenanthrene epimers without the need for long synthetic procedures.

Next we synthesized four isomeric androstanes (at C14 and C5). The C14 isomers were prepared by our equilibration method. We equilibrated each of the four epimers at different temperatures and established the equilibrium ratio and also the thermodynamical parameters. As expected, the  $14\beta$ -isomer is the most stable one; the ratio  $14\beta\text{H}/14\alpha\text{H}$  is equal to 8 and that of  $5\beta\text{H}/5\alpha\text{H}$  to 6<sup>11</sup>. The corresponding ratio in methylhydrindane is 200 and in methyldecalin is 2.3. This difference can be accounted for by a simple conformational analysis (Figure 11). It must be emphasized that although the stability ratios in androstane are similar, the rate of equilibration at C14 is much higher than at C5, 20 h being needed for 80 per cent epimerization at C14, but 400 h for 80 per cent epimerization at C5<sup>11</sup>.

Although it proved possible to use  $\text{HgBr}_2$  to introduce oxygen function into benzylic carbon atoms, we have not been able to oxidize tertiary carbon atoms using the same reagent. Looking for appropriate conditions to introduce oxygen function into such atoms, we came across an experiment

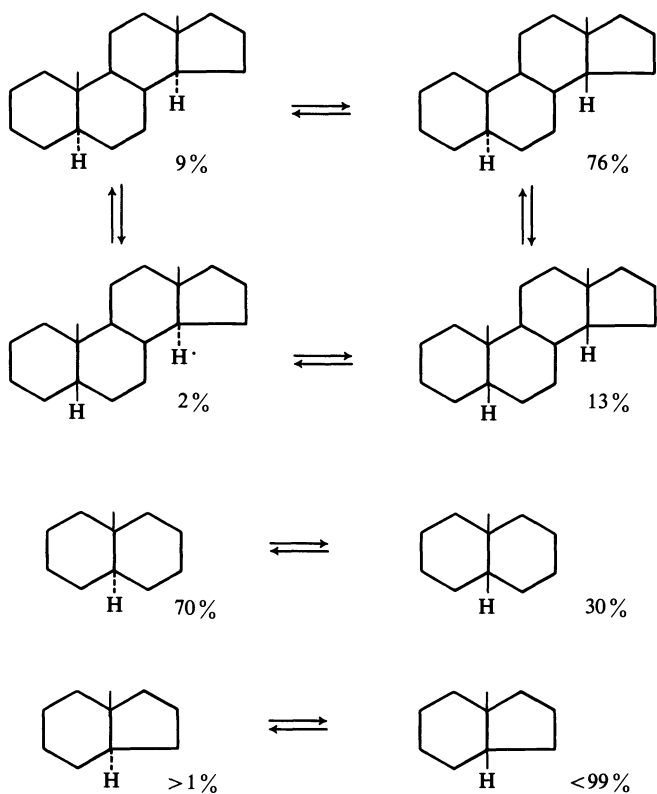


Figure 11

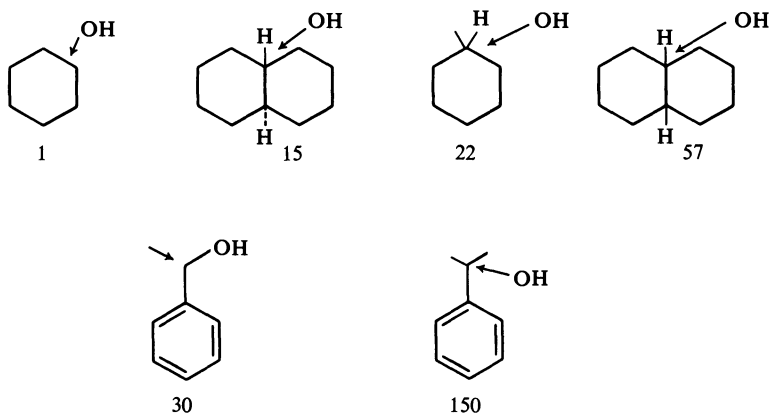
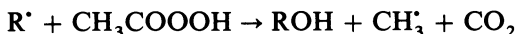
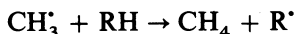


Figure 12. Relative reactivities of C—H bonds towards irradiated peracetic acid



FUNCTIONALIZATION OF NON-ACTIVATED CARBON ATOMS

described in 1961 by Heywood, Philips and Stansbury<sup>12</sup>, which used peracetic acid for hydroxylation. This reaction, although difficult to follow according to the experimental conditions, since the use of almost pure peracetic acid was prescribed, was repeated by us. We have found that it can be easily performed by irradiation of commercial peracetic acid (15–40 per cent in acetic acid) in a few solvents such as *t*-butanol, ethyl acetate, etc. (Figure 12). The products of the reaction are mainly tertiary OH derivatives, and the mechanism is a free radical chain reaction, as proposed by Heywood *et al.*



The advantages of these reactions are their insensitivity towards molecular oxygen and the use of a variety of solvents. The difference in the relative rates of hydroxylation (Figure 12) between various tertiary hydrogens made this reaction attractive to us. Compared with the hydroxylation of cyclohexane, the reaction of equatorial hydrogen atoms was faster than the axial ones by a factor of 3. The peracetic acid also hydroxylates benzylic carbon atoms; the secondary benzylic carbon atoms react at approximately the same rate as the tertiary carbon atoms<sup>13</sup>.

We have next applied this reaction to steroids. In the case of 5 $\alpha$ -androstan-17 $\beta$ -ol acetate two OH derivatives were isolated, one at C14 and the other at C5 (Figure 13)<sup>14</sup>. The isolation of the same compound, the 5 $\alpha$ -OH, from both

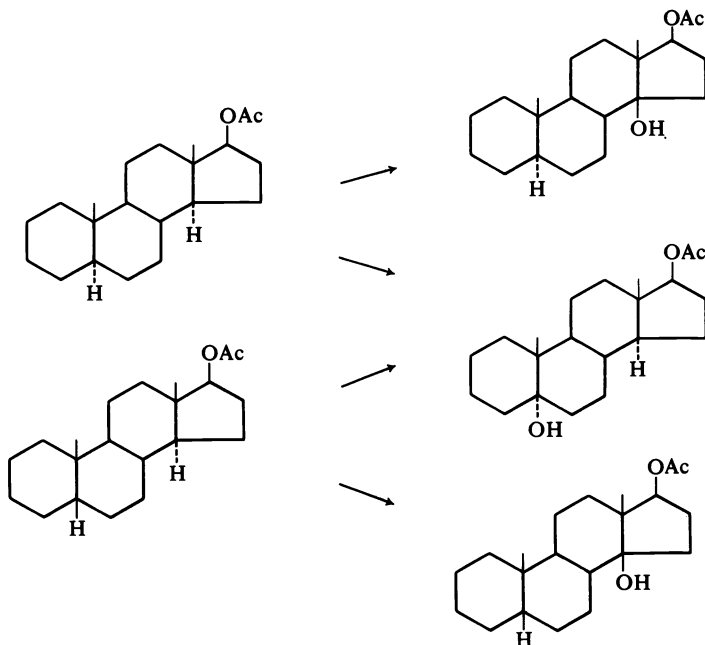


Figure 13

$5\alpha\text{-H}$  and  $5\beta\text{-H}$  derivatives indicates formation of free radical intermediates at C5. The formation of  $14\beta\text{-OH}$  points to an attack from the front side of the molecule. The main advantage of this reaction is that it can be performed in the presence of substituents such as acetoxy or epoxy groups. We were also able to perform hydroxylations at C14 and C5 even in the presence of carbomethoxy groups. As expected, hydroxylation of both  $5\alpha\text{-}$  and  $5\beta\text{-}$  etianic acids resulted in a  $5\alpha\text{-OH}$  derivative (Figure 13). However, we have obtained also a 1:1 mixture of  $14\beta\text{-}$  and  $14\alpha\text{-}$  hydroxy derivatives, starting from both  $5\beta\text{-H}$ - and  $5\alpha\text{-H}$ -etianic acids, which indicates that the peracetic acid attacked from both the upper and lower side of the molecule<sup>13</sup>. Only in one case have we isolated a small yield of compound having the OH group  $\alpha$  to the carbomethoxy group.

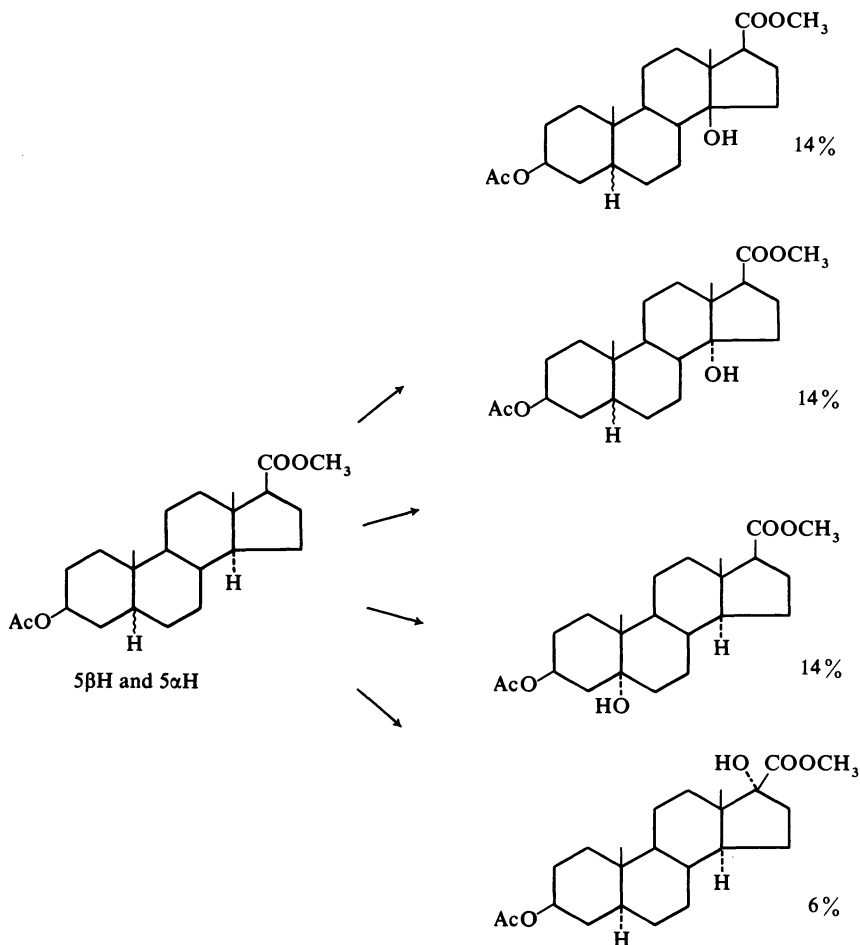


Figure 14

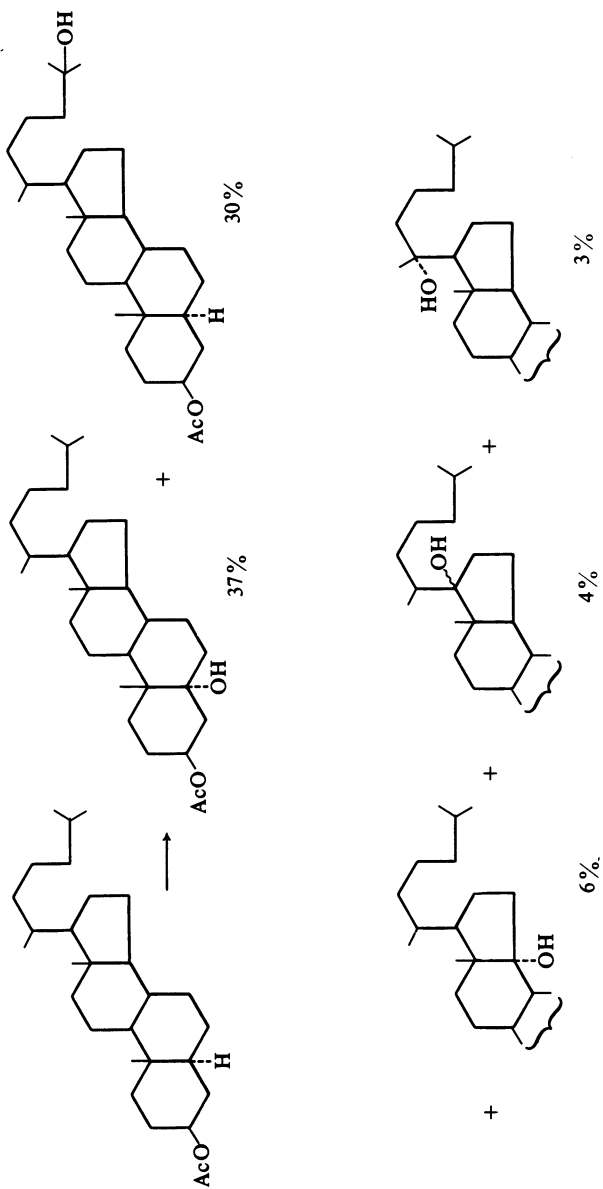


Figure 15

The advantage of this method for synthesis of cardenolides is obvious. Many years ago we synthesized digitoxigenin, using such a  $14\beta$ -hydroxy derivative as an intermediate<sup>15</sup>. More recently, a new synthesis of digitoxigenin was described which involved introduction of unsaturation into C14–C15 positions<sup>16</sup>. All these procedures involved many steps. On the other hand, direct hydroxylation at C14 described by us may be of advantage for the synthesis of digitoxigenin or other cardenolides, which possess  $14\beta$ -OH function.

Of interest also are the results obtained by peracetic acid hydroxylation of cholestanyl acetate<sup>17</sup>. The main products in this reaction are the  $5\alpha$ - and  $25$ -OH derivatives. In addition, small yields of three other compounds were obtained (Figure 15). In spite of these small yields, this procedure may be of advantage, since the alternative syntheses involve many steps.

The same reaction was repeated on a cholestane derivative possessing  $5\alpha$ -OH. We obtained as a major product the  $5\alpha,25$ -diol, which was accompanied by three other hydroxy derivatives, analogous to those described above<sup>17</sup> (Figure 16).

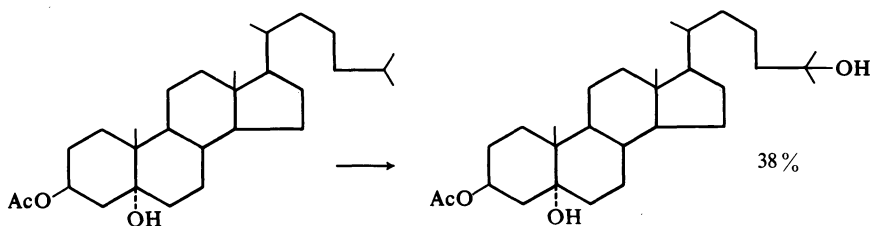


Figure 16

The use of the  $25$ -OH cholestane derivatives has recently become of interest<sup>18</sup>. Both  $25$ -OH and  $1\alpha,25$ -diOH vitamin  $D_3$  are the active metabolites of vitamin  $D_3$ , and in recent years their syntheses have been pursued in many laboratories. Our approach to these syntheses uses peracetic acid hydroxylation as a key step. Thus, cholesterol can be converted into  $5\alpha$ -OH in two steps: acetylation at C3 followed by peracetic acid treatment results in the diol, which may either be dehydrated after acetylation at C25 to C25-OH cholesterol or oxidized to the trienone. The latter, by use of Barton reaction<sup>19</sup> or similar methods, may be transformed into the  $1\alpha,25$ -diol, the precursor of the  $1\alpha,25$ -dihydroxy vitamin  $D_3$  (Figure 17).

I should also like to mention the hydroxylation of estradiol derivative, which results in high yield (60 per cent) of  $9\alpha$ -OH derivative. Further reaction of the latter compound gives the  $9\alpha,6\beta$ -diol, which may be further oxidized to the 6-ketone. Both  $9\alpha$ -OH and the  $9\alpha,6\beta$ -diol can be converted to two useful compounds (Figure 18)<sup>13</sup>.

The first step in the reaction of peracetic acid is the abstraction of the H atom by the  $CH_3$  radical. Another free radical, the *t*-butoxy radical, has a similar energy for H abstraction as the  $CH_3$  radical. Lahav and Popovitz<sup>21</sup> have chosen as the source of the *t*-butoxy radical the di-*t*-butyl

FUNCTIONALIZATION OF NON-ACTIVATED CARBON ATOMS

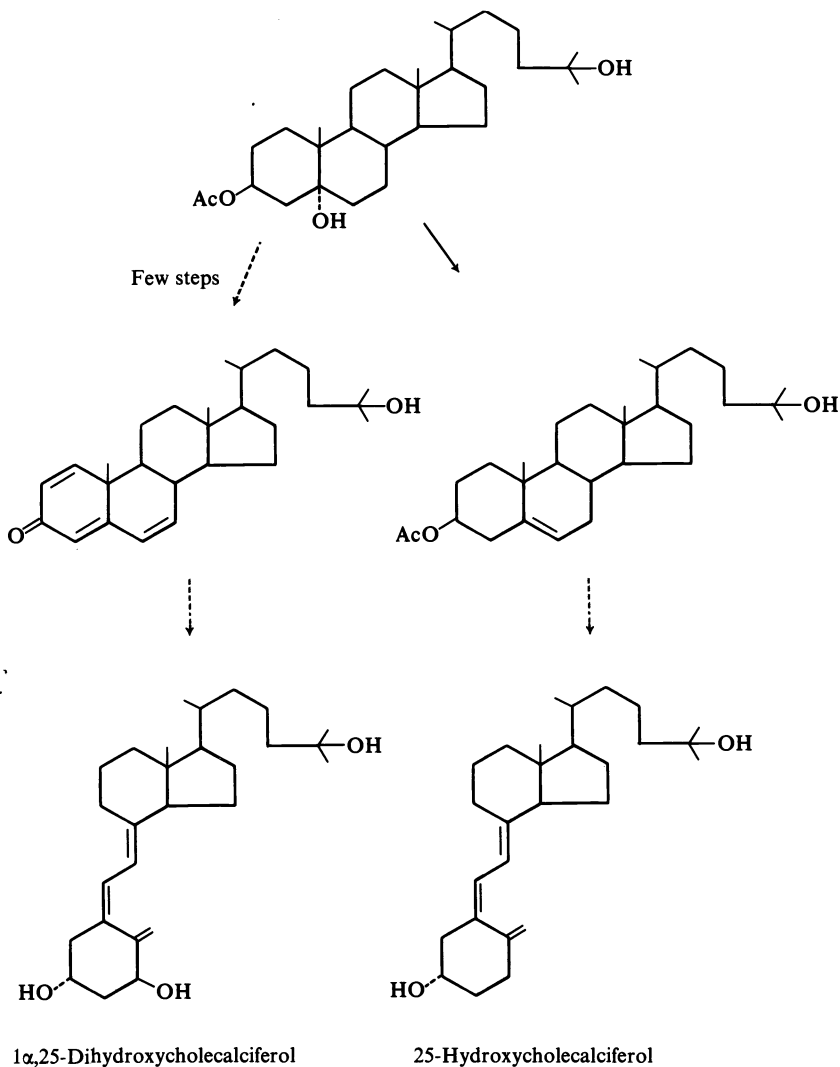


Figure 17

trioxide. This compound, which was described by Bartlett and Lahav<sup>20</sup>, is easily prepared either from *t*-butyl hydroperoxide using ozone or lead tetra-acetate or from the potassium salt of the butyl hydroperoxide and ozone. The mechanism of its formation is shown in Figure 19.

The advantage of this reagent is the low temperature required for its decomposition to the *t*-butoxy radical. Thus *t*-butyl trioxide was reacted with adamantane and *cis*- and *trans*-decalin<sup>21</sup>. Surprisingly there was obtained in the case of *trans*-decalin only a mixture of ketones and secondary alcohols, and



## FUNCTIONALIZATION OF NON-ACTIVATED CARBON ATOMS

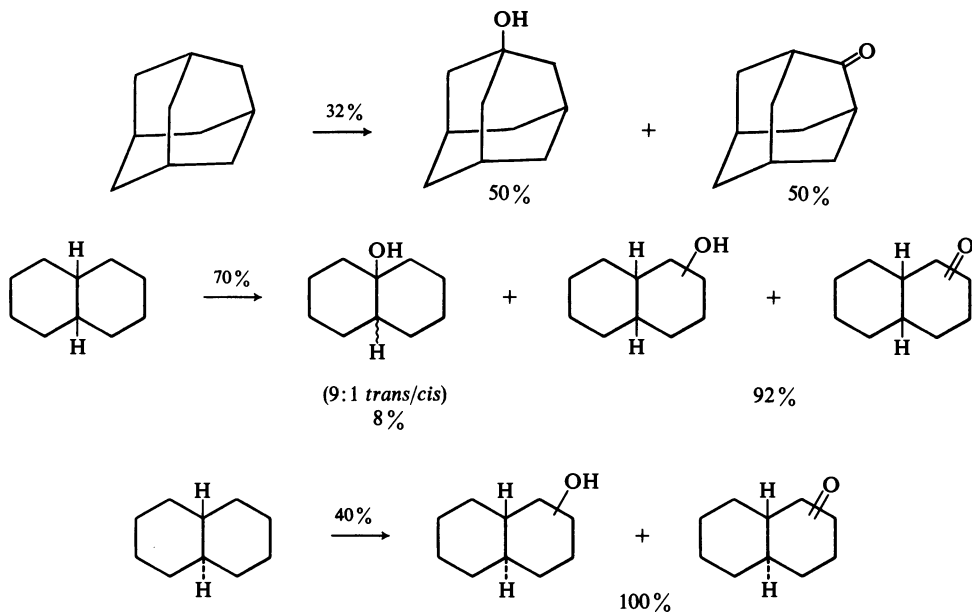


Figure 20

When androstan-17 $\beta$ -ol acetate was treated with *t*-butyl trioxide also, no tertiary OH derivatives were formed. A mixture of ketones was isolated which were all identified (Figure 21)<sup>21</sup>. The mechanism of the reaction is given in Figure 22. The first step is the formation of *t*-butoxy radicals which abstract the H atom; the radical formed then reacts with oxygen to give the peroxy radical. Termination of the reaction may be explained by a Russell mechanism which leads either to ketones or to a mixture of ketone and alcohol<sup>22</sup>. For steric reasons, the peroxy radical of the steroid does not combine with the corresponding oxy radical but with the *t*-butoxy radical, resulting in ketones only.

These results differ from those described previously, in which the *t*-butoxy radicals seemed to be similar to the CH<sub>3</sub> radical in their H abstraction ability. To investigate this point di-*t*-butyl oxalate<sup>23</sup> which decomposes at a much higher temperature (50°) than *t*-butoxy radicals was used. However, at that temperature the latter radicals undergo  $\beta$ -cleavage to give acetone and CH<sub>3</sub> radicals. Thus, by using higher temperatures, the reactive intermediates are both *t*-butoxy and methyl radicals (Figure 23).

We have compared the products from *cis*- and *trans*-decalins using the three reagents peracetic acid (in which the H abstractors are CH<sub>3</sub>), butyl trioxide (where the abstraction radical is the *t*-butoxy radical) and the oxalate (where both radicals are present) (Figure 24)<sup>21</sup>. It is apparent that in the first reagent the reaction gives mainly tertiary alcohols, the second mainly secondary alcohols and ketones and the third a mixture. Thus, in order to get reactions of pure *t*-butoxy radicals a low temperature of decomposition is necessary.

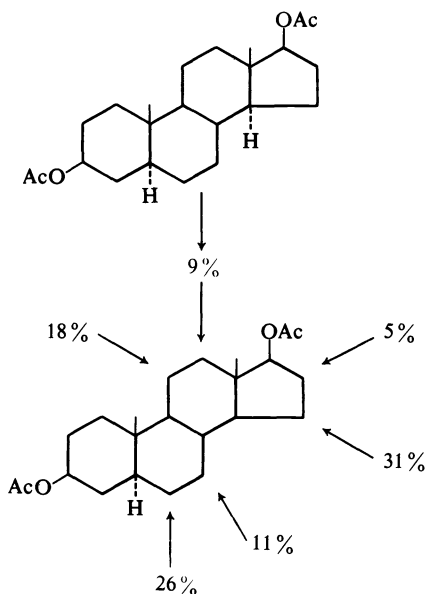


Figure 21. Distribution (%) of ketones from oxidation of androstane diacetate with *tert*-butyl trioxide

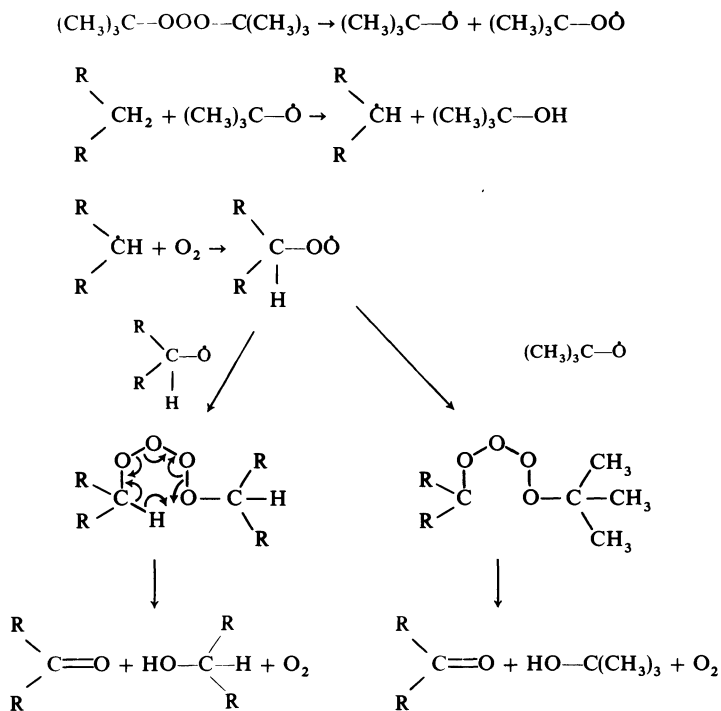


Figure 22



FUNCTIONALIZATION OF NON-ACTIVATED CARBON ATOMS

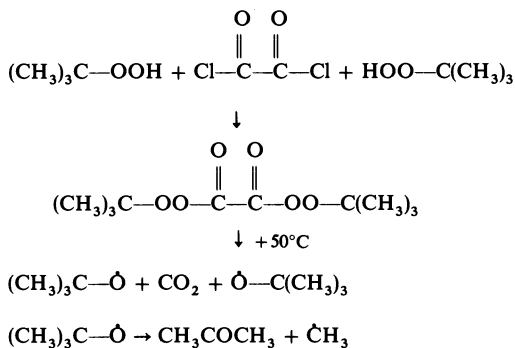


Figure 23

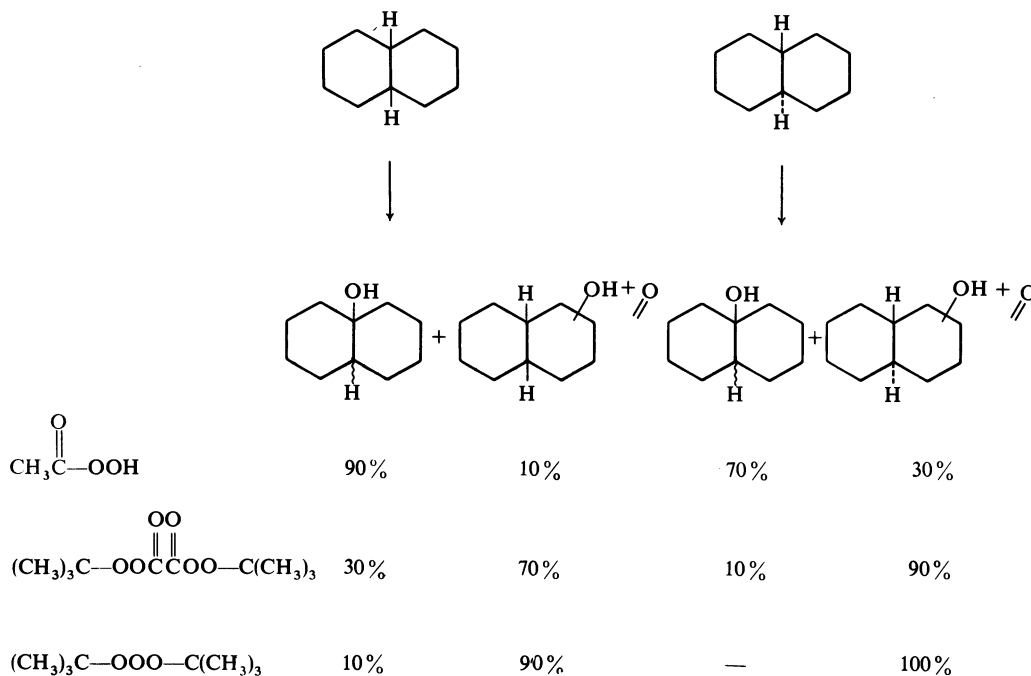


Figure 24. Distribution (%) of alcohols and ketones from oxidation of *cis* and *trans* decalins with peracetic acid, *tert*-butyl oxalate and *tert*-butyl trioxide

It is well known that ozone reacts with C—H bonds when the C atoms are substituted by either O or N. Only recently, owing to the interest in the chemistry of air pollution, the reaction of  $\text{O}_3$  with hydrocarbons became popular<sup>24</sup>.  $\text{O}_3$  is a strong electrophile; it has a dipole moment of 0.58 D. In 1938 Durland and Adkins<sup>25</sup> investigated the reaction of  $\text{O}_3$  with cholestanyl

acetate. In addition to cholestanone, they claim to have isolated a small quantity of methylisohexyl ketone. The formation of this ketone could have indicated that an oxidation occurred around the C17 of the cholestan molecule. This reaction was interesting enough to be reinvestigated by us. In addition, the same authors described the reaction of *cis*-decalin with  $O_3$ , resulting in 78 per cent *cis*-9-decalol.

In 1968 Whiting, Hamilton and their colleagues<sup>24</sup> reinvestigated the reaction of *cis*-decalin and isolated a mixture of 9-OH decalols, 80 per cent of it having *cis*-OH. We ourselves have spent some time looking for a way to understand this reaction and to apply it for the hydroxylation of carbon atoms. However, we have found that  $O_3$  reacts with most of the solvents, thus interfering with their reaction with hydrocarbons<sup>26</sup>.

Thus, investigations were done in neat liquids or in hydrocarbon solutions at  $-80^\circ$ , at which temperature stable  $O_3$  solutions are formed. When these were treated with a reducing agent or irradiated with visible light, a smooth conversion to alcohols occurred, oxygen being inserted into the C—H bond. We proposed a mechanism for this insertion reaction, which involves formation of a reversible complex between  $O_3$  and the hydrocarbon. In this complex the C—H bond is partially dissociated. The complex reacts by a thermal reaction, by irradiation with visible light or by treatment with reducing agents (KI,  $NaHSO_3$ ,  $\phi_3P$ ), resulting in insertion of an oxygen atom into the C—H bond:



Thus,  $5\alpha$ -androstane  $17\beta$ -acetate gave, when treated with ozone in pentane under illumination with visible light at  $-80^\circ$ , a mixture of alcohols, the major product being the  $9\alpha$ -OH derivative (Figure 25). When  $5\beta$ -androstane  $17\beta$ -acetate was illuminated under the same conditions, the  $5\beta$ -OH was the major product<sup>27</sup>.

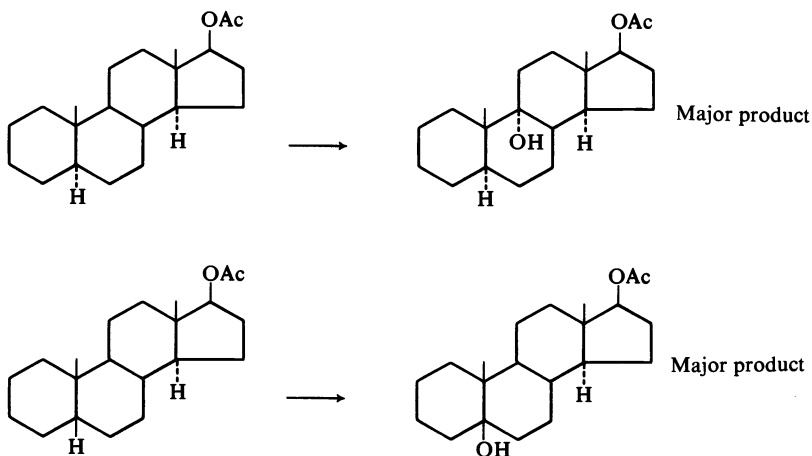
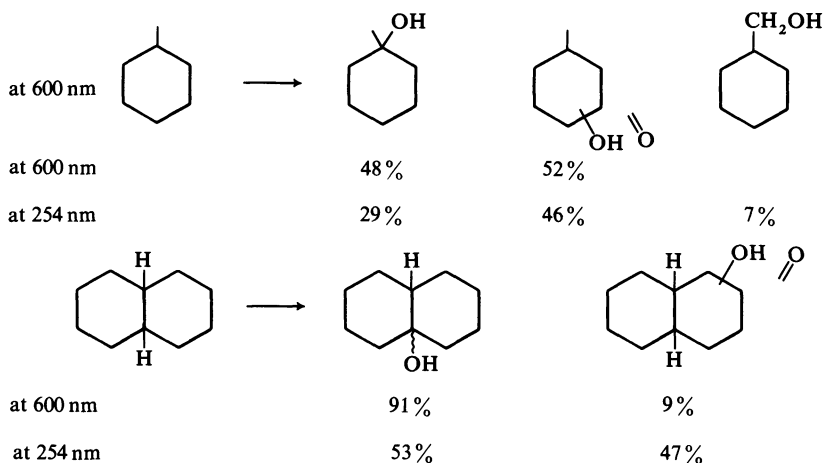


Figure 25

## FUNCTIONALIZATION OF NON-ACTIVATED CARBON ATOMS

We asked ourselves what function the light in this reaction may have. Ozone absorbs in both the visible and the u.v. spectrum, and has  $\lambda_{\max}$  at 255 and 605 nm<sup>28</sup>. The former band is due to an allowed and the latter to a forbidden transition. When irradiated with u.v. light, O<sub>3</sub> decomposes to oxygen molecule and oxygen atom, both in their excited state (singlet). However, the second transition is forbidden, and thus the decomposition of ozone at this wavelength is very slight.

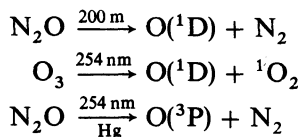
Ozone complexed with hydrocarbon has, however, a higher extinction coefficient and thus decomposes in preference to the free ozone in the thermal reaction<sup>26</sup>. Comparison of the reaction products obtained by irradiation at 254 and 600 nm reveals large differences (*Figure 26*). Whereas with long-



*Figure 26.* Distribution of products from irradiation of ozonized solutions of methylcyclohexane and *cis*-decalin with light of 600 and 254 nm

wavelength light the products are similar to those obtained by thermal reaction, with short-wavelength irradiation more secondary and primary alcohols were formed, which indicated that the oxygen atom in its excited state is responsible for these compounds. Therefore, we have also tried to use oxygen atoms as a reagent for functionalizing unreactive C atoms.

The oxygen in its singlet state is formed either when N<sub>2</sub>O is irradiated below 200 nm or, as mentioned above, when O<sub>3</sub> is irradiated at 254 nm. On the other hand, the triplet O atoms are obtained by irradiation of N<sub>2</sub>O in the presence of resonance emission of Hg at 254 nm:



The reaction of O(<sup>1</sup>D) with hydrocarbons, previously investigated only<sup>29</sup> in the gas phase, showed that this oxygen atom reacts without any energy of

activation, resulting in three different reaction pathways: (1) it inserts into the C—H bond; (2) it abstracts the H atom; (3) it eliminates the H<sub>2</sub> molecule. The alcohols and the dimeric products formed are statistically distributed among all the C atoms of the molecule. On the other hand, O(<sup>3</sup>P) atoms react differently, leading to a preferential attack on tertiary and secondary carbon atoms (Figure 27)<sup>30</sup>.

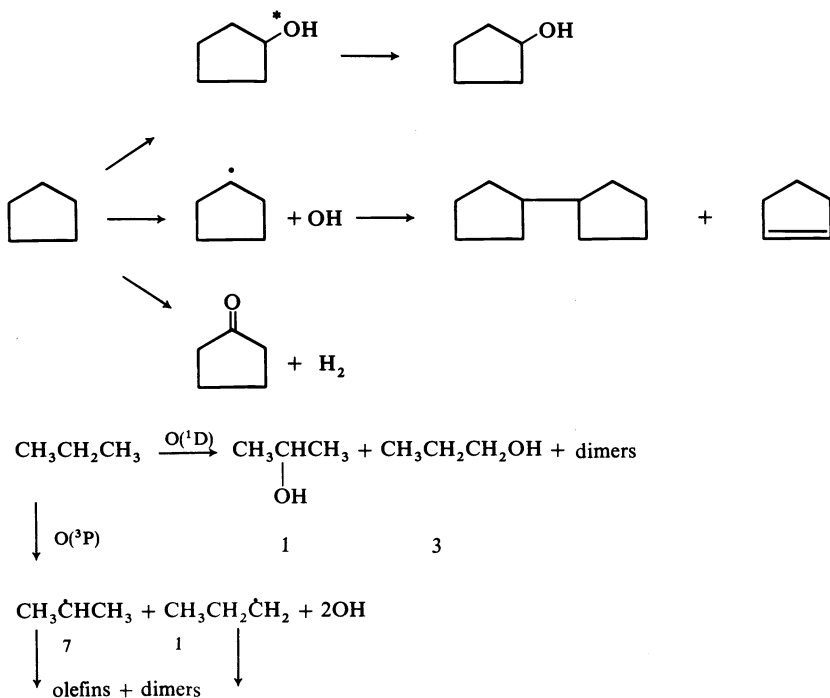


Figure 27

We have tried to use O(<sup>1</sup>D) atoms for preparative chemistry in solutions<sup>27</sup>. We have irradiated solutions of N<sub>2</sub>O in methylcyclohexane with a low-pressure mercury lamp and have isolated as expected all the possible alcohols in an almost statistical ratio. Similarly, *cis*-decalin gave the three alcohols. In both cases practically no ketones were isolated. The formation of only *cis*-9-decalol proved that the O atom inserts into the C—H bonds. The small preference for tertiary alcohols was explained by formation of O(<sup>3</sup>P) atoms, probably by some collisional deactivation of O(<sup>1</sup>D). The O(<sup>3</sup>P) atoms react preferentially with the tertiary C atoms, which results in carbon and OH free radicals. We assume also that both recombine with almost total retention of configuration, probably because of the presence of a tight solvent cage (Figure 28).

The use of oxygen atoms as reagents is merely in its infancy, and much work is still necessary to find both simple ways to produce these atoms and synthetic uses for them.

## FUNCTIONALIZATION OF NON-ACTIVATED CARBON ATOMS

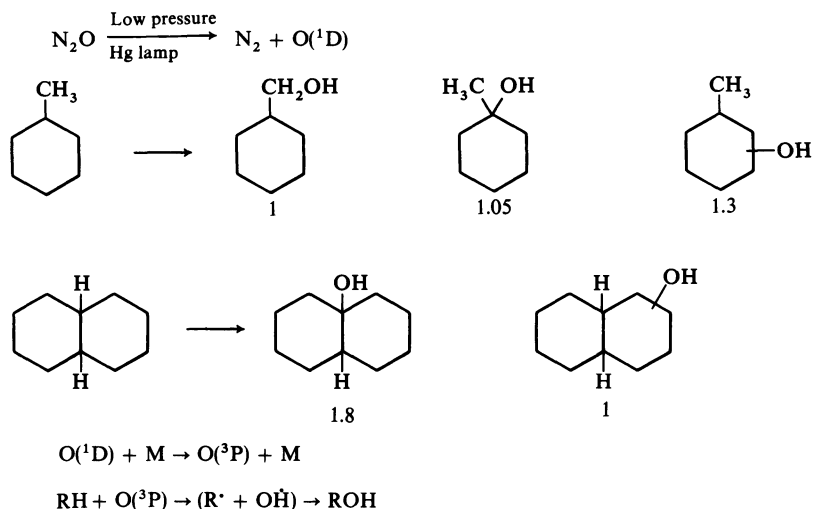


Figure 28

A situation may thus be visualized in the near future in which new reagents will be found and used to introduce oxygen and other atoms or groups both regio- and stereospecifically into seemingly 'non-active' carbon atoms.

### ACKNOWLEDGEMENT

I am deeply indebted to my associates Dr Malka Gorodetsky, Dr Noga Friedman, Dr Avner Rotman, Dalia Kogan-Freeman, Tomas Haim Varkony, Shimeon Pass, Asher Thurm and Avraham Goldfisher for their enthusiasm and devotion in carrying out the work described here.

I wish also to thank Dr Meir Lahav and Mrs Ronit Popovitz for the permission to include the results of their work on di-*t*-butyl peroxide.

These investigations were partially supported by grants from the Israeli Council for Research and Development, for which I am grateful.

### REFERENCES

- <sup>1</sup> cf. *Microbial Transformations of Steroids*, by W. Cearney and H. L. Herzog. Academic Press: New York (1967).
- <sup>2</sup> cf. *Steroid Reaction Mechanism*. Elsevier: Amsterdam (1968).
- <sup>3</sup> R. Breslow, R. Corcoran, J. A. Dale, S. Liu and P. Kalicki, *J. Amer. Chem. Soc.* **96**, 1973 (1974).
- <sup>4</sup> M. Gorodetsky and Y. Mazur, *J. Amer. Chem. Soc.* **90**, 6540 (1968).
- <sup>5</sup> M. Gorodetsky, D. Kogan and Y. Mazur, *J. Amer. Chem. Soc.* **92**, 1094 (1970).
- <sup>6</sup> E. L. Eliel, N. L. Allinger and S. J. Angyal, *Conformational Analysis*, pp 58-62. Wiley; New York (1965).
- <sup>7</sup> M. Gorodetsky and Y. Mazur, to be published.
- <sup>8</sup> R. P. Linstead, S. B. Davis and R. P. Levine, *J. Chem. Soc.* 1425 (1950);  
R. P. Linstead and R. R. Whetstone, *J. Chem. Soc.* 1428 (1950) and ref. cited therein.
- <sup>9</sup> N. L. Allinger, B. J. Gorden, J. J. Tyminski and M. T. Wuesthoff, *J. Org. Chem.* **36**, 739 (1971).

YEHUDA MAZUR

- <sup>10</sup> D. Kogan and Y. Mazur, *Tetrahedron Letters*, 2401 (1971).
- <sup>11</sup> A. Thurm, *MSc Thesis*, Feinberg Graduate School, The Weizmann Institute of Science, Rehovot (1974).
- <sup>12</sup> D. L. Heywood, B. Philips and H. A. Stansbury Jr, *J. Org. Chem.* **26**, 281 (1961).
- <sup>13</sup> A. Rotman, *PhD Thesis*, Feinberg Graduate School, The Weizmann Institute of Science, Rehovot (1974).
- <sup>14</sup> A. Rotman and Y. Mazur, *J. Amer. Chem. Soc.* **94**, 6228 (1972).
- <sup>15</sup> N. Danieli, Y. Mazur and F. Sondheimer, *Tetrahedron*, **22**, 3189 (1966).
- <sup>16</sup> R. Deghenghi, *Pure Appl. Chem.* **21**, 153 (1970).
- <sup>17</sup> A. Rotman and Y. Mazur, *J. Chem. Soc. Chem. Commun.* 15 (1974).
- <sup>18</sup> J. L. Omdahl and H. F. DeLuca, *Physiol. Rev.* **53**, 327 (1973).
- <sup>19</sup> D. R. Barton, R. M. Hesse, M. M. Pechet and E. Rizzardo, *J. Chem. Soc. Chem. Commun.* 203 (1974);  
D. R. Barton, R. M. Hesse, M. M. Pechet and E. Rizzardo, *J. Amer. Chem. Soc.* **95**, 2748 (1973).
- <sup>20</sup> P. D. Bartlett and M. Lahav, *Israel J. Chem.* **10**, 101 (1972).
- <sup>21</sup> R. Popovitz, M. Lahav and Y. Mazur, to be published; R. Popovitz, *MSc Thesis*, Feinberg Graduate School, The Weizmann Institute of Science, Rehovot.
- <sup>22</sup> C. A. Russell, *J. Amer. Chem. Soc.* **79**, 3871 (1957).
- <sup>23</sup> P. D. Bartlett, E. P. Benzing and R. E. Pincock, *J. Amer. Chem. Soc.* **82**, 1762 (1960).
- <sup>24</sup> M. C. Whiting, A. J. N. Bolt and J. H. Parish, *Advance Chem. Ser.* **77**, 4 (1968);  
G. A. Hamilton, B. S. Ribner and T. M. Hellman, *Advanc. Chem. Ser.* **77**, 15 (1968);  
S. W. Benson, *Advanc. Chem. Ser.* **77**, 74 (1968).
- <sup>25</sup> J. R. Durland and H. Adkins, *J. Amer. Chem. Soc.* **61**, 429 (1939).
- <sup>26</sup> H. Varkony, S. Pass and Y. Mazur, *J. Chem. Soc. Chem. Commun.* 437 (1974).
- <sup>27</sup> H. Varkony, S. Pass and Y. Mazur, to be published.
- <sup>28</sup> M. Griggs, *J. Chem. Phys.* **49**, 857 (1968);  
J. W. Simons, R. J. Paur, H. A. Webster III and E. J. Bair, *J. Chem. Phys.* **59**, 1203 (1973).
- <sup>29</sup> P. Michaud and R. J. Cvetanovic, *J. Phys. Chem.* **76**, 1375 (1972);  
P. M. Scott and R. J. Cvetanovic, *J. Phys. Chem.* **54**, 1440 (1971);  
J. N. Bradley, A. D. Edwards and J. R. Gilbert, *J. Chem. Soc. (A)*, 326 (1971);  
C.-L. Lin and W. B. DeMore, *J. Phys. Chem.* **77**, 863 (1973);  
W. B. DeMore, *J. Phys. Chem.* **73**, 391 (1969).
- <sup>30</sup> J. T. Herron and R. E. Huie, *J. Phys. Chem.* **73**, 3327 (1969).