AN INVESTIGATION OF THE PHOTOFRAGMENTATION OF 3β-ACETOXY-14β-HYDROXY-5α-PREGN-16-EN-20-ONE

George Efthymiadis

A Thesis

in

The Department

of

Chemistry

Presented in Partial Fulfillment of the Requirement
for the degree of Master of Science at
Concordia University
Montreal, Quebec, Canada

November 1975

TABLE OF CONTENTS

ACKNOWLEDGMENTS

The author wishes to express his appreciation to Dr. Thomas J. Adley for his help throughout this work, especially on the interpretation of mass spectra, nuclear magnetic resonance spectra, and assistance in writing this thesis.

The financial support from the Chemistry Department and assistance from other staff members are also gratefully acknowledged. In this regard, I extend my thanks to my fellow student, Mr. D. J. Kim, for the helpful exchange of ideas pertaining to this work.

ABSTRACT

GEORGE EFTHYMIADIS

AN INVESTIGATION OF THE PHOTOFRAGMENTATION OF 3β-ACETOXY-14β-HYDROXY-5α-PREGN-16-EN-20-ONE

The synthesis of the 14β-hydroxy-derivative from pregnenolone acetate has been repeated, and an improved method for the preparation of the previously reported intermediate, the 14,16-dienone, is described.

The reaction of the photochemically generated 14β-oxy radical, prepared from the 14β-hypoiodite derivative of pregnenolone has been investigated.

LIST OF SCHEMES

LIST OF FIGURES

LIST OF TABLES

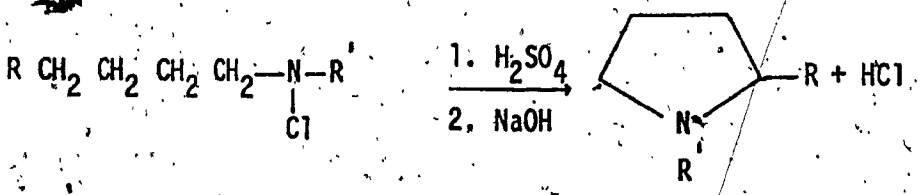
The objective of this work was to investigate the possibility of functionalization of the C-18 methyl group of a 14β-hydroxylated steroid which would serve as a significant intermediate for various biologically active steroids and steroid alkaloids such as Batrachotoxin[1-4] and Anhydrohirundegenin[5]. For this latter class of compounds, a study of the D-ring fission products derived from alkoxy radicals generated at C-14 of the steroid nucleus is discussed.

Of the various methods described in the literature, the Hofmann-Löffler-Freytag reaction[6], the Barton reaction[7], and the hypoiodite reaction[8] constitute the important methods of "remote" functionalization.

Methods of Functionalization in Steroids

The Hofmann-Loffler-Freytag Reaction.

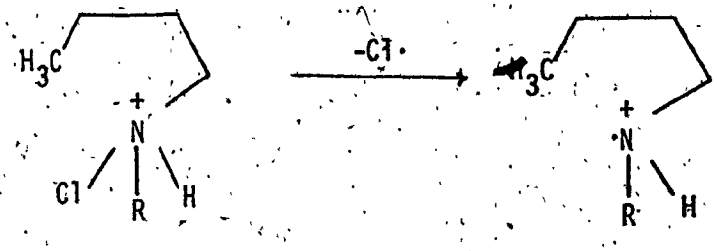
The first attempts to functionalize the C-18 angular methyl group of steroid molecules[9] were based on the Hofmann-Löffler-Freytag reaction[6] which can be formulated as the transformation of an aliphatic N-chloroamine into a pyrrolidine under thermal or photolytic conditions (scheme 1). This reaction is somewhat unusual in that it yields a five- rather than a six-membered ring.



Scheme 1

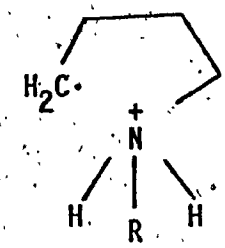
The mechanism for the cyclization of the N-haloamines has been postulated as a free radical mechanism[10] involving an intermediate δ-chloroamine salt[11]. The free radical nature of this process was demonstrated by the decomposition of δ-aliphatic chloroamines in ultraviolet light or alternatively by the addition of catalytic amounts of free radical initiators such as ferrous persulfate and ferrous ammonium sulfate. Inhibition of the pyrrolidine formation in the dark, or in the absence of chemical initiators, or in the presence of molecular oxygen provides formal support for a free radical mechanism[12].

Catalysis by acids[12] lends support to the supposition that the N-chloroamine first forms a salt which subsequently undergoes cleavage under the influence of radical initiators or UV light to furnish aminium[13] and chlorine free radicals.

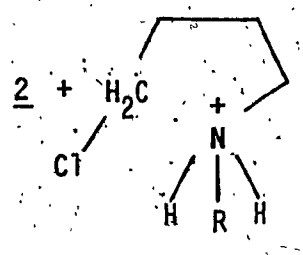


1

2



3



4

Scheme 2

The initiating step to furnish the N-haloammonium radical (2, scheme 2) is thought to involve the small fraction of N-chloro-amine present in the free base forms as only it is able to absorb UV light of sufficient energy to cause dissociation. Subsequently, it is presumed that the nascent nitrogen radical is immediately protonated[14].

The evidence for the intramolecular hydrogen abstraction[10] is based on the observation that δ-chloro-secondary amines are obtained from an N-chloro-secondary amine (3→4, scheme2) by a free radical mechanism[15]. There is no consistent support for an intermolecular hydrogen abstraction since the predominance of attack occurs at the δ-position[12]. Preferential intramolecular hydrogen abstraction prevails in the order tertiary > secondary > primary, and proceeds with retention of configuration at the δ-carbon[12].

Comparison of isotope effect studies which gave $k_H/k_D = 3.54$ with a maximum theoretical isotope effect[39] $k_H/k_D = 4.7$ (at 95°) confirms the large extent of the δ C-H bond rupture in the transition state[12]. The ensuing attack of the aminium radical on the δ-hydrogen appears to favor a linear or quasi-linear arrangement of the three participating centers, N...H...Cδ[14]. Such a linearity* explains the propensity of attack on the δ-hydrogens, i.e., 1,5 shifts involving a six-membered transition state in a staggered chair conformation[14],

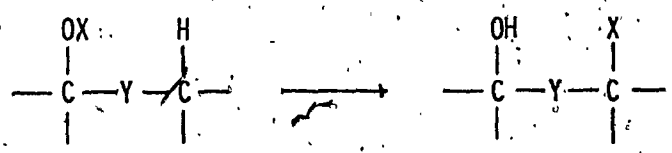
* This linearity is associated with the minimization of angle strain and steric repulsions involving non-bonded atoms in the transition state for the rearrangement[12].

and the total absence of 1,3 and 1,4 hydrogen shifts[12]. Although the 1,6 and 1,7 hydrogen shifts are feasible, these processes appear to suffer from an associated large free energy barrier (ΔG^* (1,6) - ΔG^* (1,5) $\sim$ 1.3 k cal/mole).

Disproportionation of the intermediate carbon and aminium radicals may also lead to other products, the importance of the side reactions depending largely on the nature of the starting materials[14,10b].

Photochemical transformations

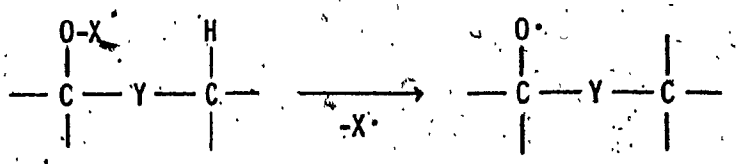
The Barton[7] and the hypoiodite[8] reactions can be represented by Scheme 3, where X= NO (The Barton Reaction), or X = I (the hydoiodite



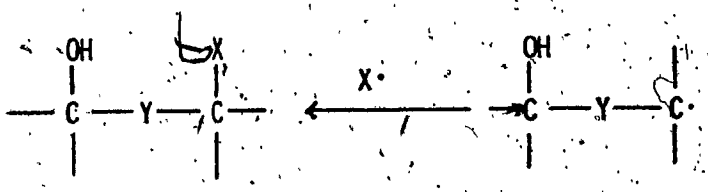
Scheme 3

reaction), and Y should be a two atom chain[21]. The first intermediate furnished by these photochemical transformations is the alkoxy radical, which is generated by the homolysis of the O-X bond under photolytic[7] conditions or a combination of thermolysis and photolysis conditions[8].

Although various pathways[16,17] are available to the alkoxy radical (5), for its stabilization[19], an important one constitutes the intramolecular hydrogen abstraction (scheme 4) whereby a new alkyl



5



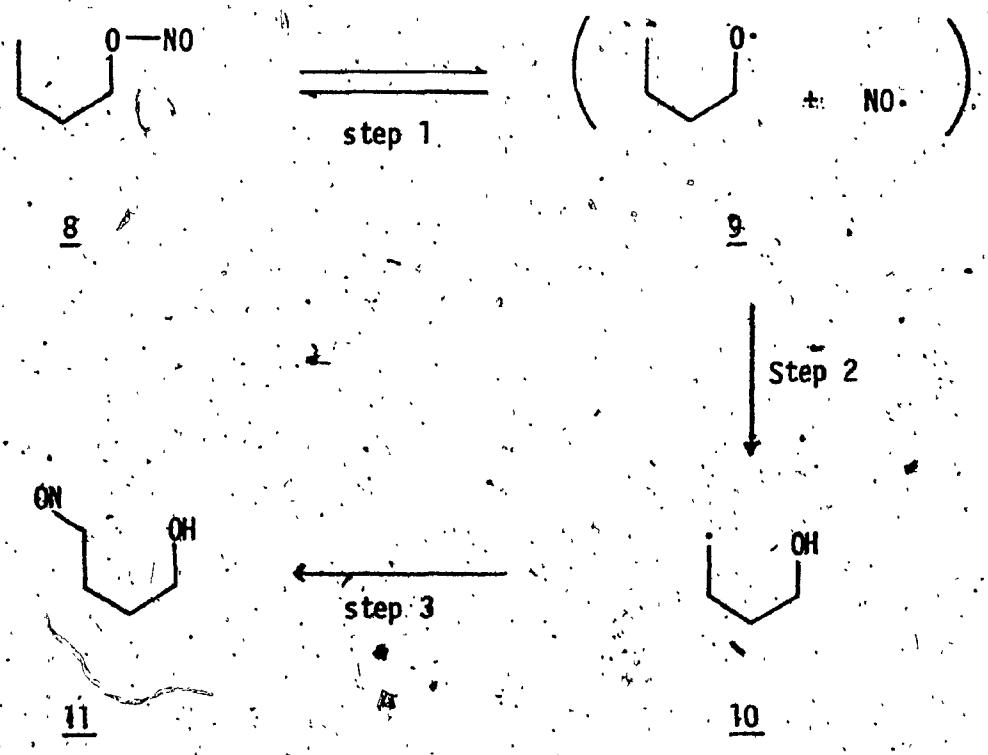
7 6

Scheme 4

free radical[20] (6) is furnished which can recombine with any free radical in the vicinity, such as X· to furnish the product[18] (7).

The Barton reaction

The overall Barton reaction can be represented by the following three discrete steps[21] (scheme 5) :



Scheme 5

(a) the photochemical cleavage of the O-H bond to furnish the alkoxy radical (9) and NO· , (b) the intramolecular hydrogen abstraction by the alkoxy radical to furnish the alkyl radical (10) , (c) the combination of (10) with NO· to furnish the product (11).

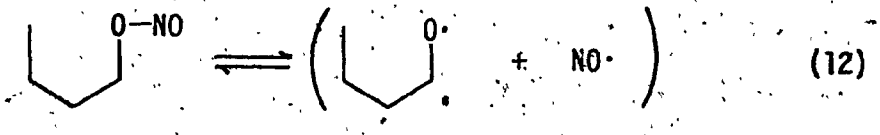
Conclusions relative to the Barton reaction

1. The Barton reaction is a true photochemical process as is suggested by the quantum yield[21], $\phi = 0.27$, and the lack of a nitrite concentration effect[22]. The quantum yield for a typical free radical chain reaction is greater than unity [18].

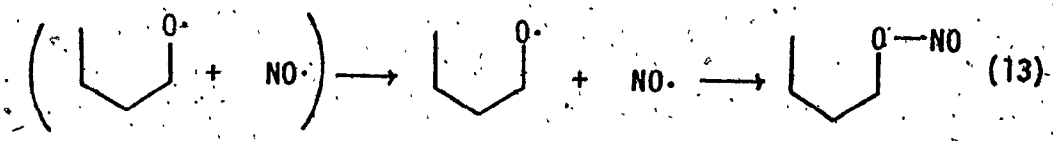
2. The Barton reaction has been shown to be essentially a non-cage, free radical process[21]. The photolysis of an equimolecular mixture of two dissimilar nitrite esters, one of which contained N^{15} (98.3% incorporation) furnished the corresponding oximes which were oxidized to the ketoximes. Mass spectral analysis showed N^{15} distributed itself equally between the two ketoximes[18]. This result disproved the previously suggested cage mechanism in which NO· is held captive during the entire reaction, and also eliminates any mechanism based on the direct bond-switching process between the two exchange sites[23].

That the quantum yield is less than unity is accounted for by the initial reversible reaction (8)→(9) thereby suggesting that the formation of the nitrite proceeds via geminate recombination[22]. Photolysis to half-completion of a second dissimilar mixture of 6β-nitrite esters having the same N^{14} and N^{15} distribution as described above furnished the oximes and the starting nitrites. As noted previously, the derived ketoximes showed the expected scrambling, (N^{15}: N^{14}, 1.15: 1.00 for one product) but the starting nitrite ester containing only N^{15} initially showed no N^{14} incorporation[23]. This last observation indicates

a primary homolysis step involving a cage process as shown by (12) and eliminates (13).



(12)



(13)

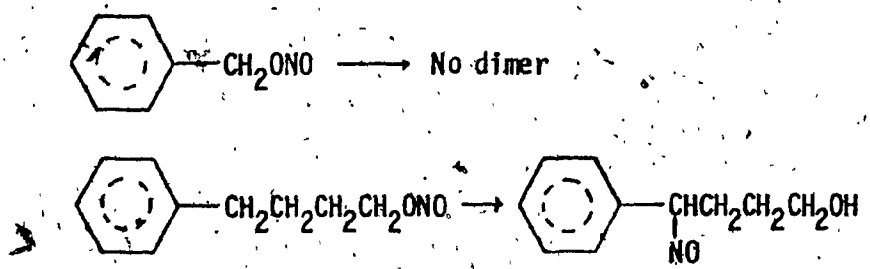
The most compelling evidence for the existence of the alkoxy radical (9) was provided by the photolysis of an N^{15}-containing nitrite steroid in presence of N^{14}-containing -t-butyl nitrite which resulted in the recovery of the nitrite steroid containing a high proportion of N^{14} (N^{15}: N^{14} ratio 1.0 : 3.45)[23].

Vapor phase investigations of the nitrite photolysis of alkyl nitrites showed that the nitrite ester suffers homolysis and that the resulting alkoxy radical[16] undergoes rapid decay to provide a carbonyl fragment and an alkyl radical. The latter, however, immediately combines with NO· which is in close proximity to it in preference to the alternate recombination with a more distant second alkyl radical[28].

3. The Barton reaction is an example of intramolecular hydrogen abstraction[24].

Although the abstraction of a hydrogen is not favoured energetically, the repulsive and steric factors[13] play a considerable role. A more detailed consideration of the factors involved in the intramolecular hydrogen abstraction suggests the existence of a six-membered transition state[24].

The predominance of the six-membered transition state in the Barton reaction was shown by the absence of remote functionalization following the photolysis of ω-phenylalkyl nitrites having an insufficient number of carbon atoms in their side chain necessary for the formation of a six-membered transition state[26]. In other instances where a five- or seven-membered transition state was required, no nitroso dimers were observed after photolysis[25,26]. Thus, 1-benzyl nitrite furnished no dimer, while 4-phenylbutyl nitrite afforded the expected dimer* (scheme 6).



Scheme 6

* In the photolysis of n-octyl nitrite, the almost complete absence of of oxime in the photolysis product indicated that the latter compound is not formed directly during the photolysis, but is produced indirectly through the nitroso monomer[22].

The possibility of a linear transition state[12] analogous to the one suggested for the Hofmann-Löffler-Freytag reaction[6] has been considered[27] (Fig. 1); for the Barton reaction, this linear arrangement does not appear essential. It was shown that the maximum angle which can be attained in the transition state derived from a 6β-nitrite ester is 146° [21].

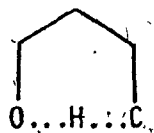


Fig. 1

The availability of a six-membered transition state although necessary is not always a sufficient condition for the intramolecular hydrogen abstraction process. The distance X-Y (fig.2) must fall within critical limits[8].

4. For the Barton reaction (scheme 5) it was shown that step 2 follows rapidly on step 1 as quenching of the radicals (9) and (10) with a hydrogen donor, e.g. deuterated thiophenol, furnished the steroid alcohol showing in its mass spectrum the incorporation of deuterium at the C-19 position[44]. The recombination of the C-radical (10) with the nitrite radical is not unprecedented, the latter being a well-known radical trap[28]. The resulting monomeric nitroso compound may then dimerize or rearrange to the oxime (11). In many cases, steric factors prevent the convergence of two steroid molecules which may explain the rearrangement to the oxime and the lack of dimerization products[24].

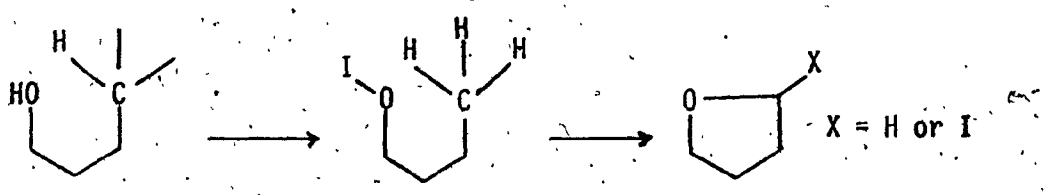
Disproportionation reactions[10b] are favoured over the rearrange-

ment reaction when the geometric and structural requirements of the Barton reaction are not fulfilled[17]. At all times, these reactions are present to an appreciable extent.

5. The pyrolysis of nitrites in the molten state does not lead to a hydrogen transfer as in the case of the photolytic process. The difference in behavior has been accounted for by an ionic mechanism not involving alkoxy radicals[29].

The hypoiodite reaction

The term "hypoiodite" denotes the homolytic cleavage of acyl hypoiodites (14b) which are prepared by the action of N-iodosuccinimide or acyl hypoiodites on alcohols[30] in non-polar solvents. Intramolecular substitution on non-activated carbon centers lying in close proximity becomes possible, the end-product of these substitutions being generally a tetrahydrofuran derivative (14c)[8]. The overall reaction is shown in scheme 7.



14a 14b 14c

Scheme 7

Hypoiodites can be generated by treatment of alcohols with t-butyl hypochlorite and iodine, or with mercuric oxide and iodine[31]. Alternatively, lead tetraacetate, silver acetate or mercuric acetate in combination with iodine have also been employed[32].

Hypoiodite formation and cleavage

Warming an equimolecular amount of iodine and lead tetraacetate[33] in carbon tetrachloride leads to processes (15) and (16) :

$$Pb(OAc)_4 + I_2 \longrightarrow Pb(OAc)_2 + 2AcOI \qquad (15)$$

$$2Ac - OI \longrightarrow 2\,CO_2 + 2CH_3I \qquad (16)$$

However, in presence of an alcohol, the acetyl hypoiodite reacts in a reversible manner as shown by process (17)[8a] :

$$CH_3\,COO\,I + ROH \rightleftharpoons RO\text{-}I + Ch_3\,COOH \qquad (17)$$

Heat or light induced reactions have been used to give products which are rationalized as having originated from hypoiodite intermediates[34]. Indeed the photolysis of acyl hypoiodites affords alkoxy radicals and iodine atoms[33]. The homolysis of the O-I bond can also be effected thermally in combination with light of wavelength 500-550 nm which is appropriate to the high absorption band of the iodine. The thermal break-up is facilitated by the presence of the electronically excited iodine atoms or the excited iodine molecule[8].

Intramolecular Hydrogen Abstraction

K. Heusler and J. Kalvoda have defined this abstraction as follows:

"Intramolecular abstraction of hydrogen corresponds to the transfer of a hydrogen atom to an attacking free radical in the same molecule, and hence to a hydrogen shift[8b]".

(a) Intramolecular hydrogen abstraction is favoured when the transition state is a six-membered ring[7] in the chair form[8b]. For the Barton reaction, the quasi-chair is the most favourable form if consideration is given to the maximum overlap of bonding orbitals in the transition state. However, the chair and boat transition states cannot be eliminated on the basis of the preceding statement[21]. The exclusivity of the six-membered ring concept has receded with the discovery that intramolecular hydrogen abstractions are also feasible with seven- or larger membered transition states having fixed reaction centers sterically aligned[8].

The few exceptions[40] to the generally favoured six-membered transition state occur only when fragmentation processes are inhibited, or when no δ-hydrogen atoms are available[42]. In the majority of cases, the overwhelming evidence for the consistent abstraction of the hydrogen bonded to the δ-carbon atom rather than hydrogen atoms (often more weakly bonded) in other skeletal positions[24,35] asserts the relevance and importance of the six-membered state[36].

(b) As in the Hofmann-Löffler-Freytag reaction, the reactivity of the hydrogen atom to be abstracted increases in the order primary < secondary < tertiary[37,38]. This is in accordance with the greater energy requirements of the primary bond rupture[16].

(c) The internuclear distance X-Y (fig. 2) between the oxygen radical and the δ-hydrogen must fall within critical limits. Dreiding models for

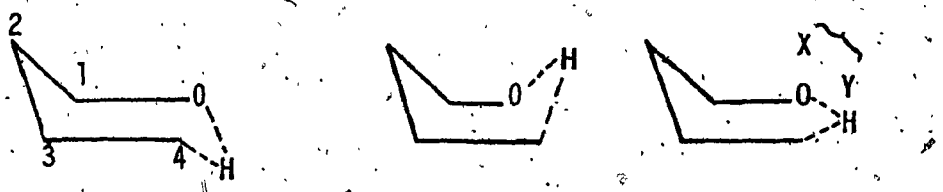


Fig. 2

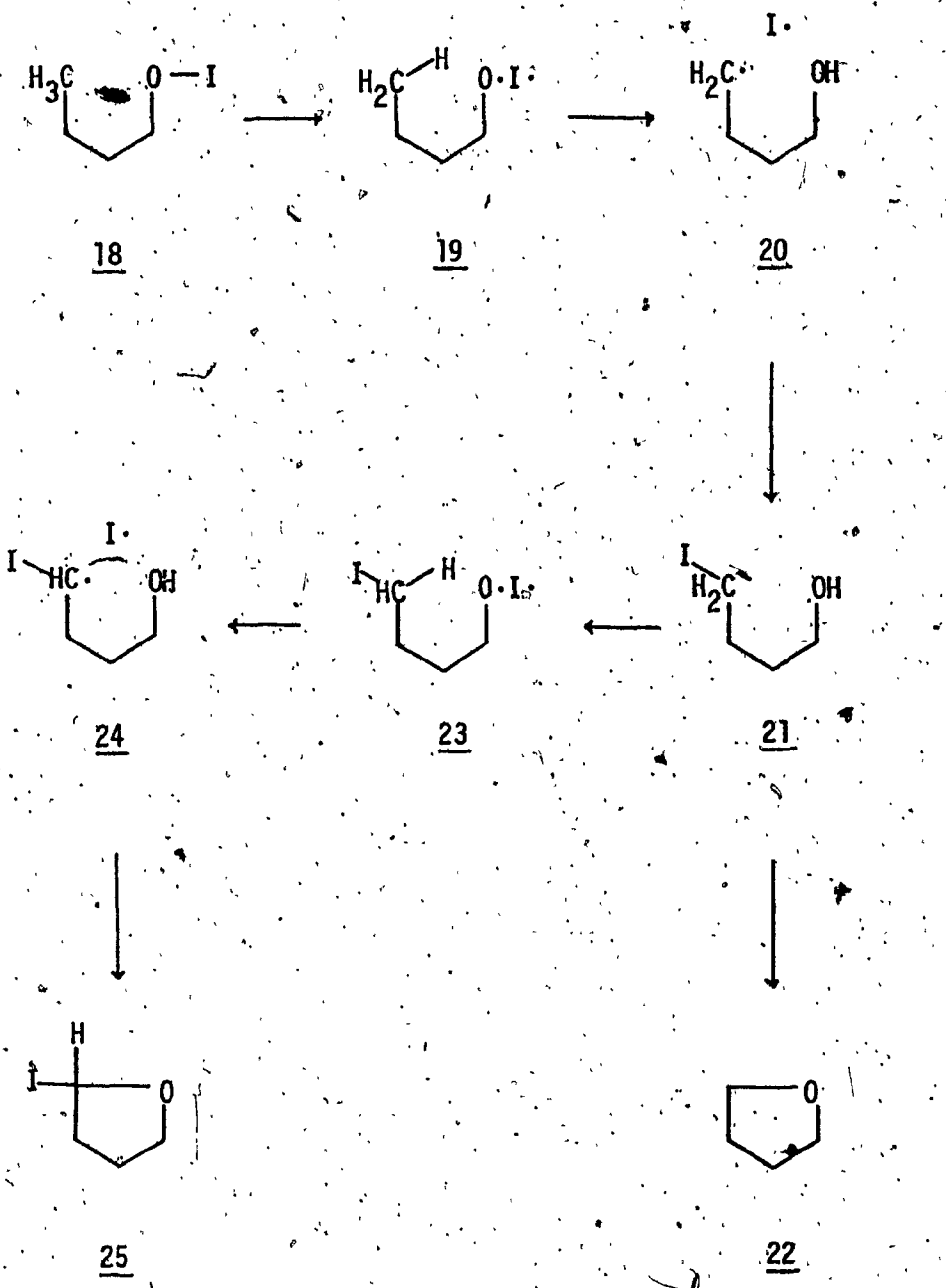
typical steroidal compounds have shown this distance to be minimally 2.1 Å when the C_4-O· distance is 2.6 Å. This minimum distance is realized only when the ·O-C_4, C_1, and C_3 lie in the same plane. For distances of C_4-O· exceeding 2.8 Å, the rate of the intramolecular abstraction becomes smaller than that of the intermolecular process, or other fragmentation reactions[8b].

The course of the hypoiodite reaction is influenced by various factors such as the degree of substitution of the attacked center[8a], the reagents employed[3g] (lead tetraacetate-iodine, mercuric iodide-iodine, etc.) and the stochiometric amounts of the reagents used[8a].

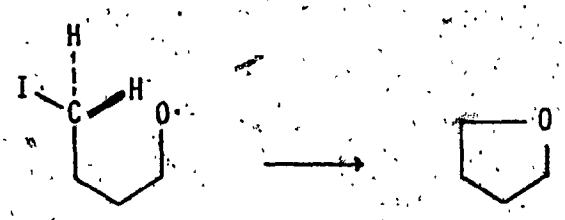
Substitution on methyl groups

The alcohol (14a) is converted into its iodo-ether (18) which undergoes a photo-induced rearrangement to furnish the first product of the hypoiodite reaction, the iodohydrin (21)[43]. Further substitution converts the iodohydrin (21) to the hemiacetal iodide (25) or to the cyclic ether (22)[48]. In specific cases, the outcome of the reaction for the formation of the final product (22) or (25) depends upon the conformation of the iodomethylene group in (23) or in the iodohydrin (21) as the relative spatial positions of the oxygen and iodine atoms determine the transition state for the reaction.

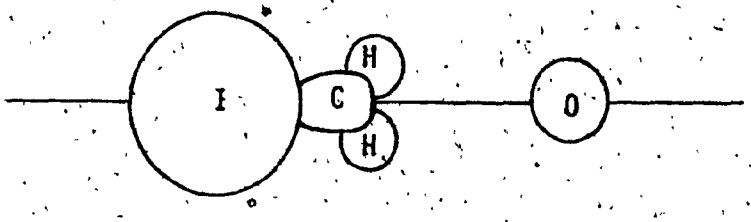
Assuming that the carbons at positions 1, 3 and 4 (scheme 9) and the oxygen atom of the iodohydrin lie in one plane, three different and extreme orientations (A, B, C, scheme 9) of the iodomethylene group in relation to the oxygen atom arise [8,45]. Only in case A is the iodine atom in the plane defined by the atoms discussed above, and the formation of a simple ether is favored by elimination of the iodine atom with inversion of configuration[8b]. This process is energetically favorable[41], and occurs only when the atoms O, C_4, and I are appropriately aligned[8a]. This steric requirement is fulfilled in the case of the 6β-hydroxy-19-iodo-steroids[30,49] where the facile rotation of the C_3-CH_2I bond is lost (scheme 9). An alternative mechanism not involving intramolecular elimination from a halohydrin has been proposed[44]. Photolysis of a 6β-nitrite ester furnished in almost equal proportions the 6β, 19-ether, the 6β-alcohol, and the 19-oxime. The ether formation can be rationalized as involving alkoxyl radicals that can abstract hydrogen from the 6β-ol of



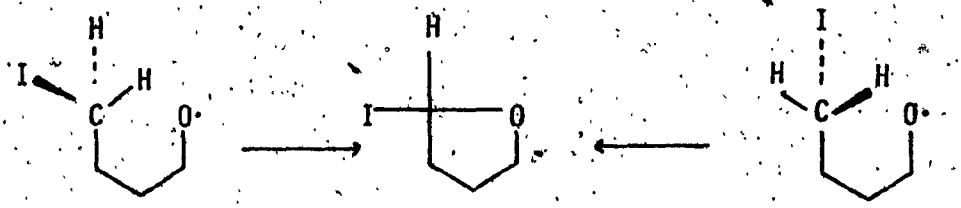
Scheme 8



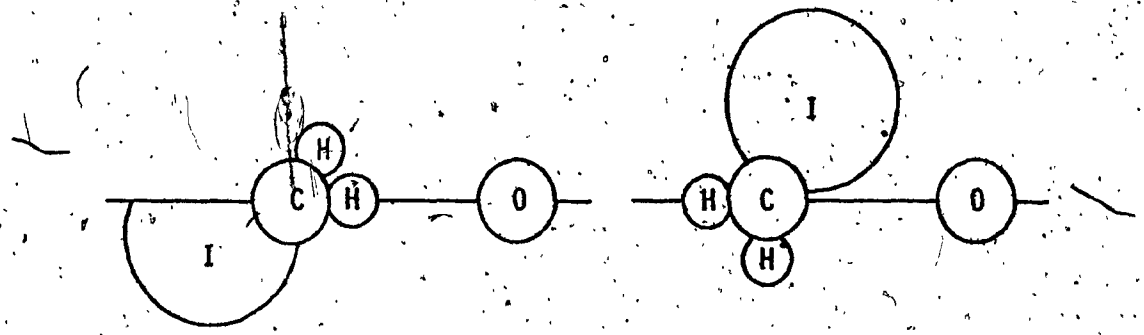
Monosubstitution



A



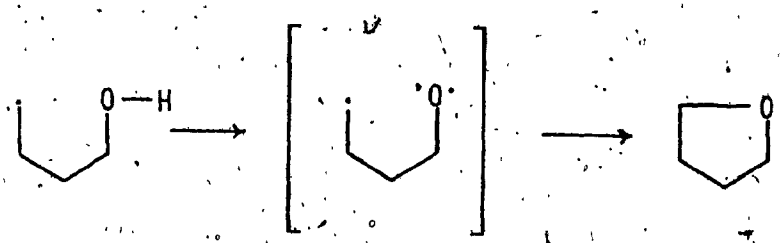
Disubstitution



B C

Scheme 9

the C-19 radical either by radical displacement on hydrogen or by formation of the 6β,19-diradical (scheme 10).



Scheme 10

In case C (scheme 9) an interaction between the iodine atom and the oxygen radical can occur, although generally the disubstitution product results, as in the case of 2β-hydroxy-19-iodo-steroids[46,47]. In case B, the configuration is ideal for the abstraction of either of the hydrogen atoms lying in the plane mentioned above, leading to disubstitution product[8], as in the case of 4β-hydroxy-19-iodo-steroids[50].

Mention must be made of the slow generation of the alkoxy radical which proceeds independently of the preferred conformation of the iodomethylene group so that monosubstitution products as well as disubstitution products are formed[8a].

Iodohydrin formation

The simple case in which the oxygen radical is not generated arises in the presence of lead tetraacetate and one equivalent of iodine. Under these conditions, the reaction stops at the iodohydrin step (21)[8a].

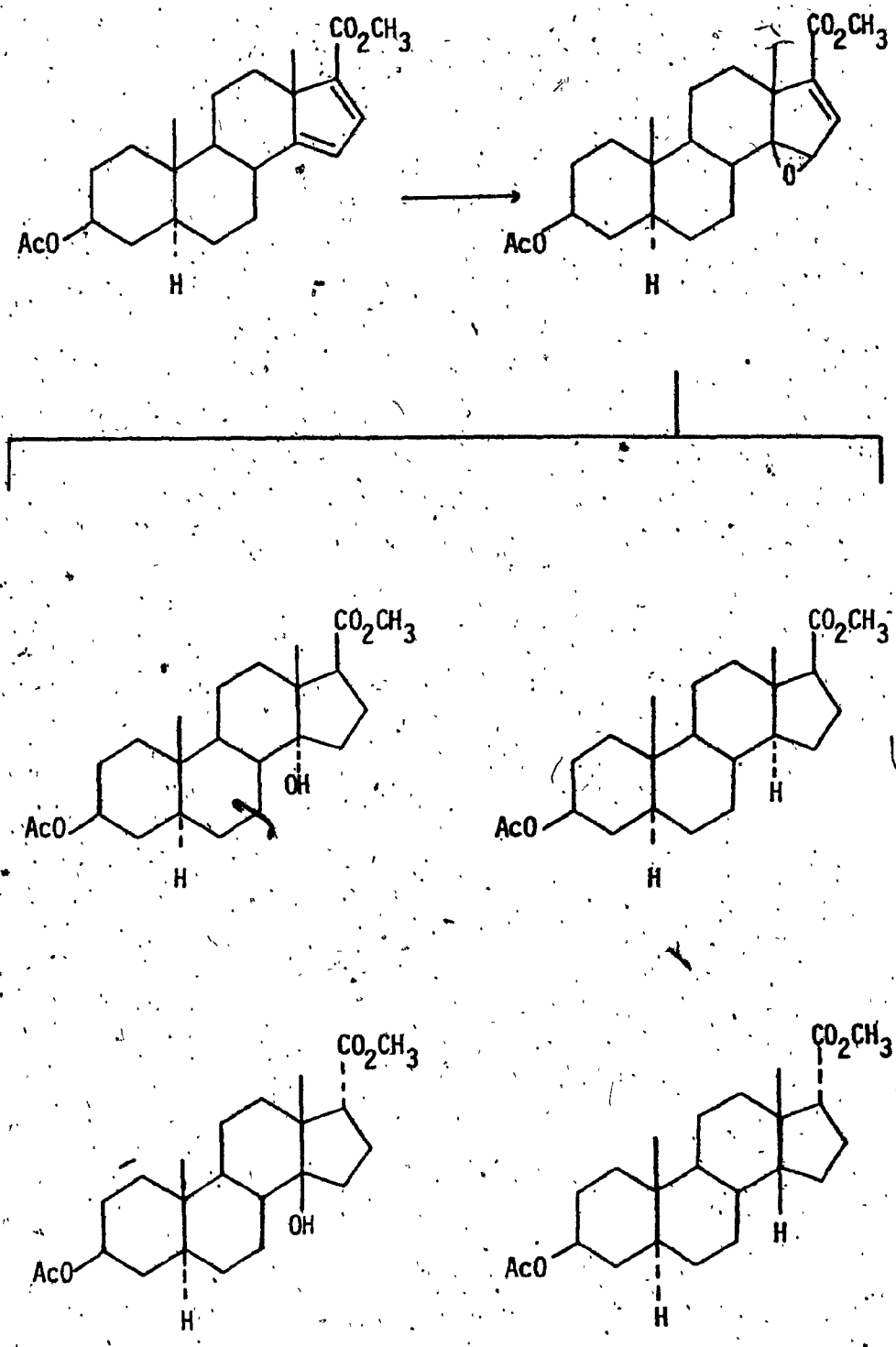
DISCUSSION

Attempts to synthesize various 14β-hydroxy - steroidal derivatives are described in the early literature, and proceed through the epoxidation of a 14,16-diene steroid, followed by full hydrogenation to yield a mixture of isomeric products[51] (scheme 11a). The subsequent reactions proceeded through the ring opening of the 14,15β-epoxide with hydrogen chloride to yield the 14,15β-hydroxy-15α-halo-derivative. Removal of the 15α-group proceeds in low yield making the method synthetically impractical[52]. More recently, a successful method for the ring opening reaction was introduced by Wehrli and Jeger[53] whereby a 14β-hydroxy-17β-substituted derivative can be synthesized in high yield. Other methods outlined in schemes 11b and 11c have also been employed for the successful 14β-hydroxylation of the D-ring steroid nucleus[54,55].

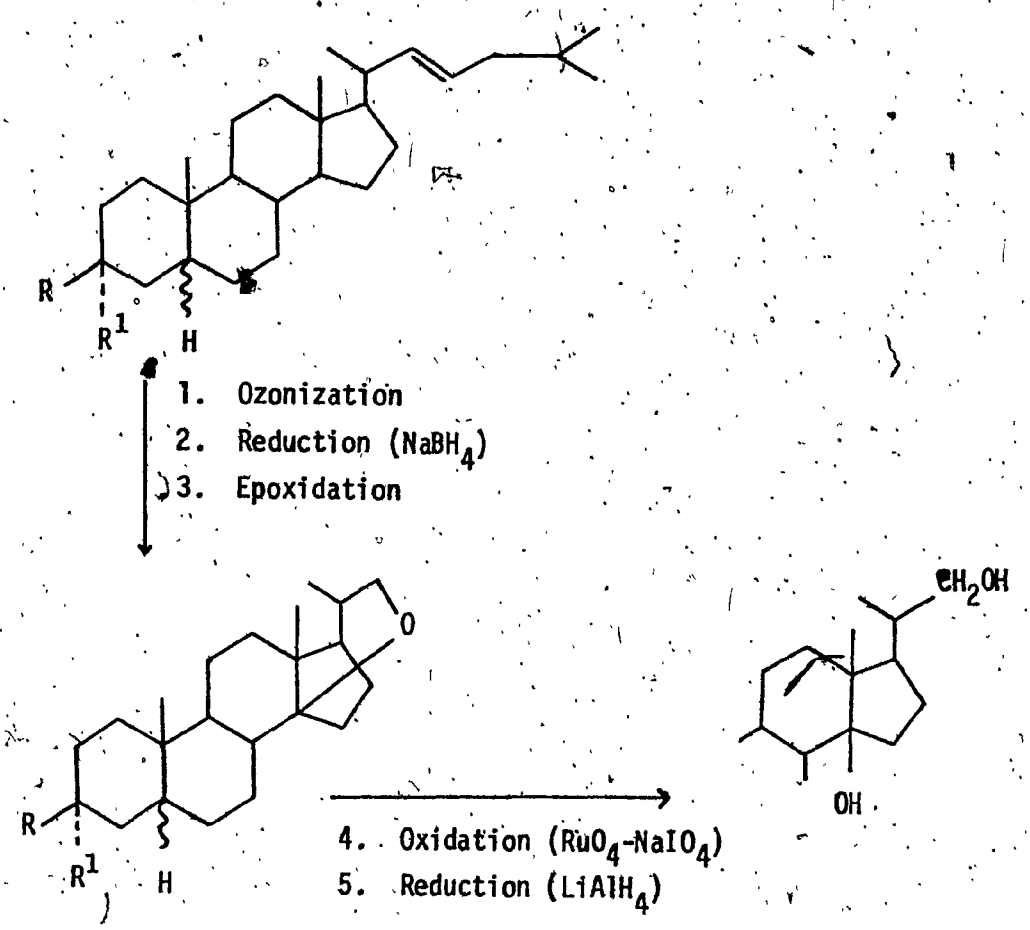
Based on these recent developments of the ring opening reactions of the 14,15β-epoxides, it was decided to employ the procedure outlined in scheme 12 for the preparation of a 14β-hydroxylated-Δ^{16}-steroid employing pregnenolone acetate as the starting material, our choice being governed by its ready availability and low cost.

Preparation of 3β-acetoxy-14β-hydroxy-5α-pregn-16-en-20-one

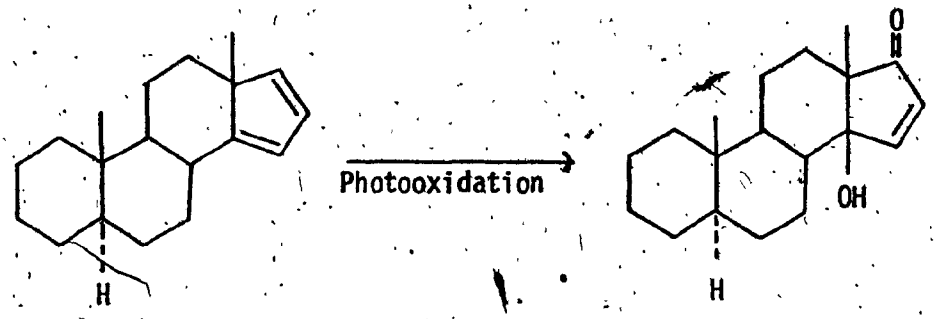
Hydrogenation of a Δ^5 isomer can in principle lead to the 5α- or 5β-isomer (fig. 3). A consideration of the steric factors involved shows that the formation of the 5β-isomer (32) requires the incoming hydrogen at C_6 to interact severely with the angular methyl group and to



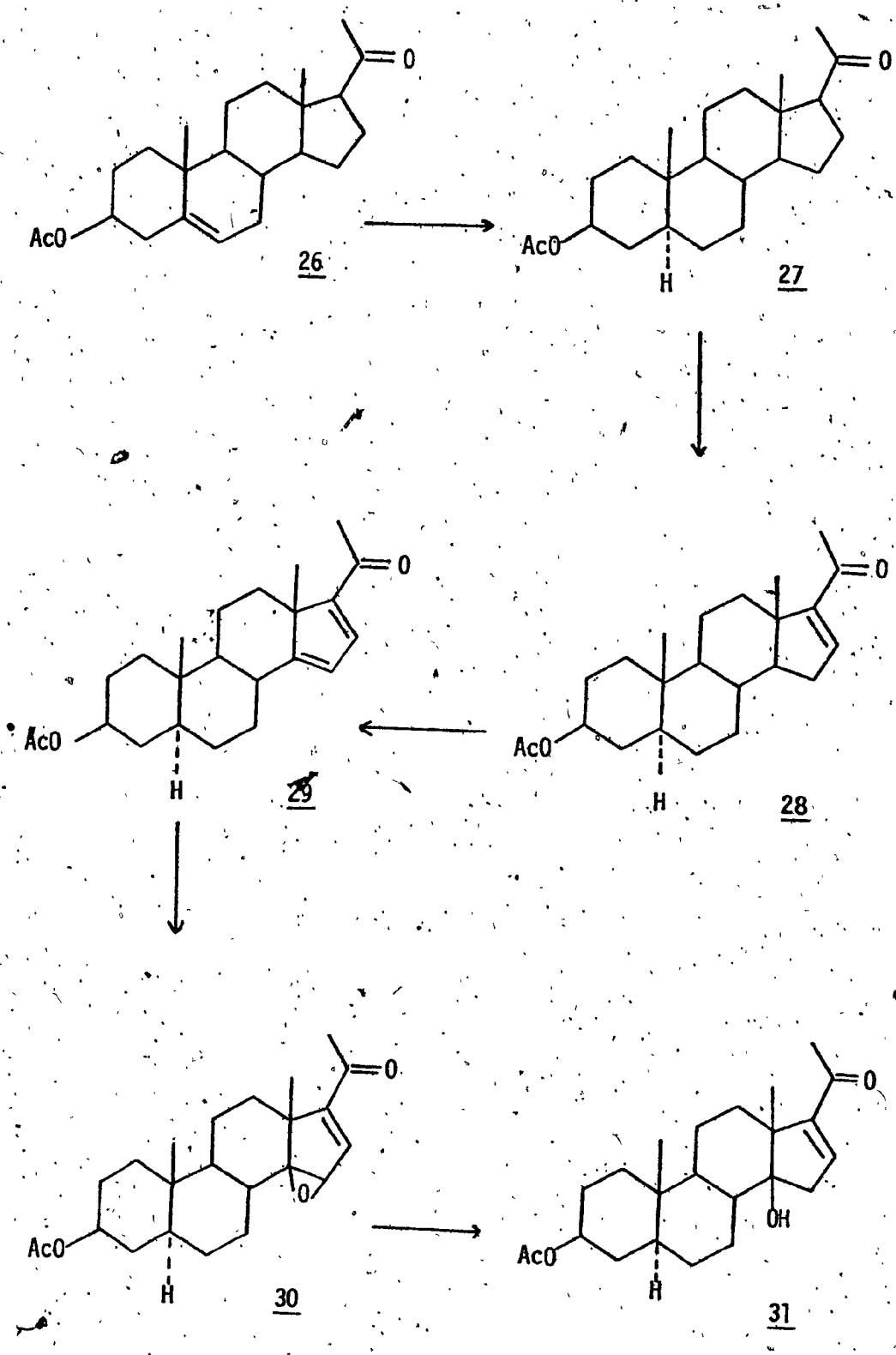
Scheme 11a



Scheme 11b

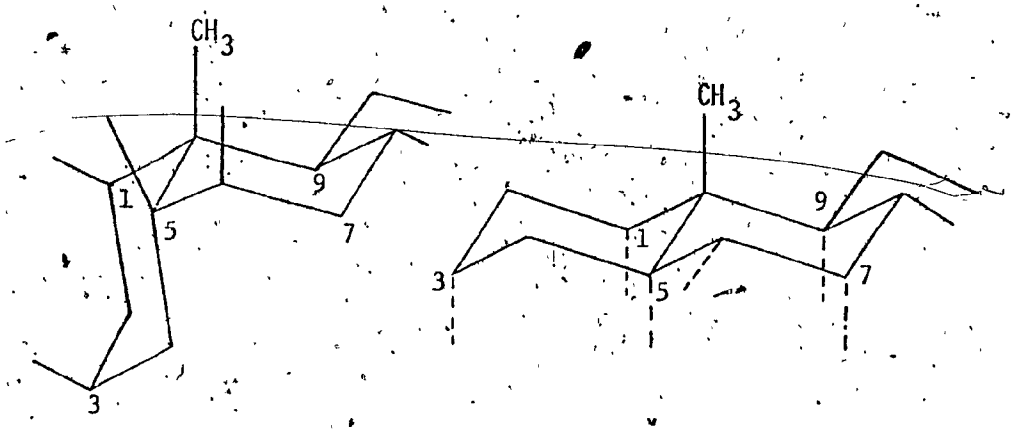


Scheme 11c



Scheme 12

a smaller extent with the hydrogens at C_8 (the 5β-hydrogen also interacts with the hydrogens at C_1 and C_3) while for the formation of the 5α-isomer (33), 1-3 interactions between the hydrogen at C_5 and the axial hydrogens at C_1, C_3, C_7, and C_9 occur. The greater stability of complex (33) accounts for the predominant formation of A/B trans[56].



32 33

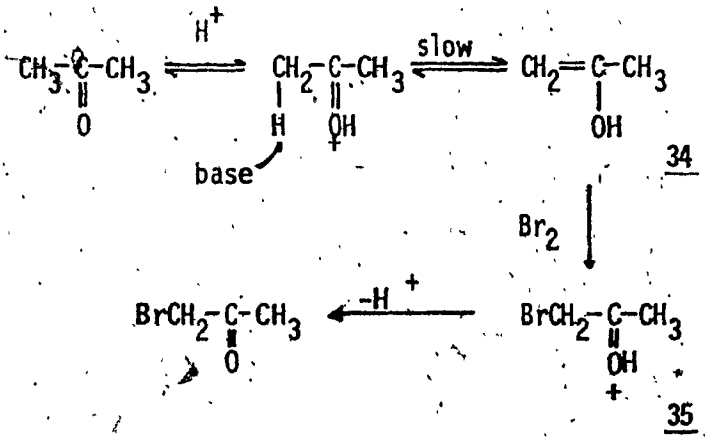
Fig.3

In our hands, the hydrogenation of pregnenolone acetate (26, scheme 12) proceeded smoothly at atmospheric pressure with Palladium-Charcoal, 5%, in ethyl acetate to afford quantitatively the expected 5α-derivative (27)[57].

The halogenation-dehydrohalogenation of ketones is the most widely applied method for the preparation of α, β-unsaturated ketones. Conjugated and isolated dienes are prepared by extension of the methods suitable for monoolefins. For this purpose, bromoketones are commonly employed as their dehydrobromination proceeds more readily than the

corresponding chloroketones. Iodoketones are generally not employed as they are less accessible[58].

The acid catalysed[59] halogenation of carbonyl compounds can be initiated in organic solvents (e.g. carbon tetrachloride, chloroform, ether) by irradiation or by use of free radical initiators[60]. Although the initiation of the reaction appears to involve free radicals, the mechanism[61] is nonetheless ionic in nature (scheme 13) and involves electrophilic attack on the enol (34) and the loss of a proton from the oxonium ion (35). For the majority of ketones, the enolization is the rate-determining step[58,60] and the overall rate of halogenation is independent of the nature and concentration of the halogen[60].



Scheme 13

This bromination of steroidal ketones was proposed originally to proceed via a stereoelectronic factor[62], i.e., the maximum overlap of the orbital of the positive halogen species with the π-orbital of the

enol-enolate double-bond thus providing the lowest energy of activation for the addition reaction[63]. In this respect, the axial orientation[64] of the entering or leaving α-substituent in the transition state for the enolization-ketonization was postulated as the more favourable approach[65]. Furthermore, the studies of the isotope effect[69] for a ketosteroid indicated the almost total rupture of the Cα-H bond in the transition state, thereby pointing to the similarity in structure between the latter and the enol[65]. Thus the kinetic product of bromination is the axially substituted ketosteroid[64,66].

The distinct advantage in the use of N-bromosuccinimide for ketone bromination resides in the fact that little HBr is produced which may catalyze aldol condensation[60]. With unsymmetrical ketones, the ease of formation of the structurally isomeric enols is enhanced by the presence of alkyl substituents. Thus, bromine attack takes place on the more highly substituted α-position. For 3β-acetoxy-5α-pregnan-20-one (27), the N-bromosuccinimide reaction yielded the kinetically favoured 17α-bromo-compound[67a]. The α-configuration of the 17-halogen follows from the fact that a free radical bromination of a 20-ketone affords the same stereoisomer as an acid catalyzed bromination which leads exclusively to the 17α-bromo derivative[67b].

Dehydrobromination of the resulting α-haloketones has been accomplished in a number of ways. With pyridine[68], poor yields are obtained, while with 2,4-lutidine[69], a mixture of products is obtained whose ratio depends on the purity of the starting material. A dehydrobromination method

introduced by Joly[70] employs an excess of lithium carbonate in dimethylformamide, the former presumably to facilitate the removal of the generated hydrogen bromide. High yields of homogeneous products are reported.

The mechanism for the dehydrohalogenation reaction was not studied extensively. The available evidence points to an E_2 trans-elimination process[71]. Dehydrobromination in dimethylformamide-lithium chloride or pyridine of a 16α-deuterio-17α-bromo-20-ketosteroid afforded the 16-deuterio-16-ene-20-keto derivative containing 0.98 and 1.03 atoms of deuterium per molecule.

The 16-dehydro derivative, 3β-acetoxy-5α-pregn-16-en-20-one (28) was obtained in high yield by the method of Joly[70]. Dehydrobromination yielded a purer product when the combination lithium chloride in boiling dimethylformamide was used under a stream of nitrogen as opposed to the combination of lithium bromide-lithium carbonate-dimethylformamide. This last combination gave an additional minor product with a similar R_f to the Δ^{16} steroid. It was not further identified. The ultraviolet spectrum of the mixture of enone and minor impurity described above was identical to that of the pure enone (28) in the region 200-260 nm. The minor product formation was not observed with the original combination (DMF-LiCl) in any of the runs.

The use of milder conditions in the Joly procedure affords regio-selective dehydrobromination in steroidal systems[70,72]. Relatively vigorous reaction conditions were arbitrarily selected to dehydrobrominate the monosubstituted bromosteroid, i.e., 3β-acetoxy-17α-bromo-

5α-pregnan-20-one.

Allylic bromination is a free radical chain process[73]. N-bromosuccinimide has been reported an effective reagent for the bromination of the allylic position of an α,β-unsaturated ketosteroid in the presence of free radical promoters or under irradiation. Thus dienones are readily accessible[74]. The mechanism for the reaction was shown to proceed with a bromine radical as the hydrogen abstracting species[75].

In the case of 3β-acetoxy-5α-pregn-16-en-20-one (28), allylic bromination either with molecular bromine or with N-bromosuccinimide was reported to yield a mixture of products[76], 3β-acetoxy-5α-pregn-14, 16-dien-20-one (29), the two isomeric compounds 3β-acetoxy-15α- and 15β-bromo-5α-pregn-16-en-20-one, 3β-acetoxy-16β,17α-dibromo-5α-pregnan-20-one, and other products. Following dehydrobromination*, the crude reaction mixture was chromatographed. In our hands, preparative thin layer chromatography described by Tschesche and co-workers[76] for the isolation of the dienone (29) could not be reproduced. Column chromatography using alumina was successful in isolating a small fraction of the dienone which was contaminated with some starting material. Trituration of the impure dienone (29) with a minimal amount of ether furnished the pure material melting at 176-178° but in yields ranging only from 10 to 20%. Our attempt to increase the yield failed when 1.5 and 2.0 equivalents

* Dehydrobromination in some runs followed the method by Tschesche and co-workers[76] and in others the method by Joly[70].

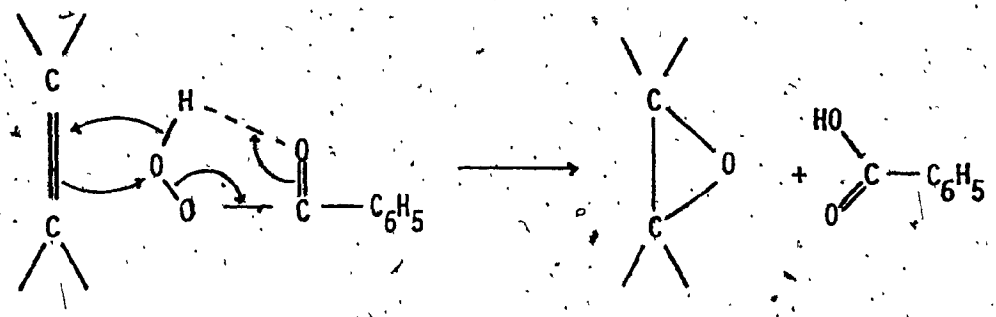
of N-bromosuccinimide were used. However, these attempts resulted in decreasing the amount of unreacted enone (28) remaining in the final reaction mixture.

Since a large number of undesirable side products (ca 10) is regularly formed in the bromination reaction, we developed a method for the purification of these complex dienone-enone mixtures without resorting to chromatography. Extraction of the crude dehydrobrominated mixture with a mixture of ethyl ether : petroleum ether, bp 66-75° (1:1) afforded a solid melting at 159-163°. Use of this solid in the subsequent reaction afforded the epoxide (30) in yields comparable to those obtained with the pure dienone, the yield of the former reaction being adjusted by taking into consideration the purity of the starting material as determined by NMR.

An improved synthetic procedure of the dienone (29) that we developed in our laboratory consisted of only initiating the reaction of the enone (28) with N-bromosuccinimide (1.5 equivalent). Following the initiation (red vapours of bromine in the condenser) the 500W tunsgsten lamp source was turned off, and the reaction mixture was refluxed until the red color imparted to the solvent disappeared completely. This procedure afforded the dienone (29) in increased amounts (40% yield, mp 164-5°).

The epoxidation of olefins proceeds via an electrophilic attack of the peracid usually on the less hindered side of the olefin to furnish

the less hindered epoxide as the major product[78]. The generally accepted mechanism[79] involves the concerted bond migration depicted in scheme 14 in a non-acid catalyzed process [78a,80].



Scheme 14

The evidence for such a path is supported by the second order kinetics of the reaction, the lack of evidence for carbonium ion formation, and the stereospecificity of addition, i.e., cis - and trans - olefins furnish cis - and trans - epoxides respectively[81].

The rate of epoxidation process is enhanced by the presence of either electron-withdrawing groups in the peracid (e.g. p-nitroperbenzoic acid) or electron-donating groups in the olefins[78b,82] and is reduced by the conjugation of the olefins with other multiple bonds or with aromatic systems which reduce the electron density at the double bond undergoing electrophilic attack[78b,83].

In the case of α,β-unsaturated ketones, the Baeyer-Villiger rearrangement may compete with the oxidation of the double bond[79]; in such

instances, use of a peracid does not lead to epoxidation and causes the reaction with the carbonyl group to become the predominant process[84]; α,β-unsaturated ketones can be effectively epoxidized with nucleophilic reagents such as sodium hydroperoxide (NaOOH)[85]. The anticipated formation of 3β-acetoxy-14,15β-epoxy-5α-pregn-16-en-20-one has also been observed experimentally[86]. Similar stereochemistry of addition has also been observed in related steroidal systems[87].

The epoxidation of 3β-acetoxy-5α-pregn-14,16-dien-20-one (29) with 1.15 equivalents p-nitroperbenzoic acid furnished high yields of 30 (ca 70%) when the reaction was stored at room temperature, and in the dark for 16 to 19 hours. The β-configuration of the epoxide was assigned on the basis of previously published work of Plattner and co-workers[86]. The NMR spectra (CCl_4) showed a downfield shift for CH_3-18 to 1.25 ppm vs 1.12 ppm in the starting material. The proton resonances of C-15 and C-16 appeared at 3.62 and 6.76 ppm respectively as broad singlets[87b].

The epoxide cleavage reaction is an S_N2[88,89] process* which proceeds with the assistance of a polar solvent[89a]. Due to the strain associated with a three-membered ring[90], bond breaking is significant in the transition state, and the ensuing nucleophilic attack predominates at the less highly substituted carbon atom of the epoxide ring[91,92].

* Epoxide cleavage reactions can also be of the S_N1 type[90].

In our hands, the reductive cleavage of the 14,15β-epoxide (30) furnished the expected 14β-hydroxy-derivative (31) identified by NMR and melting point, when the method described by Jeger and co-workers[93] was employed. Care had to be exercised to ensure that the epoxide (30) was not contaminated with traces of perbenzoic, or benzoic acid as these compounds totally inhibited the reductive cleavage. With a contaminated epoxide, the 14,16-dienone (29) was principally obtained.

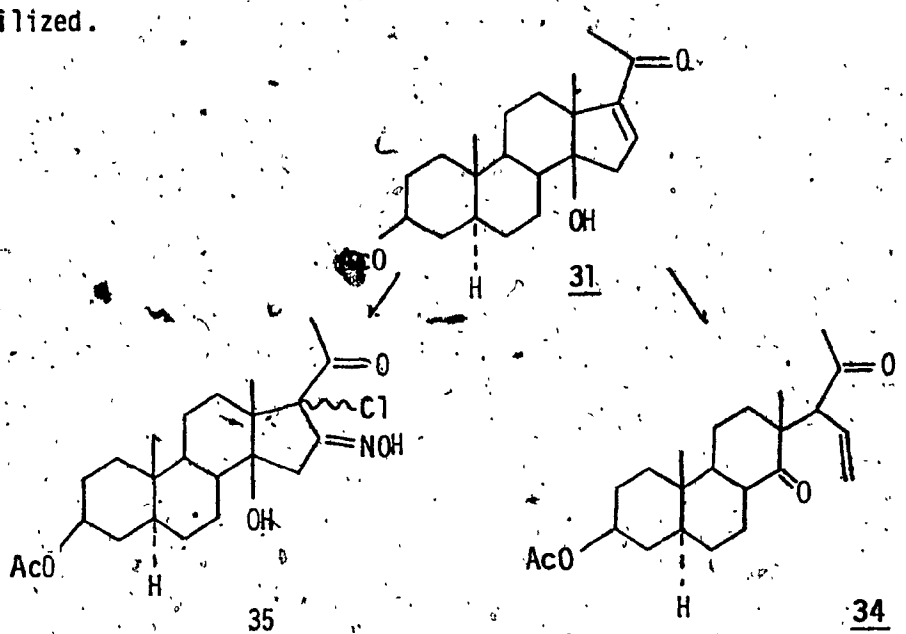
Hypoiodite reaction of 3β-acetoxy-14β-hydroxy-5α-pregn-16-en-20-one

Photochemical reactions not involving a six-membered transition state have been investigated[40,93,94]. The formation of five- and seven-membered transition states during photolysis experiments has been reported, leading to widely different products. In the former case, the photolysis of the 17β-nitrite ester of 5α-androstan-3α-acetate furnished a rearrangement product[94] while the hypoiodite reaction of a diterpene alkaloid involving a seven-membered transition state afforded an ether[40b]. The success of the last reaction has been explained in terms of steric and conformational factors.

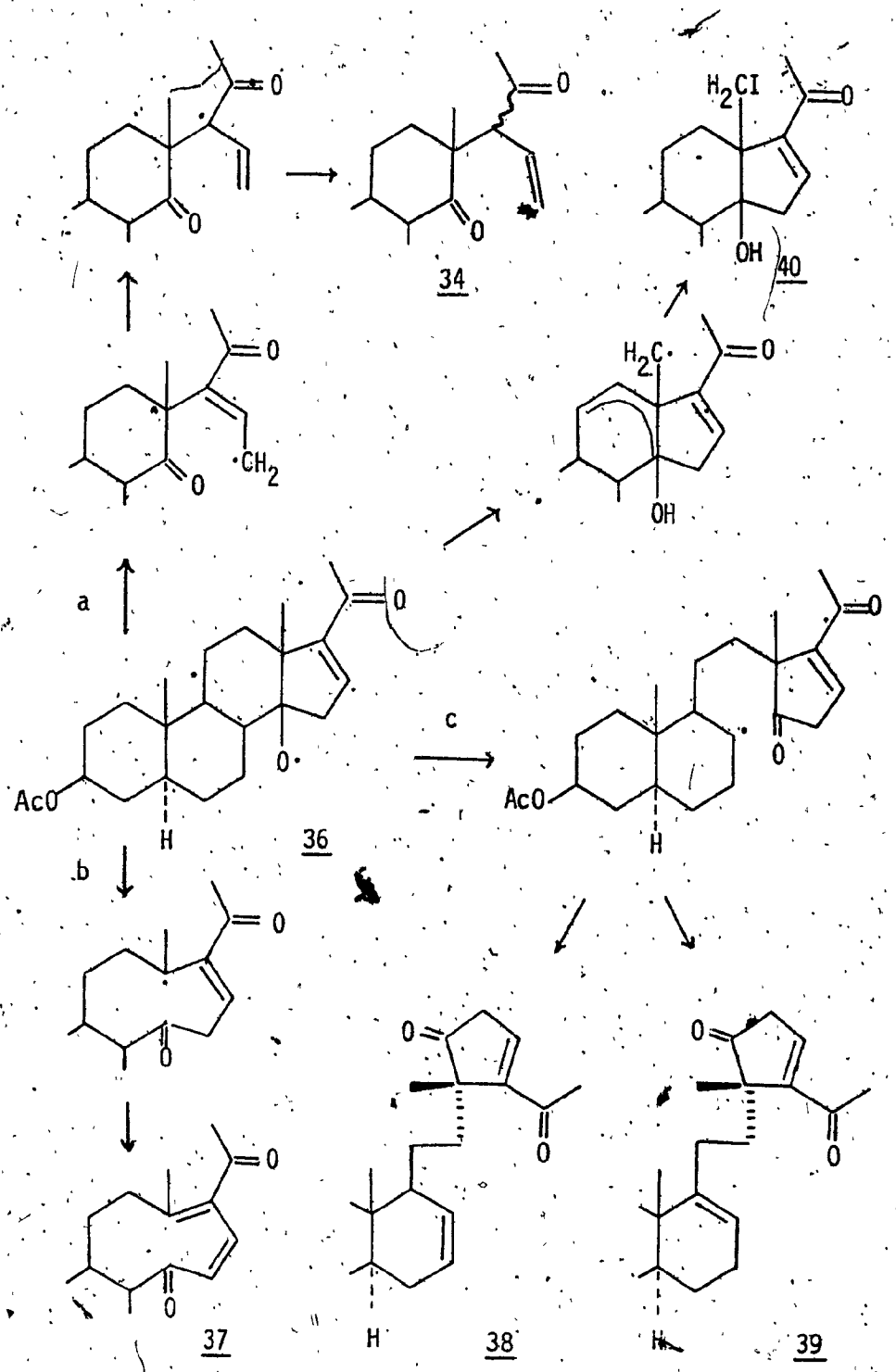
For the steroidal system under investigation, i.e., 3β-acetoxy-14β-hydroxy-5α-pregn-16-en-20-one, photolysis with light of wavelength 2537 Å (selective $\pi \rightarrow \pi^*$ excitation) yielded a photofragmentation product in low yield[93] (ca 12%, 34, scheme 15). It was of interest to study the nitrite ester photolysis and the hypoiodite reaction with the 14β-hydroxy steroid (31). The Barton reaction could not be attempted since attempts

to prepare the 14β-nitrite ester failed. Instead the nitrosyl chloride attacked the double bond at C-16, yielding presumably 35[97]. The hypoiodite reaction (with two equivalents of iodine) in cyclohexane, yielded a complex mixture of approximately ten compounds, the resolution of which was not attempted. When the reaction was carried out under the conditions of the iodohydrin reaction (one equivalent of iodine) utilizing benzene (or cyclohexane) as solvent and employing reaction times of the order of 45 minutes (5-10 minutes for cyclohexane) and irradiation with a 500W tungsten lamp, photofragmentation of the steroidal system occurred.

In scheme 16, we show some of the possible breakdown products which in principle can be obtained from the 14β-alkoxy radical (36). Inspection of the scheme reveals that the formation of compounds 37, 38, or 39 involves an intermediate secondary or tertiary radical while that of compound 34 involves the initial formation of a primary radical although stabilized.



Scheme 15



Scheme 16

The NMR of the crude reaction product revealed the presence of two signals between 5.0 and 6.0 ppm - specifically at 5.10 and 5.51 ppm - compatible with the vinylic protons CH (7) and CH (8) encountered in compounds 38 and 39 respectively. Another signal at 6.62 ppm is associated with the vinylic proton CH(16) of 31. Wehrli[93] has reported that the vinylic protons of 34 appear at 5.16 and 5.73 (see table 1). The NMR of the crude reaction product can also be interpreted for the spectral region of 0-2.30 ppm as follows :

(a) one signal at 0.82 ppm, attributable to the 19-methyl of unreacted 31. The presence of the starting material was further verified by thin layer chromatography. The NMR also showed three singlets at 0.78, 0.88, and 1.00 ppm.

(b) the next group of four singlets appeared at 1.24, 1.26, 1.34, and 1.59 ppm. The singlet at 1.26 ppm was associated with the 18-methyl of 31. The assigned chemical shift of the 18-methyl of 34 is 1.45 ppm[93].

(c) the signal at 2.00 ppm, the largest resonance line of the spectrum, is associated with the 3-$COCH_3$ group of 31, and possibly of 37, 38, and 39.

(d) the four singlets at 2.06, 2.11, 2.25, and 2.29 ppm, with the last singlet associated with the 21-methyl of 31[93].

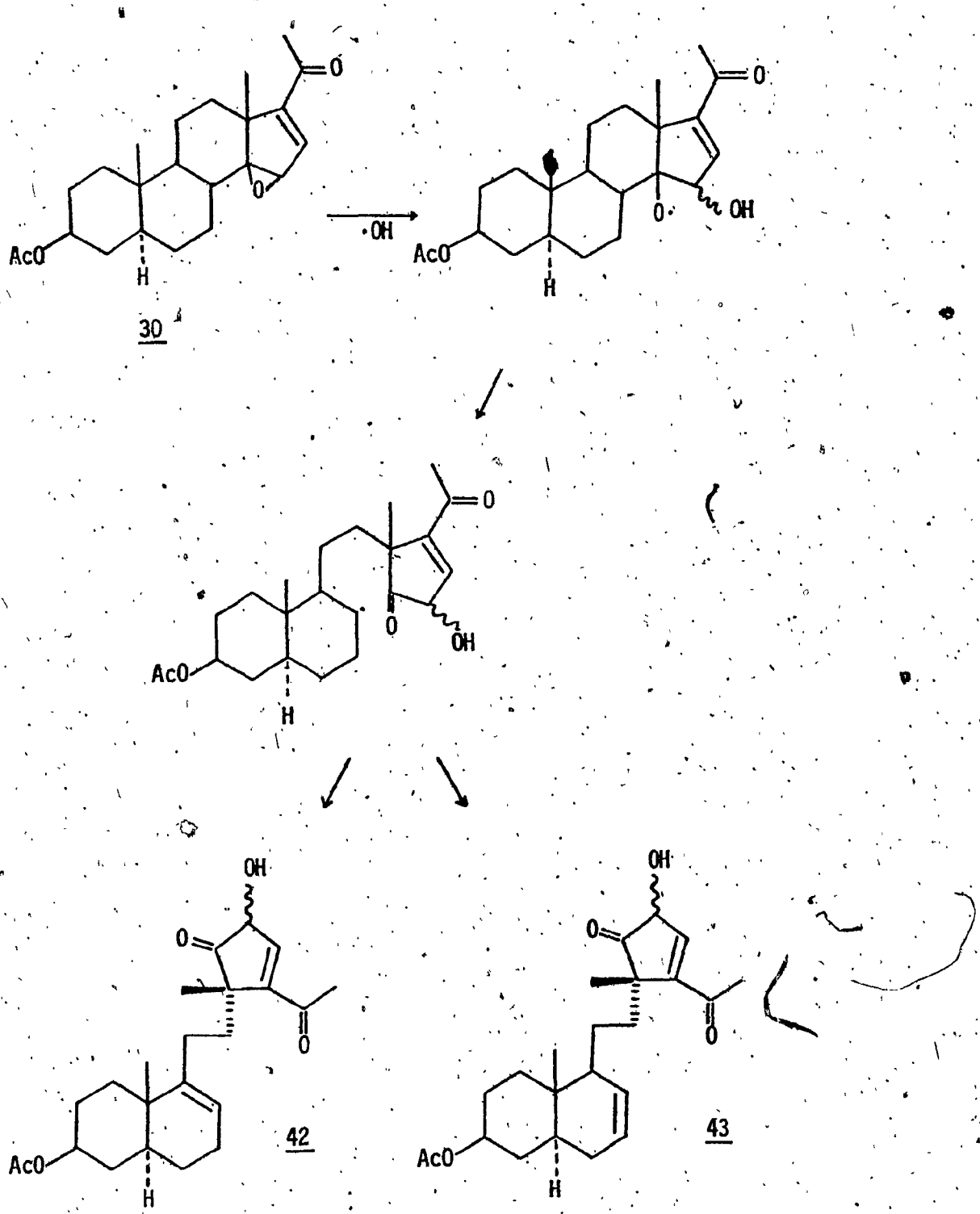
In brief four compounds appear to be present in the crude reaction mixture, one of which is the starting material (31). Compound 34 is eliminated as neither its 18-methyl or its vinylic protons appear at the reported chemical shift values (see also table 1). The cleavage processes shown in scheme 16 are thus reduced to paths (b) and (c) leaving

as possibilities compounds 37, 38, and 39. Compound 40 can also be considered as a possibility, although its formation entails the formation of the intermediate five-membered transition state, an energetically unfavourable process previously discussed.

An examination of the mass spectrum of the crude reaction product reveals p.m. i.'s at 370, 372, 374, and 388. The peak at 372 may be attributed to the presence of either 37, 38, 39, or 30, while that at 374 is probably due to the starting material (31). The p.m.i's at 388 and 370 can be explained in terms of the attack of a hydroxyl radical on the epoxide (30). The latter was estimated to be present in the starting material in amounts ranging from 10 to 20%. The hydroxyl radical is believed to have been provided by traces of water present in the solvent.

Scheme 17 proposes a path for this latter reaction for which a free radical mechanism is proposed. The end products, compounds 42 or 43, may account for the p.m.i. at 388 and the ion at m/e 370 ($388-H_2O$). An infrared spectrum revealed a broad band at 3500 cm^{-1}, indicative of compounds having a hydroxyl group in their structure, such as 31, 42 and/or 43. Finally, an ultraviolet spectrum over the region of 200 to 350 nm revealed only one maximum at 235 nm (ξ = 2169) thus eliminating 37 as a possibility.

In conclusion, the halohydrin reaction of the 14β-hydroxysteroid (31) appears to yield compounds which on the basis of the available data can reasonably be assigned to 31, 38, 39, 42 and/or 43.



Scheme 17

TABLE 1

Compound	UV	IR	m/e	N M R
31	240 (10,100)	3570,1720 1665,1600 1250	374	CH_3(19),s,0.82; CH_3(18),s,1.26; CH_3(21),s,2.28, CH(16),m, 6.62
34	283.6(205)	3085,2870 1730,1718, 1633,1250, 1030, 928	374	CH_3(19),s,0.92; CH_3(18),s,1.45; CH_3(21),s,2.30; CH(15),d,5.16 ; CH(16),m,5.73

(Ref 98)

vinylic protons
δ 5.59 ppm

In order to rationalize the final reaction products, a number of factors must be considered: (a) the distance between the reaction centers involved, (b) the stability of the intermediate radicals formed and (c) the relative lability of the bonds broken.

A Dreiding model for the 14β-hydroxy-derivative (31) showed that the distance between the oxygen atom and the 18-carbon atom is minimally 2.5 Å, therefore fulfilling one of the essential conditions for the successful hydrogen abstraction step. This last observation underlines the importance of the six-membered transition state for the hydrogen abstraction. One must also consider the stability of the intermediate radicals involved as shown in scheme 16. In general terms, the stabilities of radicals increase in the order primary < secondary < tertiary[100]. This order does not allow a rationalization of the preferred reaction rate of the alkoxy radical (36) when one considers the final products proposed 38, 39, 42, and/or 43 versus compounds 34 and 37. The first four compounds are derived from a secondary carbon radical, while 34 is derived from a primary allylic radical having a canonical tertiary radical structure (scheme 18). Compound 37 is also derived from a tertiary carbon radical.

Scheme 18

Finally, the bond dissociation energy for the C-H bond (in methane, it is 99.5 kcal/mole) is higher than for the C-C bond (in ethane, it measured as 79.1 kcal/mole)[101].

Consideration must therefore be given to the relative stability of the products rather than the intermediates (thermodynamic control) in order to rationalize the proposed reaction path. In compounds 38 and 39 as in compounds 42 and 43, the double bond in the five-membered ring is conjugated with the exocyclic carbonyl group while in 34 (derived from the allylic radical) the double bond is isolated. Finally, we would propose ^{13}C nmr as a means of detecting the reacting centers and following modifications of the B, C, and D rings of the steroid.

EXPERIMENTAL

General

1. Melting points were determined with a Gallenkamp MF-370 melting point apparatus and were uncorrected.

2. Infrared spectra were obtained employing a Perkin-Elmer 457 spectrometer.

3. A Bausch and Lomb UY-505 spectrometer was used to record ultraviolet spectra (ethanol was used as solvent in all cases).

4. NMR spectra were obtained using CCl_4 as solvent unless stated otherwise with a Varian A-60A instrument using tetramethylsilane as internal standard.

5. Mass spectra were run employing an Hitachi, type RMU-7, double focussing mass spectrometer operating at 70 e.v. Generally samples were volatilized in the indicated temperature range, 150-300°.

6. Most reactions were performed initially on small quantities in the mg range and monitored by TLC and NMR. Subsequently the reactions were scaled up to the gram scale.

7. TLC plates for monitoring reactions were prepared in 250 μm thicknesses with silica gel 7GF, Baker TLC reagent. The spots were developed with 50% H_2SO_4 in methanol. For purposes of preparative TLC, plates coated with a thickness of 1 mm were used.

8. For column chromatography, alumina (Brockman activity 1, 80-200 mesh, Fisher Scientific Co.) or silica gel, 60-200 mesh, were used.

3β-ACETOXY-5α-PREGNAN-20-ONE (27)

Pregnenolone acetate (26, 26.5g, 0.075 mole) was dissolved in ethyl acetate (530 ml) and 5.33g palladium on charcoal (5%) was added. Hydrogenation was carried out at room temperature and atmospheric pressure until no further hydrogen was absorbed (1.1 equivalent). Filtration of the catalyst and evaporation of the solvent in vacuo yielded 29g of crude material. Recrystallization from methanol afforded 24g, 90% yield of 27, mp 136-138° (lit[95] 142-143°).

NMR[99] :0.58(s), CH_3-18; 0.83(s), CH_3-19; 1.90(s), 3-$COCH_3$; 1.99(s), CH_3-21 ; 4.56(m), CH(3).

3β-ACETOXY-5α-PREGN-16-EN-20-ONE (28)

N-Bromosuccinimide (560mg, 3.14 mmole) was added to a solution of 3β-acetoxy-5α-pregnan-20-one (27, 1.0g, 2.80 mmole) in 10 ml carbon tetrachloride. The reaction mixture was refluxed with simultaneous irradiation with a 800W Tungsten lamp for 30 minutes. The cooled solution was then filtered, the solvent evaporated in vacuo, and the residue taken up in dimethylformamide (30 ml). Anhydrous lithium chloride (1.10g) was added, and the mixture refluxed for one hour in a nitrogen atmosphere. After cooling, the reaction solution was poured into ice-water and the resulting precipitate extracted with ether. The ethereal solution was washed with diluted hydrochloric acid, sodium bicarbonate solution, and water. The organic layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent and recrystallization of the solid residue from ether-hexane gave 0.80g of 28 (80% yield) mp 152-4°.

For the preparation of a purer sample, the following procedure was adopted: the product melting at 152-4° was dissolved in carbon tetrachloride, filtered, and the solvent evaporated in vacuo. Subsequent recrystallization of the solid residue from methanol yielded plates melting at 160-162° (lit[96] 164-6° ; lit[76] 167-168°) NMR[76] : 0.85 (s), CH_3-18, CH_3-19; 1.91(s) 3-$COCH_3$; 2.15(s), CH_3-21 ; 4.50 (m), CH(3) ; 6.51 (t), CH(16) with J = 2.5Hz.

3β-ACETOXY-5α-PREGN-14,16-DIEN -20-ONE (29)

Method A

A mixture of 3β-acetoxy-5α-pregn-16-en- 20-one (28, 2.93g, 8.18 mmole) and N-bromosuccinimide (1.68g, 9.40 mmole) in carbon tetrachloride (50 ml) was vigourously stirred and irradiated with a 700 W Tungsten lamp. The reaction temperature rose slowly from ambient to 78 - 79° after 40 minutes. Upon attaining this temperature, the mixture was irradiated further for 10 minutes. The cooled solution was filtered and the solvent evaporated in vacuo. The oily residue was dissolved in dimethylformamide (260 ml) and anhydrous lithium chloride (3g) was added. The reaction mixture was heated for 6.5 hours at 130-135° in a nitrogen atmosphere. The cooled reaction mixture was poured into ice-water (1. l) and the resulting precipitate was extracted with ether, which upon evaporation yielded an oil. Column chromatography of the oil employing alumina (110 g) was prepared with the solvent mixture petroleum ether, bp 66-75 : benzene (6 : 4). Elutions with the solvent ratios (6:4) and (5:5) yielded 1.15g of 28, and 0.507g of the product 29 (17% yield), the latter with the solvent ratios (4:6) and (3:7) respectively.

Method B

A suspension of N-bromosuccinimide (1.456 g, 8.2 mmole) and the enone (28, 2.80 g, 8.1 mmole) in carbon tetrachloride (100 ml) was brominated for 30 minutes as described above in method A. An additional 0.5 equivalent N-bromosuccinimide (0.70 g, 4.1 mmole) was added, and the irradiation and heating were maintained for a further 20 minutes. Following filtration and solvent evaporation, the oily residue was dissolved in t-butyl alcohol (100 ml). A 3% aqueous solution of sodium bicarbonate (100 ml) was added, and the solution stirred at room temperature for 3 days. After acidifying with 0.05 M sulfuric acid, the reaction mixture was extracted with ether. The ethereal solution was washed with water and then dried over anhydrous magnesium sulfate. The crude product was chromatographed as described in (A) yielding 446 mg of 29 (16% yield based on the enone 28). Trituration with ether furnished the pure product 29, mp 176-178° (lit[76] 181-182.5°, lit[77] 174-5°) NMR[76] : 0.966 (s), CH_3-19 ; 1.11 (s), CH_3-18; 1.93(s), 3-$COCH_3$; 2.21 (s), CH_3-21 ; 4.58 (m), CH(3) ; 5.90 (d), CH(15) with J = 2 Hz ; 7.08 (d), CH(16) with J = 2 Hz.

Method C

When the experiment was run as described in (A) for 30 minutes and a second equivalent N-bromosuccinimide was added, no significant change in the yield of 29 was obtained (13.5%).

Method D

Two duplicate experiments were run with the enone (28, 2.5g,

6.95 mmole) and two equivalents N-bromosuccinimide (1.30g, 7.30 mmole) in carbon tetrachloride (50 ml). The second equivalent of N-bromosuccinimide was added to the reaction mixture after half an hour of reflux and irradiation with a 700W Tungsten lamp. The duplication was necessary as attempts to scale up the reaction resulted in lower yields of 29. The products of the two photolysis reactions were combined and dehydrobrominated by refluxing one hour in DMF-LiCl as described in (A). The reaction mixture was poured into ice water (1. l) and the resulting precipitate extracted with a boiling mixture of ether : hexane (1 : 1). The extract was concentrated and hexane slowly added yielding a precipitate which contained trace amounts of the product 29. This precipitate was discarded. The solution of the remaining solution assumed a light yellow orange color. It was concentrated to 75 ml, filtered, and permitted to stand at room temperature overnight. Crystals were obtained, weighing 1 g, mp 159-163°. Integration of the vinylic and allylic protons over the region of 5.90-7.80 ppm gave an approximate ratio of 3:1 for the dienone: enone constituents. A second crop weighing 0.78g, mp 149-153°, was obtained by concentration of the mother liquor, and a ratio of 65:35 of the dienone: enone pair was obtained for this mixture. A third crop, weighing 0.10 g, mp 143-148° was not analyzed by NMR.

These mixed fractions of dienone:enone were used without further purification for the subsequent epoxidation reaction.

Method E

Two duplicate experiments were run with the enone (28, 1.0g,

2.8 mmole) and N-bromosuccinimide (1.5 equivalent, 0.75 g, 4.2 mmole) in carbon tetrachloride (50 ml). In each case, the reaction mixture was refluxed and irradiated with a 500W - Tungsten lamp. When the vapors of the refluxing carbon tetrachloride assumed a red color, the light source was turned off, and the reflux maintained until these solvent vapors became colorless. The products of the two photolysis reactions were combined and dehydrobrominated by refluxing for one hour in DMF-LiCl as described in (A). The reaction mixture was poured into ice-water (1. 1) and the resulting precipitate was extracted with petroleum ether, bp 66-75°. The extract was evaporated to dryness, and the solid residue recrystallized from ether to give 0.80 g (40% yield) of the product 29, mp 164-165°. Two recrystallizations from ether raised the mp to 169-171°.

3β-ACETOXY-14, 15β-EPOXY-5α-PREGN-16-EN - 20-ONE (30)

Method F

4-nitroperbenzoic acid (142 mg, 0.77 mmole) was added to a solution of 3β-acetoxy-5α-pregn-14,16-dien - 20-one (29), mp 167-9° (240 mg, 0.67 mmole) in chloroform (10 ml). The solution was stored in the dark at room temperature for 19 hours. After cooling, the solution yielded 0.10 g 4-nitrobenzoic acid. Filtration and subsequent evaporation afforded a residue which was triturated with 2-3 ml ether yielding 0.17 g of 30 (68% yield), mp 183-185°. Two recrystallizations from acetone raised the mp to 189-191° (lit[86] mp 194.5 - 195.5°) NMR : 0.88 (s), CH_3-19 ; 1.25 (s), CH_3-18 ; 1.93 (s), 3-$COCH_3$; 2.17 (s), CH_3-21 ; 3.62 (bs), CH(15) ; 4.58 (m), CH(3) ; 6.76 (bs), CH (16).

Method G

When the reaction was run as described in (F) but using the mixed fractions dienone : enone (3 : 1) mp 159-163° (0.453 g), 0.243 g (68% yield) of the epoxide 30 was obtained, mp 183-185°.

Traces of 4-nitroperbenzoic and 4-nitrobenzoic acid were removed from the successfully isolated epoxide fractions as follows : the products were dissolved in ethyl acetate (100 ml) and the organic layer was washed with 10 ml portions of potassium iodide solution (5%), sodium thiosulfate solution (2.5%), sodium bicarbonate solution (3%) and finally with water until the last wash was neutral to litmus paper. The organic layer was dried over anhydrous magnesium sulfate, and the solvent evaporated in vacuo. Close to quantitative yields of 30 were usually obtained by this method.

3β-ACETOXY-14β-HYDROXY-5α-PREGN-16-EN-20-ONE (31)

Palladium on barium sulfate 5% (0.465 g) was added to a solution of 3β-acetoxy-14,15β-epoxy-5α-pregn-16-en-20-one (30, mp 183-5°, 0.465 g, 1.24 mmole) in 50 ml methanol containing 2% by volume cyclohexene. After a reflux period of 30 minutes, the solution was filtered, and the filtrate evaporated to dryness. Trituration with cyclohexane yielded 0.450 g of a mixture of the 14β-hydroxy-derivative 31 and unreacted starting material 30, mp 158-160°.

Recrystallization of 0.350 g of the crude precipitate from 10 ml carbon tetrachloride yielded 0.089 g, mp 167-170°. A second recrystallization from acetone-hexane yielded 0.039 g, mp 185-187° (lit.[93] 191°).

NMR ($CDCl_3$)[93]:0.84 (s), CH_3-19 ; 1.28 (s), CH_3-18 ; 2.01 (s), 3-$COCH_3$; 2.28 (s), CH_3-21; 2.30 + 2.68, CH (15) ; 4.70 (m) + 4.62 (m), CH(3) ; 6.62 (m), CH(16).

HYPOIODITE REACTION OF 3β-ACETOXY-14β-HYDROXY-5α-PREGN-16-EN-20-ONE.

Method H

A stirred suspension of calcium carbonate (0.06 g, 0.6 mmole) and lead tetraacetate 10.180 g, 0.4 mmole) in cyclohexane (40 ml) was refluxed for one hour. Solid iodine (0.032 g, 0.13 mmole) and the 14 - hydroxy-steroid (31, 0.69 g, 0.16 mmole) were then added, and the mixture refluxed and irradiated with a 500W Tungsten lamp for 7.5 minutes. The reaction mixture was filtered to remove the lead diacetate and the clear red filtrate was washed with dilute sodium bicarbonate solution, and finally with water. The organic phase was dried over anhydrous magnesium sulfate, filtered, and freed of solvent. The residue was chromatographed over silica gel (60-200 mesh) employing as eluant benzene : petroleum ether, bp 66-75° (1:1) to give two fractions weighing less than 0.005 g each :

(i) the first was obtained with the solvent system, benzene : petroleum ether, bp 66-75° (7:3) and showed p.m.i.'s at m/e 372 and 374. TLC confirmed the presence of a mixture

(ii) the second fraction was obtained with solvent system benzene : ethyl acetate (99:1) showed p.m.i.'s at 370 and 380.

Method I

The same reaction as described in (H) was run for 45 minutes with

benzene as the solvent. The reaction product was extracted with 150 ml petroleum ether, bp 66-75°. Concentration of the extract to 15-20 ml afforded after overnight standing, a single large yellowish crystal. TLC revealed several spots of similar intensity and of Rfs as had been observed in (H). Mass spectral analysis revealed peaks at 370, 372, 374, and 388. UV_{235} (2169), IR 3500 (broad), 2940, 2860, 1730 with shoulders at 1740, 1705 and 1610 cm^{-1}. NMR ($CDCl_3$) : 0.82 (s), 0.78 (s), 0.88 (s), 1.00 (s); 1.24 (s), 1.26 (s), 1.34 (s), 1.59 (s) ; 2.00 (s) ; 2.06 (s), 2.11 (s), 2.25 (s), 2.29 (s) ; 4.80 (m) ; 5.10 (m) ; 5.51 (m) ; 6.62 (m).

BIBLIOGRAPHY

1. J. W. Daly, B. Witkop, P. Bommer, and K. Bienman, J. Am. Chem. Soc., 87, 124 (1965).

2. a) T. Tokuyama, J.W.Daly, B. Witkop, I.L. Karle, and J. Karle, J. Am. Chem. Soc., 90, 1917 (1968); b) ibid., 91, 3931 (1969).

3. E. X. Albuquerque, J.W.Daly, and B. Witkop, Science, 172, 995 (1971).

4. a) R. Imhof, R.E. Gossinger, W. Graf, H. Berner-Frenz, H. Wehrli, Helv. Chim. Acta, 55 (4), 1151 (1972); b) R. Imhof, E. Gossinger, W. Graf, L. Berner-Frenz, H. Berner, R. Schaufellerger, H. Wehrli, ibid., 56 (1), 139 (1973); c) R. Imhof, F. Marti, B.P. Schaffner, H. Wehrli, ibid., 56 (3), 1078 (1973).

5. R. Imhof, I. Marti, B.P. Schaffner, and H. Wehrli, ibid., 56 (6), 1920 (1973).

6. a) A.W. Hofmann, Ber., 16, 558 (1883); b) K. Loffler, and C. Freytag, ibid., 42, 3427 (1909); R. Lukes and M. Fules, Coll. Czech. Chem. Comm., 20, 1227 (1955).

7. a) D. H. R. Barton, J.M. Beaton, L.E. Geller, M. M. Pechet, J. Am. Chem. Soc., 82, 2640 (1960); b) ibid., 83, 4076 (1961).

8. a) K. Heusler and J. Kalvoda, Synthesis, 501 (1971); b) K. Heusler and J. Kalvoda, Angew. Chemie, Int. Ed., 3, 525 (1964).

9. a) E. J. Corey, and W. A. Hertler, J. Am. Chem. Soc., 81, 5209 (1959); b) ibid., 80, 2903 (1958) ; c) J. Buchshacher, J. Kalvoda, D. Arigoni, O. Jeger, ibid., 80, 2905 (1958).

10. a) S. Wawzonek, and J.P. Thelen, ibid. 72, 2118 (1950); b) S. Wawzonek, M. F. Nelson, Jr., and J. P. Thelen, ibid., 73, 2806 (1951).

11. G. H. Coleman, Proc. Iowa Acad. Sci., 46, 217 (1939).

12. E. J. Corey, and W. R. Hertler, J. Am. Chem. Soc., 82, 1657 (1960).

13. H. C. McBay, and O. Tucker, J. Org. Chem., 19, 869 (1954).

14. M. E. Wolff, Chem. Revs, 63, 55 (1963).

15. S. Wawzonek, and T. P. Culberston, J. Am. Chem. Soc., 81, 3367 (1959).

16. P. Gray, and A. Williams, Chem. Revs., 59, 239 (1959).

17. P. Kabasakalian, E. R. Townley, and M. D. Yudis, J. Am. Chem. Soc., 84, 2718 (1962).

18. R. O. Kan "Organic Photochemistry" Mc-Graw Hill Book Co., 1966, pp 233-260.

19. A. L. Nussbaum, R. A. Wayne, E. Yuan, O. Zagneetko, and E. P. Oliveto, J. Am. Chem. Soc., 84, 1070 (1962).

20. a) D. H. R. Barton, and J. M. Beaton, ibid., 83, 4083 (1961); b) ibid., 84, 199 (1962); c) M. Akhtar, D. H. R. Barton, J. M. Beaton, and H. G. Hortman, ibid., 85, 1512 (1963); d) D. H. R. Barton, E. P. Oliveto, T. Strauss, A.S. Capomaggi, and H. Reimann, ibid., 83, 4481 (1961).

21. M. Akhtar "Advances in Photochemistry" Vol.2, edited by W. A. Noyes, G. S. Hammond, and J. N. Pitts, Jr., Interscience Publishers, 1964, pp 263-300.

22. P. Kabasakalian, and E. R. Townley, J. Am. Chem. Soc., 84, 2711 (1962).

23. M. Akhtar, and M. M. Pechet, ibid., 86, 265 (1964).

24. A. L. Nussbaum, and C. H. Robinson, Tetrahedron, 17, 35 (1962), and references there cited.

25. C. H. Robinson, O. Gnoj, A. Mitchell, E. P. Oliveto, and D. H. R. Barton, ibid., 21 (4), 743 (1965).

26. P. Kabasakalian, E. R. Townley, and M.D. Yudis, J. Am. Chem. Soc., 84, 2716 (1962).

27. C. Walling, and J. Padwa, ibid., 85, 1957 (1963).

28. a) N. N. Semonov, Angew. Chem., 69, 775 (1957); b) C. N. Hinshelwood, ibid., 69, 446 (1957).

29. D. H. R. Barton, G. C. Ramsay, and D. Wege, J. Chem. Soc.,(c), 1915 (1967).

30. Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, Experentia, 17, 475 (1961) and subsequent publications.

31. M. Akhtar, and D. H. R. Barton, J. Am. Chem. Soc., 86, 1528 (1964).

32. a) Reference 30; b) Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, A. Wettstein, Helv. Chim. Acta, 45, 1317 (1962).

33. a) D. H. R. Barton, and E. P. Serebryakov, Proc. Chem. Soc., 309 (1962); b) D. H. R. Barton, H. P. Faro, E. P. Serebryakov, and N. F. Woolsey, J. Chem. Soc., 2438 (1965).

34. M. Akhtar, and D. H. R. Barton, J. Am. Chem. Soc., 86, 1528 (1964).

35. See discussion by M. Swarc and J. H. Brinks in "Theoretical Organic Chemistry", Butterworths, London, 1961, p 143 and seq.

36. a) M. Akhtar, and S. March, Tetrahedron Letters, 2475 (1964); b) J. W. Apsimon, and O. E. Edwards, Canad. J. Chem., 40, 896 (1962); c) W. L. Meyer, and A.S. Levinson, Proc. Chem. Soc., 15 (1963); d) R. F. C. Brown, Austral. J. Chem., 17, 47 (1964).

37. P. F. Beal, and J. E. Pike, Chem. and Ind., 1050 (1960).

38. P. Kabasakalian, and E. R. Townley, J. Am. Chem. Soc., 84, 2724 (1962).

39. K. B. Wiberg, Chem. Revs., 55, 713 (1955).

40. a) D. H. R. Barton, and J. R. Hanson, Chem. Commun, 117 (1965); b) J. R. Hanson, Tetrahedron, 22, 1701 (1966).

41. a) E. W. R. Steacie "Atomic and Free Radical Reactions" Reinhold Publishing Corp., New York, 1954; b) P. Gray, Trans Faraday Soc., 52, 344 (1956).

42. P. G. Sammes, Synthesis, 636 (1970).

43. K. Heusler, and J. Kalvoda, Helv. Chim. Acta, 46, 2732 (1963).

44. M. Akhtar, D. H. R. Barton, and P. G. Sammes, J. Am. Chem. Soc., 87, 4601 (1965).

45. J. Kalvoda, K. Heusler, P. Wieland, G. Anner, and A. Wettstein, Gazz. Chim. Ital., 93, 140 (1963).

46. K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, Helv. Chim. Acta, 46, 352 (1963).

47. K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, ibid, 45, 2575 (1962).

48. Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, A. Wettstein, ibid., 45, 1317 (1962).

49. a) Reference 30; b) K. Heusler, J. Kalvoda, Ch. Meystre, G. Anner, and A. Wettstein, ibid., 45, 2161 (1962).

50. K. Heusler, and J. Kalvoda in "Organic Reactions in Steroid Chemistry" edited by J. Fried and J. A. Edwards, Van Nostrand Reinhold Co., 1972, pages 237-287.

51. a) L. Ruzicka, Pl. A. Plattner, H. Heuser, and J. Pataki, Helv. Chim. Acta, 29, 936 (1946); b) Pl. A. Plattner, L. Ruzicka, H. Heuser, J. Pataki, and Kd. Meier, ibid., 29, 942 (1946).

52. Ch. Engel, and G. Bach, Steroids, 593 (1964).

53. H. Wehrli, and O. Jeger, Ger. Offen, 2, 136, 635, 03 Feb. 1972, Swiss Appl. 11, 243/70, 24 July 1970, 79 pages.

54. E. Capsi, and D. J. Alberhart, US 3, 828, 029, 06 Aug. 1974; Appl. 262, 395, 13 June 1972, 7 pages.

55. J. C. Beloeil, and M. Fetizon, C. R. Hebd. Seances Acad. Sci., ser. C. 1974, 279-(9), 347 (1975).

56. L. F. Fieser, and M. F. Fieser in "Steroids", Reinhold Publishing Co., New York, 1959, pages 271-274.

57. a) J. Y. F. Paterson, and W. Klyne, Biochem. J., 42, ii (1948; b) S.G. Levine, and M.E. Wall, J. Am. Chem. Soc., 81, 2829 (1959); c) M. M. Janot, F. Laine, Q. Khuong-Huu, and R. Goutarel, Bull. Soc. Chim. France, 111 (1962).

58. Reference 50, pages 265 - 363.

59. E. W. Warnhoff, J. Org. Chem., 28, 887 (1963).

60. H. O. House "Modern Synthetic Reactions" W. A. Benjamin Inc., New York, 1965, pages 134-162.

61. R. Villotti, H. J. Ringold, and C. Djerassi, J. Am. Chem. Soc., 82, 5693 (1960).

62. E. J. Corey, and R. A. Sneen, ibid., 78, 6269 (1956).

63. E. W. Warnhoff, J. Org. Chem., 887 (1963).

64. a) E. J. Corey, J. Am. Chem. Soc., 75, 2301 (1953; b) E. J. Corey, ibid., 76, 175 (1954); c) E. J. Corey, Experentia, 9, 329 (1953).

65. a) Ref 62; b) H. E. Zimmerman in "Molecular Rearrangements" edited by P. de Mayo, Wiley-Interscience, New York, 1963, pages 345-372; c) H. Schechter, M. J. Collis, R. Dessy, Y. Okuzami, and A. Chen, J. Am. Chem. Soc., 84, 2905 (1962).

66. J. Valls, and E. Toromanoff, Bull. Soc. Chim. France, 758 (1961).

67. a) N. L. Wendler, R. P. Graber, and G. G. Hazen, Tetrahedron, 3, 144 (1958); b) S. Rakhit, R. Deghenghi, and Ch. R. Engel, Can. J. Chem., 41, 703 (1963) and references therein.

68. C. Djerassi, J. Am. Chem. Soc., 71, 1003 (1949).

69. a) E. W. Warnoff, J. Org. Chem., 27, 4587 (1962); b) H. R. Nace, and R. N. Iacona, ibid., 29, 3498 (1964).

70. R. Joly, J. Warnant, G. Nomine, and D. Bertin, Bull. Soc. Chim. France, 366 (1958).

71. N. L. Wendler, D. Taub, and H. Kuo, J. Am. Chem. Soc., 82, 5701 (1960).

72. M. P. Hartshorn, and E. R. H. Jones, J. Chem. Soc., 1312 (1962).

73. a) C. Walling "Free Radicals in Solution" Wiley, New York, 1957, pages 347-396; b) M. L. Poustma, J. Am. Chem. Soc., 85, 3511 (1963).

74. A. J. Solo, and B. Singh, J. Org. Chem., 30, 1658 (1965).

75. a) R. E. Pearson, and J. C. Martin, J. Am. Chem. Soc., 85, 354, 3142 (1963); b) B. P. McGrath, and J. M. Tedder, Proc., Chem. Soc., 80 (1961); c) D. S. Skell, D. L. Tuleen, and D. D. Readio, J. Am. Chem. Soc., 85, 2850 (1963); d) E. Hedaya, R. L. Hinman, and S.

Theodoropoulos, ibid, 85, 3052 (1963).

76. R. Tschesche, F. Riemhofer, and G. Snatzke, Chem. Ber., 98, 1188 (1965).

77. Pl. A. Plattner, Kd. Meier, and H. Heuser, Helv. Chim. Acta, 30, 905 (1947).

78. a) B. M. Lynch, and K. H. Pausacker, J. Chem. Soc., 1525 (1955); b) H. B. Henbest, Proc. Chem. Soc., 159 (1963).

79. J. March "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure" McGraw-Hill Book Co., New York, 1968, page 620; the Baeyer-Villiger Reaction, page 822.

80. N. N. Swartz, and J. H. Blumberg, J. Org. Chem., 29, 1976 (1964).

81. a) L. P. Witnauer, D. Swern, J. Am. Chem. Soc., 72, 3364 (1950); b) D. Swern, ibid., 70, 1235 (1948).

82. D. Swern, Org. Reactions, 7, 378 (1953).

83. Y. Ogata, and I. Tabushi, J. Am. Chem. Soc., 83, 3440 (1961).

84. H. M. Walton, J. Org. Chem., 22, 1161 (1957).

85. N. C. Yang, and R. A. Finneger, J. Am. Chem. Soc., 80, 5845 (1958).

86. Pl. A. Plattner, L. Ruzicka, H. Heuser, E. Angliker, Helv. Chim. Acta, 30, 385 (1974).

87. a) E. Gossinger, W. Graf, H. Wehrli, ibid., 54, 2785 (1971); b) F. L. Berner-Frenz, H. Berner, W. Graf, H. Wehrli, ibid., 53, 2258 (1970); c) Graf, H. Berner, L. Berner-Frenz, E. Gossinger, R. Imhof, and H. Wehrli, ibid., 53, 2267 (1970).

88. a) S. Winstein, and R. B.Henderson in "Heterocyclic Compounds" edited by R. C. Elderfield, Vol.1, Wiley, New York, 1950, pages 1-60; b) R. E. Parker, and N.S. Isaacs, Chem. Revs., 59, 737 (1959).

89. a) A. Feldstein, and C. A. Vanderweef, J. Am. Chem. Soc., 76, 1626 (1954); b) R. Fuchs, and C.A. Vanderweef, ibid., 76, 1631 (1954).

90. J. G. Buchanan, and H.Z. Sable in "Selective Organic Transformations"

edited by B. S. Thyagarajan, Vol.2, Wiley-Interscience, New York, pages 4-13.

91. Reference 60, pages 112-113.

92. a) A. S. Hallworth, and H. B. Henbest, J. Chem. Soc., 4604 (1957); b) H.C. Brown, S. Ikegami, and J. H. Hawakami, J. Org. Chem, 35, 3243 (1970).

93. F. Marti, H. Wehrli, and O. Jeger, Helv. Chim. Acta, 56 (3), 1078 (1973)

94. C. H. Robinson, O. Gnoj, A. Mitchell, E. P. Oliveto, D. H. R. Barton, Tetrahedron, 21 (4), 743 (1965).

95. S. Levine, and M. Wall, J. Am. Chem. Soc., 81, 2826 (1959).

96. M. E. Wall, H. E. Kenney, and E. S. Rothman, J. Am. Chem. Soc., 77, 5665 (1955).

97. Dong Je Kim, private communication, 1975.

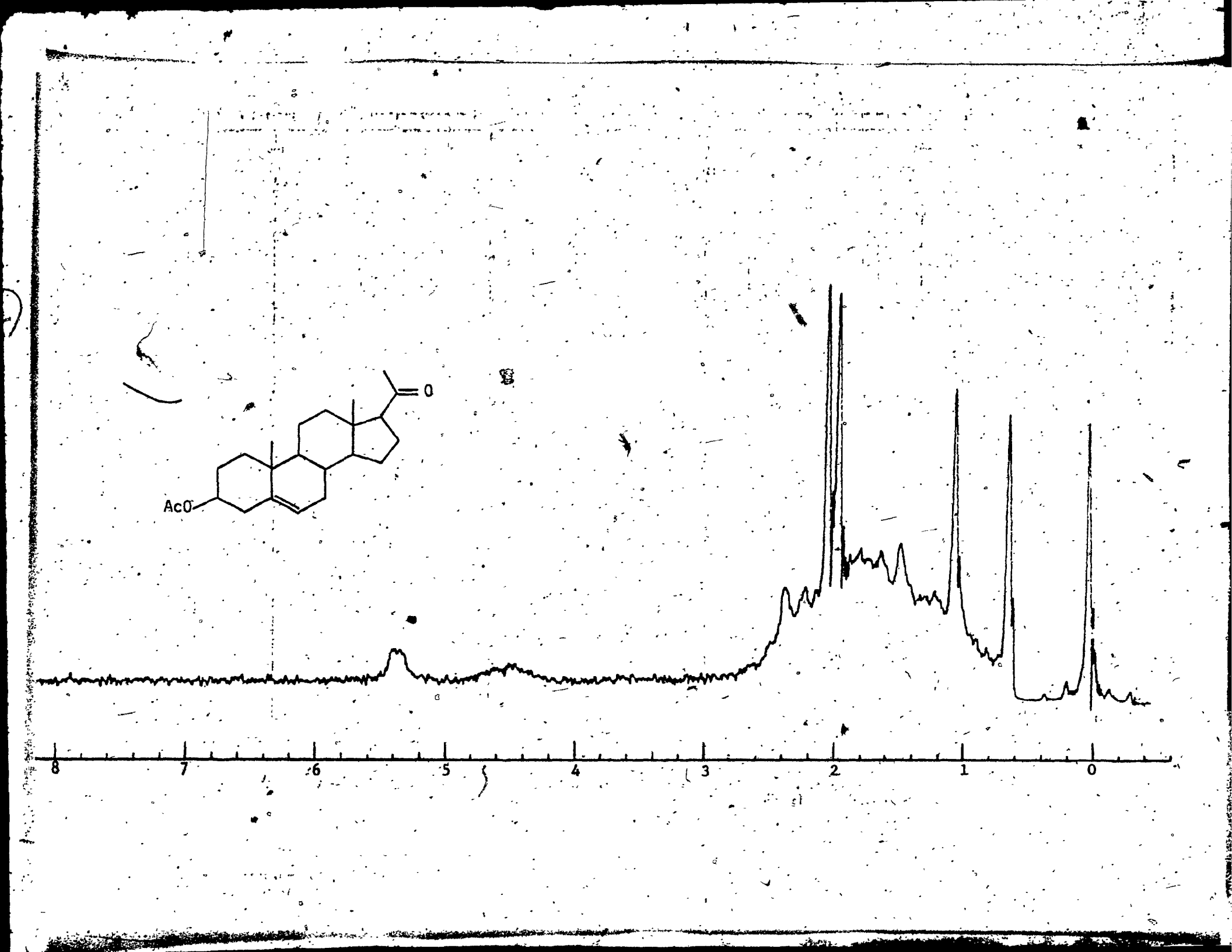
98. a) K. B. Wiberg, and B. J. Wist, J. Am. Chem. Soc., 83, 1226 (1961); b) T. A. L. Anet, and M. Z. Haq, ibid., 87, 3147 (1965).

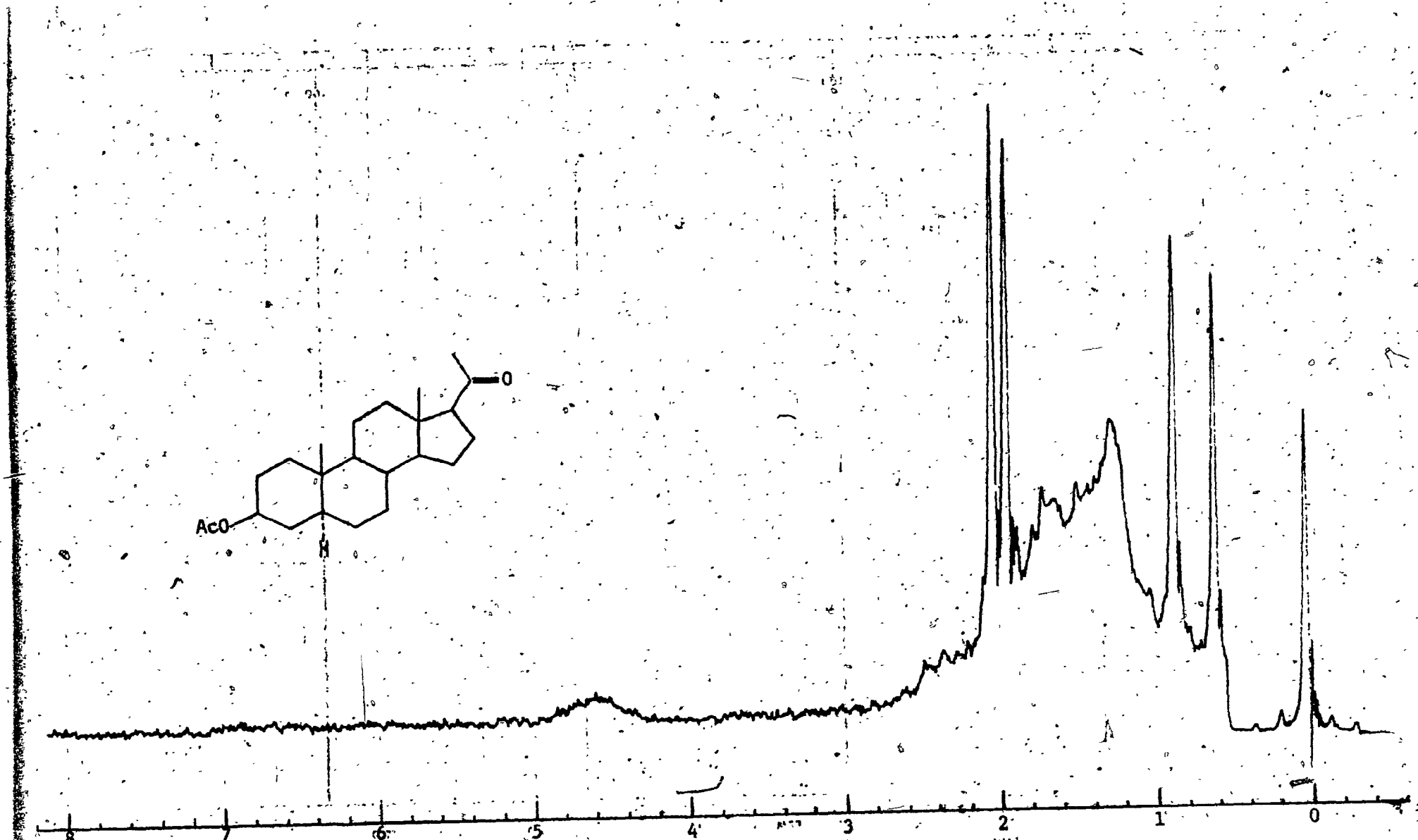
99. K. Jankowski, and C. Berse, Can. J. Chem., 46 (11), 1835 (1968).

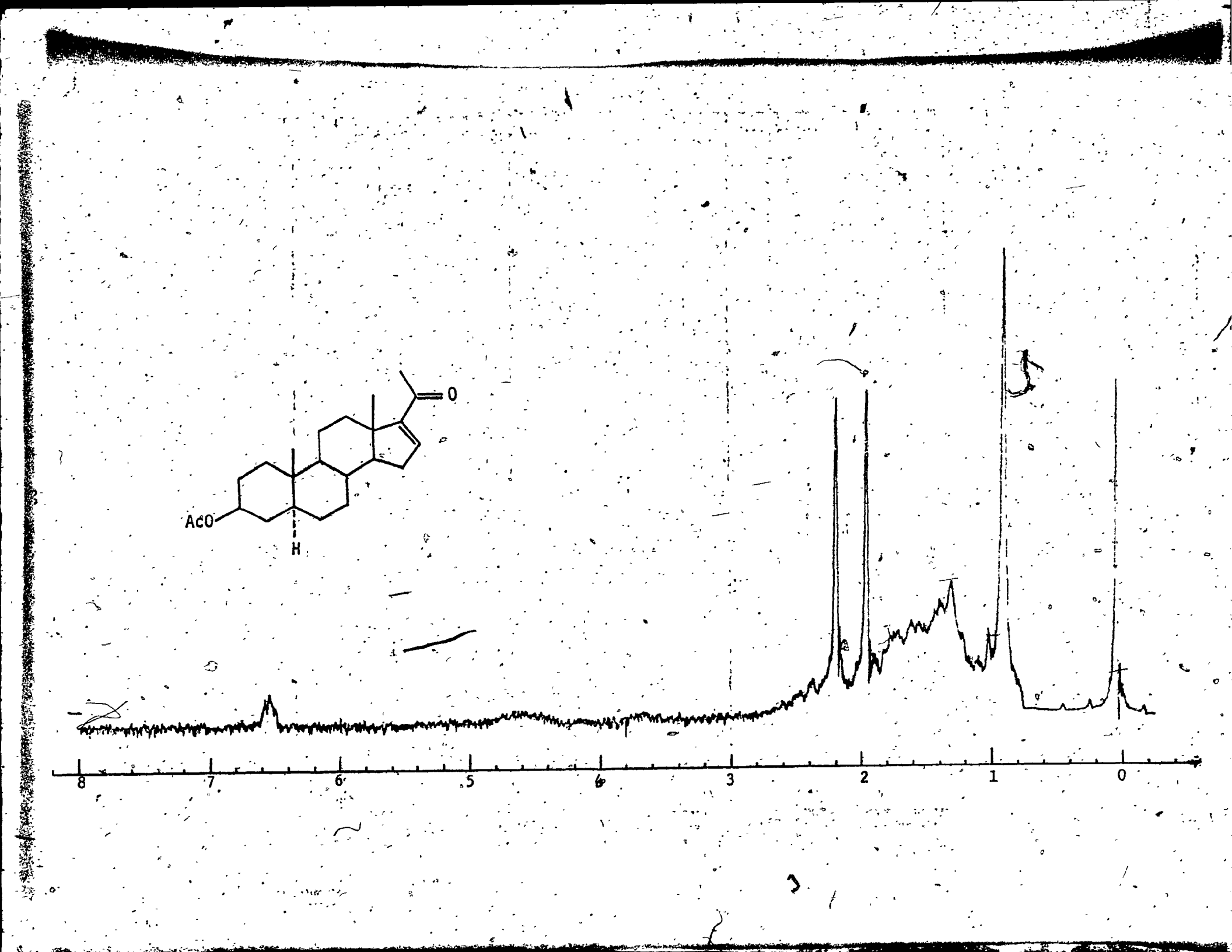
100. W. A. Pryor "Free Radicals" Mc-Graw Hill Book Co., New York, page 207, 1966.

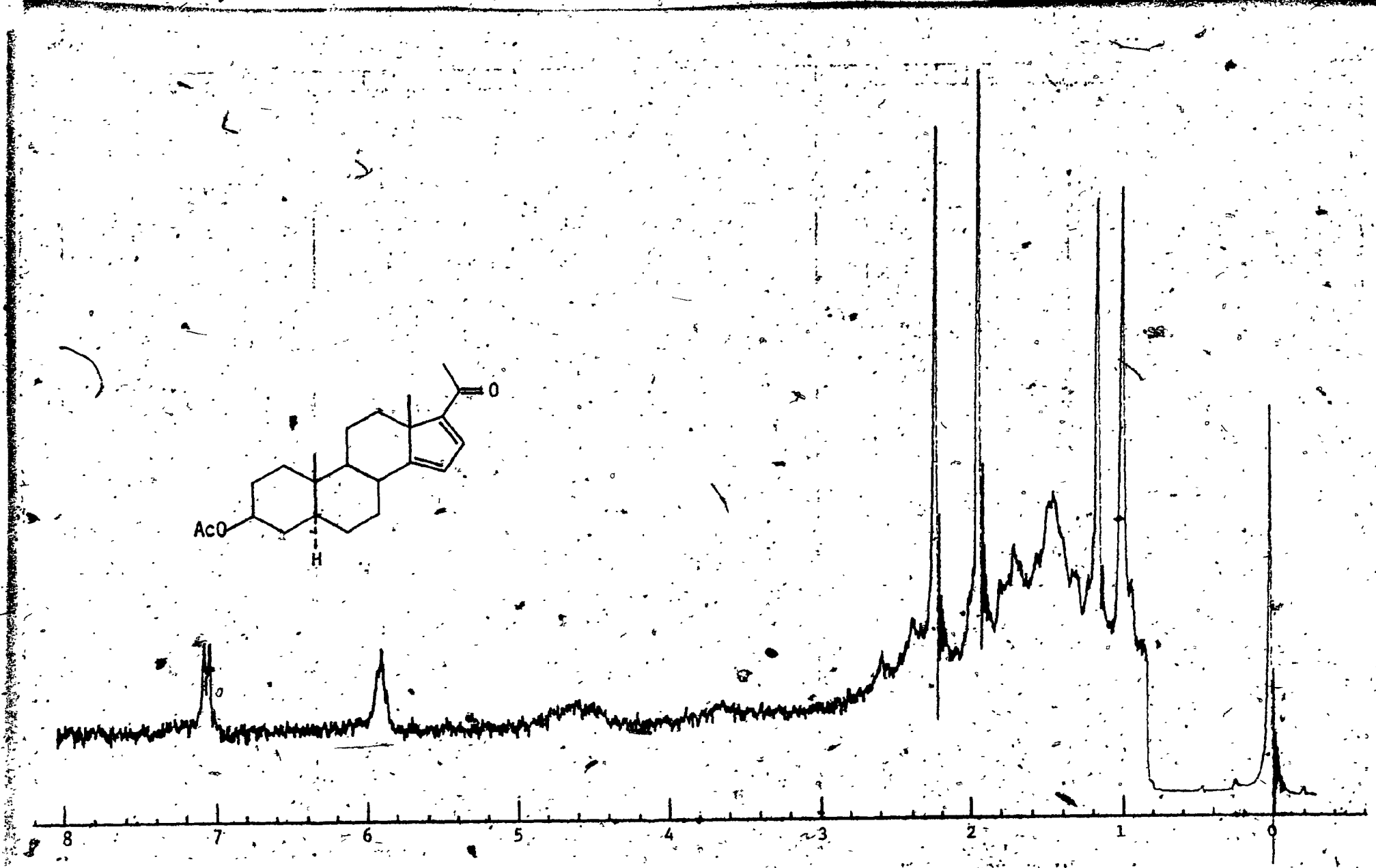
101. Reference 79, page 26.

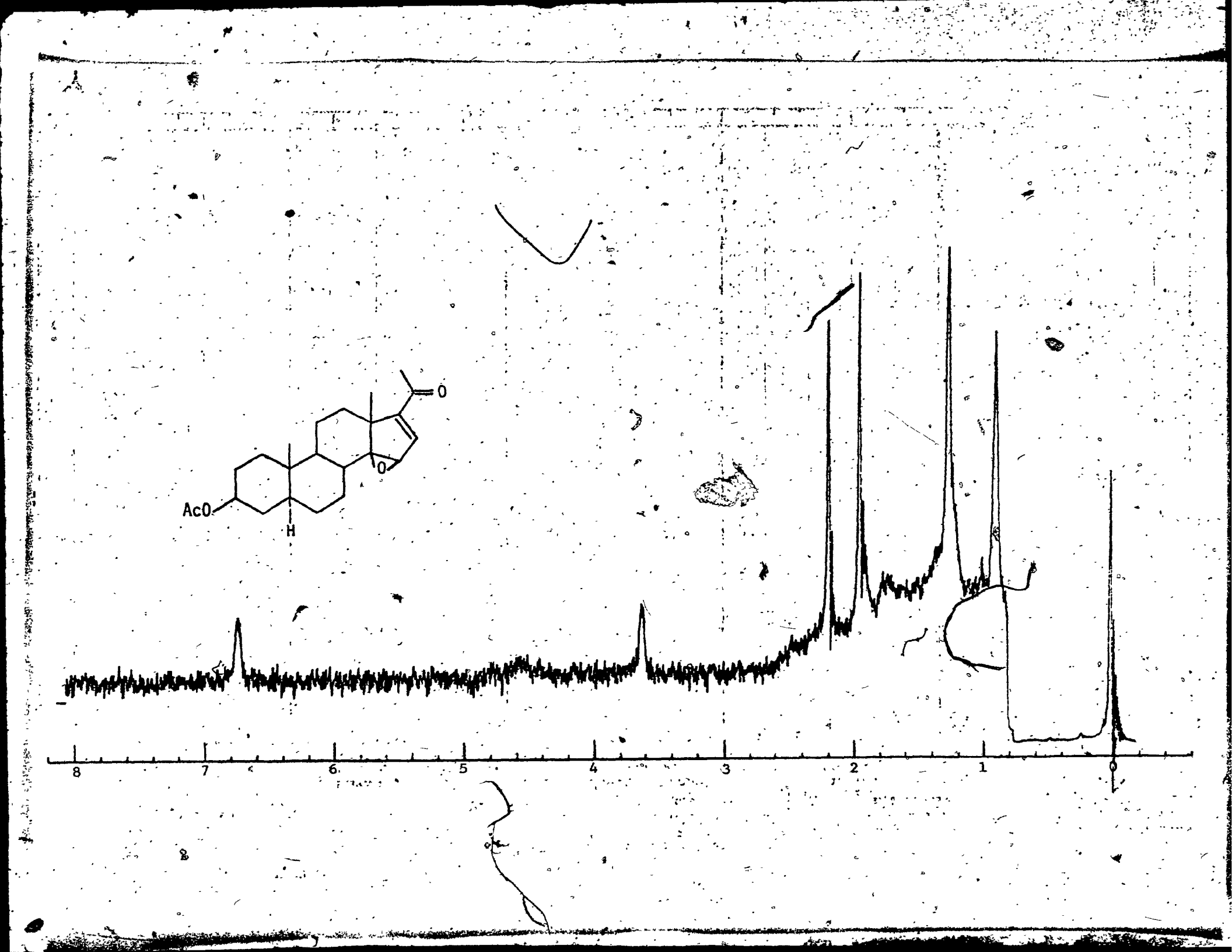
LIST OF NMR SPECTRA

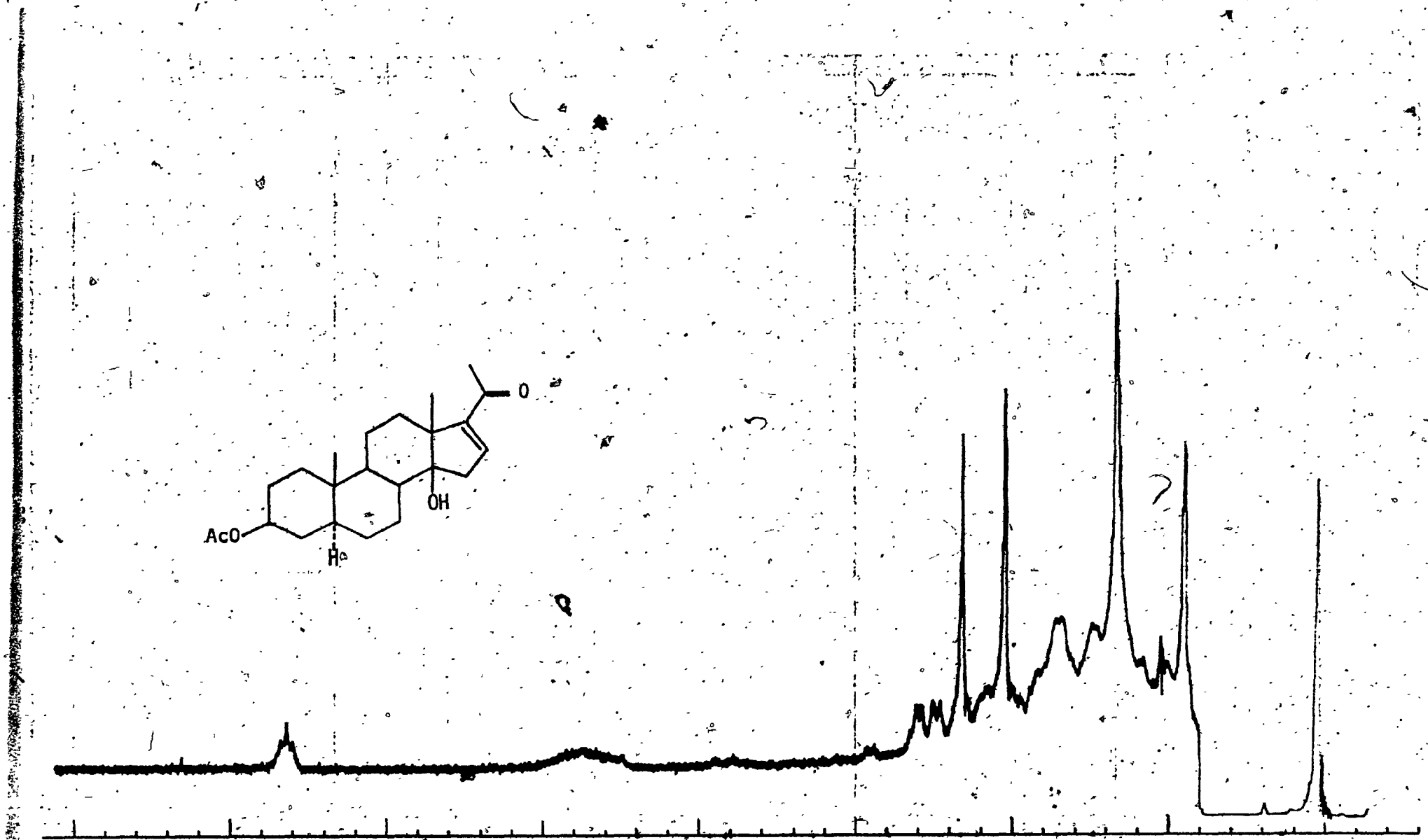

O
AcO
8
7
6
5
4
3
2
1
0


AcO
O
H
8
6
5
4
3
2
1
0


O
AcO
H
8
7
6
5
4
3
2
1
0


AcO
O
H
8
7
6
5
4
3
2
1
0


AcO
O
O
H
8
7
6
5
4
3
2
1
0


O
OH
AcO
Hα
8
7
6
5
4
3
2
1
0

8
7
6
5
4
3
2
1
0

ABBREVIATIONS

b = broad

bs = broad singlet

d = doublet

m = multiplet

s = singlet

t = triplet