Reaction of 1-Fluoro-2-methylnaphthalene with Sodium Amide and Piperidine.—The reaction was run as described[3] for the bromonaphthalenes, and the basic products were purified by fractional distillation at reduced pressure. A colorless liquid, b.p. 134° (2 mm.), $n^{18}D$ 1.6060, was obtained in 84.5% yield (reckoned as 1-piperidino-2-methylnaphthalene).

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50. Found[23]: C, 85.38; H, 8.82.

1-Piperidino-2-methylnaphthalene from 1-Bromo-2-methylnaphthalene.—As a check on the identity of the above product, 22.1 g. of 1-bromo-2-methylnaphthalene and 35 cc. of piperidine were heated in a sealed tube 82 hours at 200°. The basic products were isolated by standard procedures including distillation at reduced pressure. The liquid so obtained was treated with *p*-toluenesulfonyl chloride in pyridine to remove primary and/or secondary amines apparently derived solely from the piperidine,[3] and the remaining basic product was finally purified by distillation at reduced pressure. A clear oil (2.1 g., 9%), b.p. 137–141° (3–4 mm.), $n^{19}D$ 1.6051, was so obtained. Its infrared spectrum was identical to that of the product described immediately above.

The products of the two reactions are identical, and the substance is almost surely 1-piperidino-2-methylnaphthalene. If the piperidino group is anywhere but the 1-position, an unprecedented rearrangement has occurred in two separate instances.

Attempted Reaction of α-Naphthyl Methyl Sulfone with Piperidine.—This experiment was run to check on the unlikely possibility that the production of III from this sulfone and the sodium amide–piperidine reagent might have been due solely to the action of the piperidine in the reagent. The sulfone and piperidine were combined just as in the earlier experiment except that sodium amide was omitted. The mixture was refluxed two hours. No III was obtained, and 86% of the sulfone was recovered in a state of high purity.

CHAPEL HILL, N. C.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Stereoelectronic Control in Enolization–Ketonization Reactions[1]

BY E. J. COREY AND R. A. SNEEN

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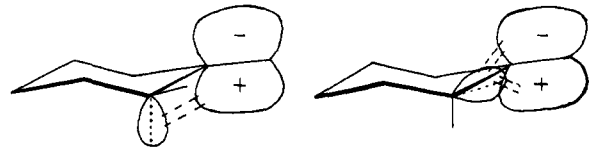
The stereochemistry of the enolization of 3β-acetoxycholestan-7-one to the Δ⁶-en-7-ol and of the ketonization of this enol have been studied using deuterium tracer. With hydrogen bromide as catalyst in chloroform solution the axial hydrogen at C_6 is lost in enolization 1.2 times as rapidly as the equatorial hydrogen (corrected for isotope effect); for the reverse reaction, ketonization, an axial hydrogen is gained *ca.* 1.5 times as rapidly as an equatorial hydrogen. These values, which in theory should be identical, are in reasonably good agreement and indicate that despite a strong steric retardation of the gain and loss of an axial hydrogen, axial attack is still at least as favorable as equatorial attack. Correction for this steric effect gives the result that stereoelectronic factors favor axial attack over equatorial attack by a factor of at least 12. The acetic acid catalyzed enolization–ketonization reaction is even more specific and axial attack is favored over equatorial attack by a total factor of at least 9 with a stereoelectronic component of at least 50. The kinetic isotope effect of deuterium in enolization of 7-ketosteroids has been found to be *ca.* 7.4, close to the theoretical maximum at 10°. A thermodynamic explanation is presented to explain the variation in degree of stereoelectronic control with reactivity of the reagent and supporting data are cited from a comparison of chlorination and bromination experiments. The occurrence of a high degree of stereoelectronic control is postulated to explain the exclusive axial attack observed in reactions of steroidal 4,5,6-allyl cations.

It has been shown previously[2] that the bromination of steroid ketones *via* the corresponding enols is characterized in several cases, and perhaps generally, by an effect which directs the incoming bromine substituent to the axial rather than the equatorial position. Opposing this effect is the classical steric effect, which directs a large substituent such as bromine to the less crowded equatorial orientation. The net result of these two effects, which influence the relative rates of formation of the epimers with axial and equatorial bromine, is clear in those cases where the bromoketone which is isolated is the unstable epimer, formed for kinetic rather than for steady-state reasons. In such instances the importance of the non-steric effect is apparent since the major product has invariably been found to be the epimer with axial bromine.[2]

It has been proposed that the orienting influence which is responsible for this stereochemical preference is stereochemical–electronic in nature and depends on the difference in degree of delocalization of electrons in perturbed axial and equatorial bonds which are alpha to an exocyclic π-orbital. Reference to Fig. 1 indicates the relationship between stereochemical orientation and the extent of delocalization of exocyclic σ-electrons to an adjacent exocyclic π-orbital. Since the transition state for enolization–ketonization type processes



axial interaction (bonding) equatorial interaction (non-bonding)

Fig. 1.

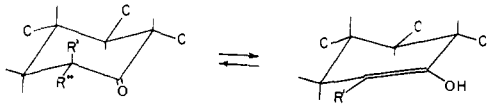
is stabilized by bonding between the alpha and carbonyl carbon atoms involving σ–π delocalization as shown in Fig. 1, there should be a preference for loss or gain of an axial α-substituent over an equatorial α-substituent. Or, in slightly different terms, there is better bonding in the transition state for enolization–ketonization when the entering or leaving α-substituent possesses the axial orientation than the alternative equatorial orientation. Because the structure of the transition state for such processes is intermediate between the structures of the enol and ketone or ketone conjugate acid, the bond being formed to or broken from C_α will not possess pure axial or equatorial character and the considerations expressed in Fig. 1 are extreme. However, as the transition

(1) Presented at the Fifth Conference on Organic Reaction Mechanisms, Durham, N. H., September, 1954. Taken from the Ph.D. thesis of Richard A. Sneen, University of Illinois, 1955.

(2) E. J. Corey, THIS JOURNAL, **76**, 175 (1954).

state structure approaches that of the ketone the magnitude of the stereoelectronic discrimination[3] should increase in favor of axial attack.

The present paper describes the results of some experiments designed to provide further information concerning the operation and magnitude of stereoelectronic discrimination in enolization–ketonization processes of cyclohexanones. The study of this aspect of enolization–ketonization with hydrogen as the leaving or entering group requires a stringently prescribed system: the cyclohexane ring in the substrate being studied should be chair-formed, but should not be subject to change during reactions to a different chair-form, *i.e.*, axial and equatorial substituents should maintain their orientation; there should be an α-methylene group in the ketone and enolization should take place so as to involve only that α-carbon atom; an isotope labeling-analytical technique must be available to differentiate between axial and equatorial α-hydrogens; both enolization and ketonization processes must be irreversible. The type of substrate system required is



R′ = D, R″ = H
R′ = H, R″ = D

R′ = H or D

3β-Acetoxycholestan-7-one labeled stereospecifically at C_6 with deuterium was selected as the most convenient and satisfactory substrate. It was apparent that enolization of this 7-ketosteroid takes place to give the Δ^6-enol instead of the Δ^7-enol from the fact that bromination of the 7-ketosteroids affords only the 6-bromo derivatives[4] as well as from other data. Furthermore, the bromination reaction proceeds to give *ca.* 55% yield of the thermodynamically less stable epimer with the 6β- (axial) orientation of bromine, which consequently is the primary product of the reaction of the Δ^6-enol with bromine. This suggests that if enolization of the 7-ketone is carried out in the presence of excess bromine, the enol will be trapped as soon as it is formed by reaction with bromine to give the 6β-bromo-7-ketone which is isolable without further modification. Thus, enolization could be studied as an effectively irreversible process in this system. In addition, as will be brought out below, methods are also available for the study of ketonization as an irreversible process.

Synthesis.—One of the key substances in this stereochemical study, 3β-acetoxy-6β-deuterocholestan-7-one (VI), was synthesized from cholesterol as shown in Fig. 2. 3β-Acetoxy-Δ^6-cholestene (III) was prepared most readily from 3β-acetoxy-7α-bromocholestan-6-one (II) by a two-step conversion with sodium borohydride to the bromohydrin followed by dehydroxy-bromination with zinc–acetic acid. The same Δ^6-olefin was obtained by the same two-step route from 3β-acetoxy-6β-bromocholestan-7-one. Oxidation of the Δ^6-olefin with perbenzoic acid proceeded stereospecifically and gave the 6,7α-oxide IV which upon reduction with lithium aluminum hydride afforded cholestan-3β,7α-diol identical with an authentic sample. Selective partial acetylation of the diol furnished the 3-monoacetate derivative which was also identical with an authentic sample. These data establish that the starting 6,7-epoxide is the 6,7α-isomer. The stereochemistry of this 6,7-oxide also follows from the fact that it differs from the known 6,7β-oxide.[2] Reduction of the 6,7α-epoxide with lithium deuteride followed by partial acetylation with acetic anhydride–pyridine gave 3β-acetoxy-6-deuterocholestan-7α-ol (V) which must by the method of synthesis be the 6β-deutero epimer. Chromic acid oxidation of this substance under mild conditions in a two-phase system yielded 3β-acetoxy-6β-deuterocholestan-7-one (VI) with no detectible loss of deuterium as determined by quantitative deuterium analysis. The deutero ketone so obtained contained 2.10 relative atom per cent. deuterium which corresponds to 1.01 ± 0.02 atoms deuterium per molecule. Infrared analysis showed a characteristic doublet due to C–D stretching vibrations at 2134 and 2164 cm.$^{-1}$,[5] the latter band being slightly stronger than the former.

For reasons which appear below it was anticipated that the reduction of 3β-acetoxy-6β-bromocholestan-7-one with zinc–O-deuteroacetic acid would lead to a predominance of the 6β-deutero-7-ketone over the 6α-deutero-7-ketone and in fact the 3β-acetoxy-6-deuterocholestan-7-one produced in this way manifested C–D stretching absorption in the infrared only slightly different from that of the authentic 6β-deutero-7-ketone described above. This finding led to a simple synthesis of 3β-acetoxy-6α-deuterocholestan-7-one by the reduction of 3β-acetoxy-6α-deutero-6β-bromocholestan-7-one by zinc–acetic acid. The 6-deutero-7-ketone so produced exhibited infrared absorption at 2132 and 2181 cm.$^{-1}$ with slight absorption at 2164 cm.$^{-1}$. The weakness of the band at 2164 cm.$^{-1}$, which is a strong band in the spectrum of the 6β-deutero-7-ketone, indicates that the 6-deutero-7-ketone produced by reduction of 3β-acetoxy-6α-deutero-6β-bromocholestan-7-one is over 90% pure 6α-deutero epimer and that the bands at 2132 and 2181 cm.$^{-1}$ are characteristic of this isomer. In addition it is apparent from this observation and the spectrum of the 6-deutero-7-ketone produced from 3β-acetoxy-6β-bromocholestan-7-one by zinc–deuteroacetic acid reduction, that this reduction product is over 90% pure 6β-deutero-7-ketone.

Experiments on the Stereochemistry of Enolization.—The synthesis of 6α- and 6β-deutero-3β-acetoxycholestan-7-one provided the necessary substrates for the study of the stereochemistry of the enolization reaction under irreversible conditions. The labeled ketone, in cold chloroform

(3) The stereoelectronic factor in chemical reactions as used herein can be defined as one which acts because of the restriction placed on the geometry of the transition state and the location of perturbed electrons by the energy-lowering requirement of maximum bonding in the transition state, *i.e.*, the requirement of that orientation of atoms and groups which provides the most effective electron delocalization. Although the term has not been used exclusively in this sense, it seems advantageous to restrict it to the above definition.

(4) T. Barr, I. M. Heilbron, E. R. H. Jones and F. S. Spring, *J. Chem. Soc.*, 334 (1938).

(5) See E. J. Corey, M. G. Howell, A. Boston, R. L. Young and R. A. Sneen, THIS JOURNAL, **78**, 5036 (1956).

solution (0–10°), was treated with an excess (1.35 equivalents) of bromine and a small amount of hydrogen bromide and the reaction which ensued was followed colorimetrically to an end-point of essentially constant optical density. At this point, with free bromine still present in excess, the reaction was quenched by shaking the solution with aqueous sodium bicarbonate and the 6β-bromo-7-ketone was isolated by rapid crystallization under conditions which do not allow enolization of the 7-ketone. The fact that the brominations were conducted in the presence of excess bromine ensures the irreversibility of the enolization step if it can be assumed, as seems reasonable from previous kinetic studies on ketone halogenation,[6] that at the low concentrations of hydrogen bromide involved bromination of the enol is much faster than protonation. The possibility that the brominated product might exchange deuterium under the conditions of the reaction is implausible both because of the presence of excess bromine, which should convert any bromoenol to the known dibromide,[4] and since the less stable isomer is obtained as the product.

Bromination of 3β-acetoxy-6β-deuterocholestan-7-one containing 1.01 ±0.02 atoms of deuterium per molecule gave a mixture of 3β-acetoxy-6β-bromocholestan-7-one and 3β-acetoxy-6α-deutero-6β-bromocholestan-7-one containing an average of 0.85 ±0.02 and 0.88 ±0.02 atom of deuterium per molecule for two separate bromination experiments. Thus, the ratio of equatorial loss to axial loss during enolization amounts to 6.4 for the 6β-deutero-6α-hydrogen-7-ketone.

Bromination of a sample of 3β-acetoxy-6α-deuterocholestan-7-one, contaminated with sufficient 6β-deutero epimer to account for about 10% of the total deuterium and containing an average of 0.553 ±0.003 atom of deuterium per molecule produced a mixture of 3β-acetoxy-6β-bromocholestan-7-one and 3β-acetoxy-6α-deutero-6β-bromocholestan-7-one containing an average of 0.493 ±0.004 atom of deuterium per molecule. Correcting for contamination of the starting material by the 6β-deutero epimer gives the result that starting with 6α-deutero epimer containing an average of 0.498 ±0.003 atom per molecule a mixture of 3β-acetoxy-6β-bromocholestan-7-one and 3β-acetoxy-6α-deutero-6β- bromocholestan-7-one containing an average of 0.446 ±0.004 atom of deuterium per molecule is produced. Thus, in this case the ratio of axial loss to equatorial loss is 8.6 ± 1.

From these data both the kinetic isotope effect of deuterium and the stereochemical discrimination can be calculated using the approach of Curtin and Kellom.[7] Let y be defined as the isotope effect, (hydrogen removed/deuterium removed), in the absence of a positional effect, and let z be defined as the positional or stereochemical effect (axial removed/equatorial removed) in the absence of an isotope effect. Then $y/z = 6.4$ and $yz = 8.6$, whence $y = 7.4 \pm 0.5$ and $z = 1.2 \pm 0.05$. There is inherent in these calculations the assumption that the isotope effect is approximately the same for loss of axial and equatorial hydrogen isotope. The observed isotope effect is close to the theoretical maximum (7.9 at 10°) and to that of 7.7 which has been observed for the enolization of acetone.[8] The positional effect reflects the resultant of *all effects* influencing the stereochemistry of proton loss during enolization and indicates a preference for loss of an axial hydrogen.

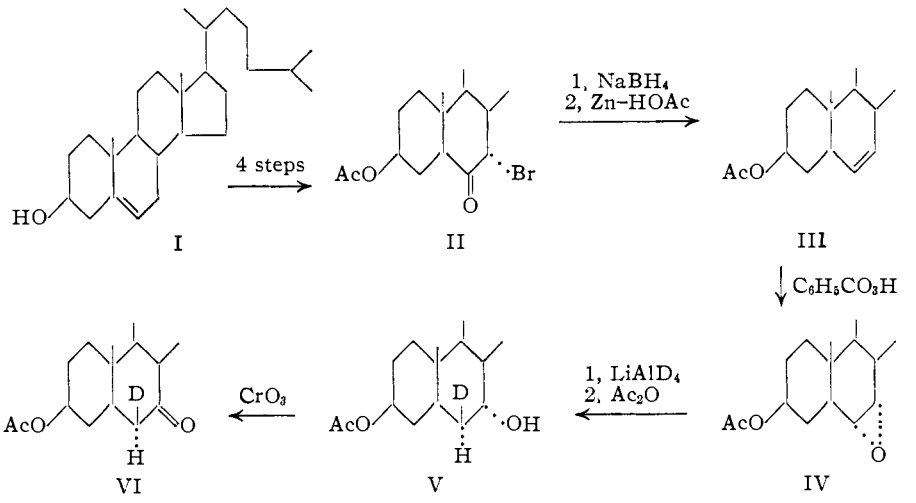
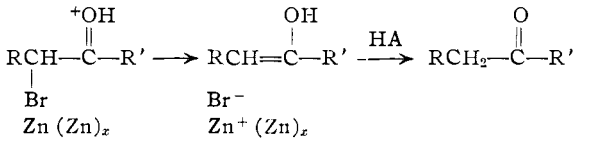


Fig. 2.

Experiments on the Stereochemistry of Ketonization.—The reduction of α-bromoketones to the corresponding ketones by zinc in acidic media is commonly considered as proceeding by way of an enol intermediate



If such is the case, and the enol is in a medium which allows irreversible ketonization, this technique could be applied to gain stereochemical information in the 7-ketosteroid system, and, indeed, this possibility did materialize. Reaction of *either* 3β-acetoxy-6β-bromocholestan-7-one or 3β-acetoxy-6α-bromocholestan-7-one with zinc dust–O-deuteroacetic acid afforded the same mixture containing *ca.* 90% of 3β-acetoxy-6β-deuterocholestan-7-one and 10% of 3β-acetoxy-6α-deuterocholestan-7-one, as determined by infrared analysis. The production of the same mixture from each epimeric bromo-

(6) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., p. 231.

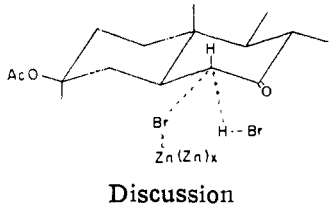
(7) D. Y. Curtin and D. B. Kellom, THIS JOURNAL, **75**, 6011 (1953).

(8) O. Reitz, *Z. physik. Chem.*, **A179**, 119 (1937). This value, obtained for hexadeuteroacetone, probably includes a secondary isotope effect; see W. D. Emmons and M. F. Hawthorne, Abstracts 129th A.C.S. Meeting, p. 28-N.

ketone provides strong evidence that there is a common intermediate which is most likely the enol. Reaction of 3β-acetoxy-6α-deutero-6β-bromocholestan-7-one with zinc–acetic acid produces as expected a mixture containing 90% 3β-acetoxy-6α-deuterocholestan-7-one and 10% 3β-acetoxy-6β-deuterocholestan-7-one. The agreement between these results indicates the irreversibility of ketone formation, as does the absence of any 6,6-dideutero-7-ketone in the reduction mixture.[9]

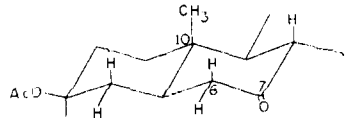
Reduction of 3β-acetoxy-6β-bromocholestan-7-one with zinc–deuterium bromide–chloroform, under essentially the same conditions of solvent and acid catalysis employed in the study of enolization described above, produces a mixture containing *ca.* 60% 3β-acetoxy-6β-deuterocholestan-7-one and 40% 3β-acetoxy-6α-deuterocholestan-7-one. This composition of this mixture is in fairly good agreement with that predicted to result from protonation of the Δ⁶-enol by deuterium bromide in chloroform on the basis of the positional effect (1.2) observed for enolization in deuterium bromide–chloroform (predicted composition: 55% 6β-deutero epimer, 45% 6α-deutero epimer). The zinc–hydrogen bromide reduction of 3β-acetoxy-6α-deutero-6β-bromocholestan-7-one gives *ca.* 40% of the 6β-deutero-7-ketone and 60% of the 6α-deutero-7-ketone, as expected from the above results. No 6,6-dideutero-7-ketone could be detected in any of the above reactions and it was shown in separate experiments that 3β-acetoxycholestan-7-one, the product, does not exchange with deuterium bromide–zinc under the reaction conditions.

In contrast to these results which seem to fit into a pattern of consistency and to indicate that the Δ⁶-enol is an intermediate, stands the reduction of 3β-acetoxy-6α-bromocholestan-7-one with zinc–deuterium bromide. This reaction, which is very much slower than the corresponding reaction of the 6β-bromo epimer, affords a mixture containing *ca.* 95 and 5%, respectively, of 6α- and 6β-deutero-3β-acetoxycholestan-7-one. It seems likely that this reaction is analogous to the reaction of 3β-iodocholestane with zinc–deutero acid mixture to give 3β-deuterocholestane[5] rather than one which proceeds *via* the Δ⁶-enol and may simply be a case of electrophilic substitution by hydrogen with retention of configuration[5]



Discussion

The magnitude of the isotope effect observed for the enolization of 3β-acetoxy-6-deuterocholestan-7-one (7.4) indicates almost complete rupture of the α-C–H bond in the transition state and suggests a model for the transition state which is considerably more like the enol in structure than like the ketone conjugate acid. The same conclusion has been drawn with regard to enolization–ketonization in other systems on the basis of different evidence.[10] The positional effect of 1.2 in favor of axial proton loss in the hydrogen bromide catalyzed enolization of the 7-ketosteroid agrees fairly well with the value *ca.* 1.5 in favor of axial proton addition which was found for the reverse process, the hydrogen bromide-catalyzed ketonization of the Δ⁶-enol-steroid, and together these values show clearly that the stereoelectronic factor is *at least large enough to cancel out the steric factor favoring equatorial attack.* The steric factor originates because the interference to axial (β) attack at C_6 (chiefly by the axial (β) angular methyl group at C_{10}) is much more serious than any steric interactions interfering with equatorial attack at C_6 and its considerable size is obvious from addition reactions to the Δ⁶-double bond which take place predominantly from the α- rather than the β-direction despite the fact that these are



stereoelectronically equivalent. Thus, the reaction of 3β-acetoxy-Δ⁶-cholestene with perbenzoic acid is stereospecific and yields only the 6,7α-epoxide in isolable amounts. Similarly, as is well known, initial α-attack is highly favored in additions to the Δ⁵-double bond, *e.g.*, epoxidation, bromination and hydrogenation. Assuming a steric component of the positional factor of *ca.* 10 in favor of α, *i.e.*, *equatorial* attack at C_6, the stereoelectronic positional factor for attack at C_6 in enolization ketonization would have to be 12–15 in favor of *axial* attack. The importance of the stereoelectronic factor is made especially clear by the recent studies of Zimmerman on the stereochemistry of enolization–ketonization in the absence of possible stereoelectronic control which indicate a high sensitivity to steric control.[10] In the absence of any stereoelectronic effect, enolization would be expected to involve the equatorial hydrogen of a 7-ketosteroid exclusively.

The data on ketonization of the Δ⁶-en-7-ol to the 7-ketone, which are summarized in Table I, show a strikingly higher positional factor in favor of axial attack for ketonization–enolization in acetic acid (at least 9) than in the presence of hydrogen bromide (1.2 – 1.5). The greater extent of axial attack in the former case could be due to steric reasons because of the smaller steric requirements of acetic acid relative to hydrogen bromide, or to enthalpy

TABLE I

Isomer of 3β-acetoxycholestan-7-one	Conditions	Compn. of product, % 6β-Deutero isomer	6α-Deutero isomer
6β-Bromo	Zn–DOAc	90	10
6α-Bromo	Zn–DOAc	90	10
6α-Deutero-6β-bromo	Zn–HOAc	10	90
6α-Deutero-6β-bromo	Zn–HBr–$CHCl_3$	40	60
6β-Bromo	Zn–DBr–$CHCl_3$	60	40

(9) The presence of 6,6-dideutero-7-ketone can be detected easily because of its characteristic infrared absorption.[5]

(10) See H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955); THIS JOURNAL, **78**, 1168 (1956).

changes in the rate-determining step which enhance stereoelectronic control. The enthalpy change for the rate-determining step, which is due to the difference in acidity of hydrogen bromide and acetic acid, can be correlated with a change in the structure of the transition state using the postulate of Hammond.[11] Assuming that the enolization–ketonization process studied here follows the course shown below which has been established rigorously for several specific cases,[6] and consider-

$$\underset{(K)}{RCH_2\overset{O}{\overset{\|}{C}}R} + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\text{fast}}{A^- + \underset{(KH^+)}{RCH_2\overset{+OH}{\overset{\|}{C}}R}} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{\text{slow}}{RCH{=}\overset{OH}{\overset{|}{C}}{-}R + HA}$$
(E)

ing only the rate-determining step, $KH^+ + A^- \rightleftarrows E + HA$, as the acid strength of HA is varied, a change will occur in ΔH for that step. Strong acids will increase ΔH for enol formation and will increase the resemblance of the transition state structure to the enol and thereby *decrease* the importance of the stereoelectronic factor. This situation is illustrated graphically in Fig. 3. It is reasonable on this basis that the weaker acid, acetic acid, should exhibit a more selective axial attack in enolization–ketonization processes.

The tendency of bromine to adopt the axial orientation in the bromination of an enol would seem to indicate that stereoelectronic control is unusually large in this case since the opposing steric effect is certainly quite large. In connection with the above considerations of the effect of changing the reagent on the degree of stereoelectronic control, a study was made of the chlorination of the Δ^6-en-7-ol system. Unlike the bromination reaction, chlorination produced no isolable 6β-halo-7-ketone, but only 6α-halo-7-ketone in *ca.* 50% yield. It seems likely that this product is the primary product because it is formed in the presence of an excess of chlorine. Since the steric effect with chlorine should be smaller than that with bromine in the halogenation of the Δ^6-en-7-ol system, the stereoelectronic factor must be considerably less important with chlorine than with bromine. This result is in line with the greater electrophilicity of chlorine and the thermodynamic correlation discussed above and indicates that the transition state possesses more enol character in the chlorination than in the bromination of an enol.

Another instance from this work which may possibly involve stereoelectronic discrimination is the debrominative enolization of the epimeric 3β-acetoxy-6-bromocholestan-7-ones with zinc dust and acid. The formation of the enol occurs considerably faster with the 6β-bromo epimer than with the 6α-bromo epimer, as would be anticipated on stereoelectronic grounds. However, it is also possible that the rate difference is due in part to a difference in thermodynamic stability of the bromoketones. A similar difference in reactivity has

(11) G. S. Hammond, *J. Org. Chem.*, **77**, 334 (1955).

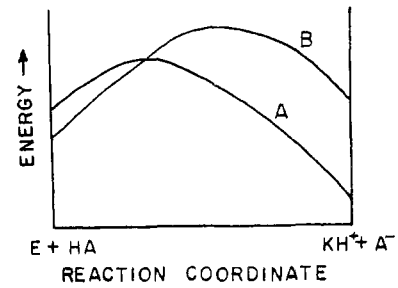
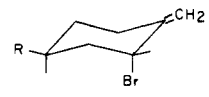


Fig. 3.—Enolization–ketonization with catalysis by a strong acid and a weak acid, represented by curves A and B, respectively.

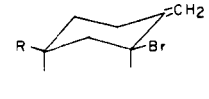
been observed previously in the reaction of zinc–acetic acid with 2α-hydroxytestosterone diacetate and 2β-hydroxytestosterone diacetate to give testosterone acetate.[12] The 2β-acetate (axial acetoxy) is deacetylated much more readily than the 2α isomer (equatorial acetoxy).

Since a high predominance of axial attack had been realized in the O-deuteroacetic acid ketonization of the enol of 3β-acetoxycholestan-7-one, debrominative enolization of a few other α-bromoketosteroids in deuteroacetic acid was studied. Zinc–deuteroacetic acid reduction of 3β-acetoxy-5α-bromocholestan-6-one yielded 3β-acetoxy-5α-deuterocholestan-6-one (axial deuterium). Similar treatment of 3β-acetoxy-7α-bromocholestan-6-one afforded what appears to be a single 3β-acetoxy-7-deuterocholestan-6-one on the basis of infrared analysis (C–D stretching absorption at 2138 cm.$^{-1}$), which is probably the 7α-deutero isomer (axial deuterium). Reduction of 2α-bromocholestan-3-one afforded a 2-deuterocholestan-3-one, the infrared spectrum of which was almost identical with 2β-deuterocholestan-3-one (axial deuterium). These cases indicate a general and strong preference for axial attack in the protonation of steroid enols by acetic acid.

All of the above data indicate a substantial degree of stereoelectronic control in enolization–ketonization type processes of cyclohexanone systems, an effect which could not have been predicted with certainty, but which agrees well with orbital–structural theory. It is obvious that the results of these findings apply not only to enolization–ketonization processes, but also to a wide variety of reactions of cyclohexane systems in which an exocyclic double bond becomes endocyclic, together with the reverse processes. Thus, for example, the solvolysis of VII should be considerably faster than VIII; where R is a large anchoring group.



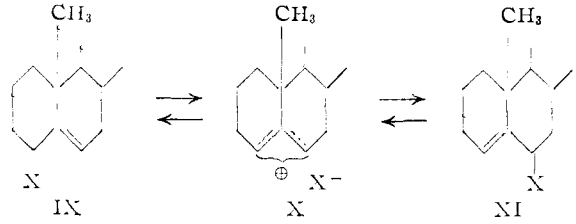
VII



VIII

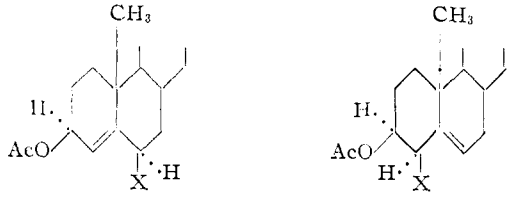
Perhaps the most striking conclusions as to the magnitude of such stereoelectronic effects follow from a consideration of $\Delta^4 \rightleftarrows \Delta^5$ interconversions in the steroid series which proceed *via* 4,5,6-allyl cations, IX $\rightleftarrows$ X $\rightleftarrows$ XI. The known transforma-

(12) F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, *ibid.*, **75**, 4712 (1953).



IX X XI

tions of this type are invariably stereospecific and involve preferential axial substitution of the 4,5,6-allyl cation to give a 4β-substituted Δ⁵-olefin or a 6β-substituted Δ⁴-olefin. Thus, acetolysis of 6β-bromo- or 6β-chloro-3β-acetoxy-Δ⁴-cholestene (XII) affords exclusively 3β,4β-diacetoxy-Δ⁵-choles-



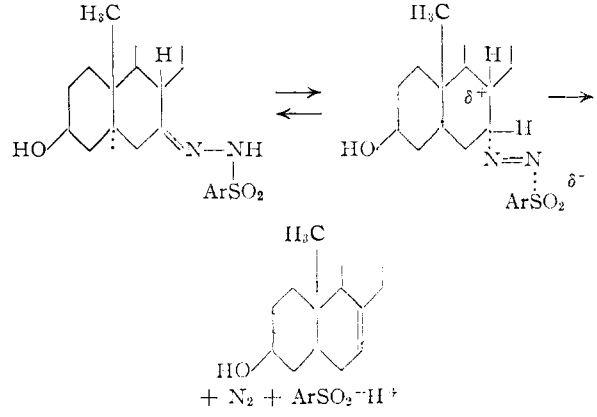
XII, X = Cl, Br
XV, X = OAc

XII, X = OAc
XIV, X = OH

tene (XIII).[13] Treatment of 4β-hydroxy-3β-acetoxy-Δ⁵-cholestene (XIV) with hot acetic acid followed by acetylation affords 3β,6β-diacetoxy-Δ⁵-cholestene (XV). Reaction of cholesteryl acetate with selenium dioxide, which probably proceeds by way of the 4,5,6-allyl cation, affords the 4β-hydroxy derivative XIV[14] as the only isolable product. In none of these cases has equatorial substitution been observed despite the fact that it is highly favored sterically. Moreover, the 4β- and 6β-substitution products are thermodynamically less stable than the corresponding 4α- and 6α-epimers.[15]

An analogous situation apparently occurs in the methanolysis of epicholesteryl tosylate which yields in addition to Δ³,⁵-cholestadiene, 4β-methoxy-Δ⁵-cholestene and 6β-methoxy-Δ⁴-cholestene.[16] The last two products probably result by 4 → 3-hydrogen rearrangement to give the 4,5,6-allyl cation followed by stereospecific reaction with methanol. All of these results can be correlated as characteristic of the 4,5,6-allyl cation system and can be reasonably attributed to stereoelectronic control, of the type discussed above, which favors axial attack during formation or destruction of the 4,5,6-allyl cation.[17]

In connection with the investigation of the stereochemistry of enolization in the 7-ketosteroid system which has been described herein, another point of interest with regard to this specific system deserves comment. As mentioned previously, enolization of a 7-ketosteroid takes place to produce a Δ⁶-enol by loss of a hydrogen from C₆, instead of by loss of a hydrogen from C₈ to give a Δ⁷-enol. The reason for the predominance of enolization involving C₆ over that involving C₈ would appear, at least in part, to be the shielding of the 8β-hydrogen by the angular methyl groups at C₁₀ and C₁₃.[2] In contrast to enolization, 1,2-elimination reactions of certain 7-substituted steroids yield Δ⁷-olefins instead of Δ⁶-olefins. Thus, it was observed during studies on the synthesis of 3β-acetoxy-Δ⁶-cholestene that the reaction of 3β-acetoxycholestan-7-one with *p*-toluenesulfonyl hydrazide and base[18] affords 3β-hydroxy-Δ⁷-cholestene and no detectable Δ⁶-olefin. In this reaction, which can be formulated reasonably as shown, the transition state for the product-determining step apparently depends less on the accessibility of the leaving hydrogen (which would favor the Δ⁶-olefin) and more on some other factor such as strain differences between Δ⁶- and Δ⁷-olefin systems (which would favor the more stable Δ⁷-olefin). The dehydration of 3β-acetoxycholestan-



+ N_2 + $ArSO_2^-H^+$

7α-ol with phosphorus oxychloride–pyridine, presumably by way of a phosphorus ester, also produces Δ⁷-olefin exclusively[19] and seems to be subject to the same influences. It seems reasonable to assume from these data that in elimination reactions leading to Δ⁶- or Δ⁷-unsaturated structures, the greater the amount of positive charge at C₇ in the transition state the greater the ratio of Δ⁷- to Δ⁶-olefin produced. It is also evident that when formation of Δ⁶-olefin is not possible in an elimination reaction of a 7-substituted steroid and considerable assistance is required for proton removal from C₈, 1,2-hydride migration from C₈ to C₇ might be competitive with 1,2-elimination. Such is apparently the case in the reactions of 7α- and 7β-bromocholesteryl benzoates with pyridine which give in each case 3β-benzoyloxycholesta-5,8(9)-diene[20] instead of 3β-benzoyloxycholesta-5,7-diene.

Experimental[21]

3β-Acetoxy-7α-bromocholestan-6-one (II).—A solution containing 8.55 g. of bromine (3% excess) dissolved in 100 ml. of acetic acid was added dropwise to a solution of 23.4 g. of 3β-acetoxycholestan-6-one[22] in 300 ml. of ether and 60 ml. of acetic acid and the resulting solution was maintained

(13) V. A. Petrow, O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 135 (1943).

(14) O. Rosenheim and W. W. Starling, *ibid.*, 377 (1937).

(15) K. Florey and M. Ehrenstein, *J. Org. Chem.*, **19**, 1331 (1954).

(16) D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955); Becker and Wallis, *J. Org. Chem.*, **20**, 353 (1955).

(17) Reactions of steroid 7,8,9-allyl cations also appear to be subject to stereoelectronic control; L. F. Fieser and M. A. Romero, THIS JOURNAL, **75**, 4716 (1953); H. Heusser, R. Anliker, K. Eichenberger and O. Jeger, *Helv. Chim. Acta*, **35**, 936 (1952).

(18) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

(19) W. Buser, *Helv. Chim. Acta*, **30**, 1379 (1947).

(20) K. Tsuda, K. Arima and R. Hayatsu, THIS JOURNAL, **76**, 2933 (1954).

(21) Microanalyses by Mr. Josef Nemeth and associates, spectral data obtained by Mr. James Brader.

(22) R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948).

at reflux for 22 hours. The ether was evaporated under reduced pressure and the acetic acid solution was diluted with water to turbidity. The crude material which crystallized was collected and recrystallized from acetic acid–water, yielding 20.4 g. of 3β-acetoxy-7α-bromocholestan-6-one (II), m.p. 143.8–146.8° (74%), reported[23] m.p. 144–145°.

3β-Acetoxy-Δ⁶-cholestene (III). Procedure A.—To a solution of 4.2 g. of 3β-acetoxy-7α-bromocholestan-6-one in 150 ml. of isopropyl alcohol was added a solution of 424 mg. of sodium borohydride in 100 ml. of isopropyl alcohol. The reaction mixture was maintained at room temperature for 2 hours and the excess hydride was decomposed with dilute aqueous sulfuric acid. The total reaction mixture was concentrated under reduced pressure to 50 ml., diluted with 10:1 ether–methylene chloride and extracted with water. The ether layer was dried (sodium sulfate) and concentrated to dryness. The oily residue was dissolved in 300 ml. of acetic acid, 12 g. of zinc dust was added and the solution was heated under reflux for 10 minutes. The hot solution was filtered and the unused zinc was washed with warm acetic acid. The combined filtrates were concentrated almost to dryness under reduced pressure, diluted with ether and extracted with water. The ethereal solution was evaporated and the solid residue was recrystallized from ethanol–water; yield 2.73 g. (79%), m.p. 106–107.5°, $[\alpha]^{20}D$ −96.5° (chloroform); reported[24] m.p. 104–106°, $[\alpha]^{24}D$ −88°.

Procedure B.—To a solution of 186.5 mg. of 3β-acetoxy-6β-bromocholestan-7-one in 10 ml. of isopropyl alcohol was added a solution of 25 mg. of sodium borohydride in 10 ml. of isopropyl alcohol. The reaction mixture was allowed to stand at room temperature for 2 hours and the product was isolated and treated with zinc–acetic acid at reflux for 15 minutes. The olefin was isolated as described above, m.p. 103–105° (28.5 mg.), m.p. not depressed upon admixture with the material prepared by procedure A.

3β-Acetoxy-6,7α-oxidocholestane (IV).—To a solution of 4.012 g. of 3β-acetoxy-Δ⁶-cholestene in 25 ml. of chloroform was added 100 ml. of a solution of perbenzoic acid in chloroform (26.3 mg. acid/ml. of solution). After 72 hours at room temperature the solution was extracted with 5% aqueous sodium hydroxide and then with water and concentrated to dryness. Recrystallization from ethanol–water yielded 3.47 g. of IV, m.p. 172–174°, 83.1%. Filtration through a column of alumina in 7:3 benzene–cyclohexane raised the m.p. to 177.8–178.3°, $[\alpha]^{24}D$ −31.9° (chloroform).

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.24; H, 10.79.

6,7α-Oxidocholestan-3β-ol.—To 164 mg. of 3β-acetoxy-6,7α-oxidocholestane dissolved in 10 ml. of isopropyl alcohol was added a solution of 0.3 g. of potassium hydroxide in 5 ml. of isopropyl alcohol and the resulting solution was heated on a steam-bath for 30 minutes. The solution was concentrated *in vacuo* to 3 ml., diluted with several times its volume of water and filtered. Recrystallization from acetone–water afforded 132 mg. of 6,7α-oxidocholestan-3β-ol (89.2%), m.p. 141.3–143.5°, $[\alpha]^{25}D$ −35° (chloroform). A mixture m.p. with authentic 6,7β-oxidocholestan-3β-ol, m.p. 157.5–158.5°,[2] was depressed to 139–142°.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.13; H, 11.31.

6β-Deuterocholestan-3β,7α-diol.—To a solution of 3.07 g. of 3β-acetoxy-6,7α-oxidocholestane in 100 ml. of anhydrous ether was added 880 mg. of lithium aluminum deuteride. The reaction mixture was allowed to reflux for 72 hours and the excess deuteride was decomposed with ethyl acetate followed by water. The mixture was diluted with ether–dilute aqueous hydrochloric acid and shaken. The ethereal solution was washed with water, dried and evaporated. Recrystallization of the residue from ethanol–water afforded 2.53 g. (90.5%) of 6β-deuterocholestan-3β,7α-diol, m.p. 153–154.5°, reported for cholestan-3β,7α-diol m.p. 152°.[25] Reduction of the 6,7α-oxide with lithium aluminum hydride in the way described above gave authentic cholestan-3β,7α-diol.

3β-Acetoxy-6β-deuterocholestan-7α-ol (V).—A mixture of 854 mg. of 6β-deuterocholestan-3β,7α-diol, 10 ml. of dry pyridine and 6.3 ml. of a pyridine solution containing 55.2 mg. of acetic anhydride per ml. (0.6 mole excess anhydride) was allowed to stand at room temperature for 68 hours. The excess anhydride was decomposed with water and the pyridine solution was diluted with ether, extracted twice with dilute aqueous hydrochloric acid and once with water. The aqueous washings were extracted with fresh ether and this ethereal layer was washed with water. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness *in vacuo*. The solid residue was crystallized from ethanol–water, yielding 866 mg. of crude 3β-acetoxy-6β-deuterocholestan-7α-ol, m.p. 110–114°. This material was purified by chromatography on a solumn of Florisil (180 × 14 mm.), 646.5 mg. of pure monoacetate, m.p. 117.2–118.2°, being eluted with 3–2 cyclohexane–benzene. Repeated crystallization furnished the analytical sample, m.p. 118.2–118.7°; reported[26] for 3β-acetoxycholestan-7α-ol, m.p. 117°.

Anal. Calcd. for $C_{29}H_{49}DO_3$: C, 77.80; H, 11.48. Found: C, 77.41; H, 11.33.

The combined mother liquors from the first crystallization and from the chromatogram were concentrated to an oily residue, 50 ml. of 10% sodium hydroxide in methanol was added and the solution was refluxed for 2 hours. The solution was concentrated *in vacuo* to 10 ml., diluted with ether, and extracted twice with 5% hydrochloric acid and then with water. The ether was evaporated and the residue crystallized from ethanol–water, affording 239 mg. of 3β-acetoxycholestan-3β,7α-diol, m.p. 143–148.5°. The yield of pure 3β-acetoxy-6β-deuterocholestan-7α-ol based on recovered starting material was 96.7%.

3β-Acetoxy-6β-deuterocholestan-7-one (VI).—To a solution of 3β-acetoxy-6β-deuterocholestan-7α-ol in 6 ml. of benzene (previously cooled to 5°) was added an ice-cooled solution containing 0.25 g. of sodium dichromate monohydrate and 0.25 g. of chromic anhydride in 0.4 ml. of acetic acid and 2 ml. of water. The temperature was allowed to rise slowly to a maximum of 16° (tap-water cooling) and the stirred reaction mixture was allowed to react at this temperature for an additional 10 hours. The reaction mixture was poured into a separatory funnel and the inorganic layer was removed. The organic solution was extracted three times with cold 10% aqueous sodium bicarbonate and finally with cold water and the solvent was then removed *in vacuo*. The crystalline residue was dissolved in 3–1 methanol–methylene chloride and filtered through a cotton plug. The methylene chloride was boiled off and, upon cooling, 171 mg. of 3β-acetoxy-6β-deuterocholestan-7-one, m.p. 150.6–151.1°, was obtained. An additional 19 mg. of ketone was obtained from the mother liquor, m.p. 148.3–148.8°, yield 90.0%; reported[27] for 3β-acetoxycholestan-7-one, m.p. 142–143°.

Anal. Calcd. for $C_{29}H_{47}DO_3$: C, 78.15; H, 11.08. Found: C, 78.23; H, 10.99.

Deuterium analysis revealed the presence of 2.10 relative atom per cent. deuterium, corresponding to 1.01 atoms excess deuterium per molecule.

3β-Acetoxy-6β-bromocholestan-7-one.—A freshly prepared solution (20 ml.) of bromine in chloroform (136 mg. of bromine per ml.) was added dropwise to a stirred solution of 6.42 g. of 3β-acetoxycholestanone-7 in 50 ml. of chloroform over a period of 5 minutes. External cooling was applied so that the rate of decoloration was maintained at a fairly constant level (17–18°). After the addition was completed, stirring was continued for an additional 5 minutes and the reaction mixture was then poured into an ice-cooled 5% aqueous sodium bicarbonate solution. The water layer was removed and the organic layer was washed with a cold bicarbonate solution and then with cold water. The chloroform solution was concentrated to dryness *in vacuo* and the residue was crystallized from acetone, yielding 4.066 g. of crystalline material (53.5%), m.p. 170.2–173°. Further recrystallization from the same solvent provided 3.03 g. of 3β-acetoxy-6β-bromocholestan-7-one, m.p. 178.3–179° (lit.[4] m.p. 173–175°).

(23) I. M. Heilbron, E. R. H. Jones and F. S. Spring, *J. Chem. Soc.*, 801 (1937).

(24) D. H. R. Barton and W. J. Rosenfelder, *Nature*, **164**, 316 (1949); O. Wintersteiner and M. Moore, *ibid.*, **164**, 317 (1949).

(25) L. F. Fieser and H. Heyman, *Helv. Chim. Acta*, **35**, 631 (1952).

(26) O. Wintersteiner and M. Moore, THIS JOURNAL, **65**, 1503 (1943).

(27) A. Windaus and E. Kirchner, *Ber.*, **53**, 614 (1920).

The first acetone mother liquor was concentrated to dryness *in vacuo* and the residue was recrystallized repeatedly from aqueous acetic acid, affording 0.86 g. of 3β-acetoxy-6α-bromocholestan-7-one, m.p. 143–144° (reported[4] m.p. 142–143°) as the minor product. The ratio of 6β- to 6α-bromoketone produced in the bromination is estimated to be of the order of four and is certainly greater than three.

3β-Acetoxy-6α-chlorocholestan-7-one.—To a solution of 961 mg. of 3β-acetoxycholestan-7-one (XII), 6 ml. of chloroform, and a few drops of a saturated solution of hydrogen chloride in acetic acid was added 2.6 ml. of a carbon tetrachloride solution containing 66 mg. of chlorine per ml. of solution, and the reaction was allowed to proceed at room temperature for 15 minutes. Another 2.6 ml. of the chlorine in carbon tetrachloride solution was added and the reaction mixture was swirled periodically over a period of 10 minutes. The solution was diluted with ether and extracted twice with 5% aqueous sodium hydroxide and once with water. The solvent was removed *in vacuo* and the solid residue was crystallized from acetone, affording 730 mg. of yellow crystals, m.p. 140–150°. Recrystallization from *n*-heptane yielded 422 mg. (47.5%) of 3β-acetoxy-6α-chlorocholestan-7-one, m.p. 168–168.2°, $[\alpha]^{21}D$ −8.8.

Anal. Calcd. for $C_{29}H_{47}O_3Cl$: C, 72.69; H, 9.89. Found: C, 72.44; H, 9.40.

The α-orientation of chlorine is indicated from the ultraviolet absorption of the chloroketone, λ_{max} 280 mμ (95% alcohol),[4] from its stability to isomerization (see below) and from molecular rotation differences.

3β-Acetoxy	M_D	ΔM_D
Cholestan-7-one	−160°	0
6β-Bromocholestan-7-one	+183	+343°
6α-Bromocholestan-7-one	− 46	+114
6α-Chlorocholestan-7-one	− 42	+118

Attempted Isomerization of 3β-Acetoxy-6α-chlorocholestan-7-one.—To 45 mg. of 3β-acetoxy-6α-chlorocholestan-7-one and 10 ml. of acetic acid were added a few drops of a solution containing hydrogen chloride in acetic acid. The reaction mixture was heated under reflux for 16 hours, the acetic acid was evaporated *in vacuo*, and the residue was crystallized from ethanol–water, affording 28 mg. of 3β-acetoxy-6α-chlorocholestan-7-one, m.p. 165–166.5°. A mixture melting point with starting material was not depressed.

Bromination of 3β-Acetoxy-6β-deuterocholestanone-7.—A solution of 160.5 mg. of 3β-acetoxy-6β-deuterocholestanone-7 in 3 ml. of chloroform was cooled to 0° and added to 5.1 ml. (36% excess) of a freshly prepared solution of bromine in chloroform (15.3 mg. of bromine per ml.) which had been placed in a test-tube and cooled to 0°. A few drops of a saturated hydrogen bromide in chloroform solution was added and the reaction mixture was allowed to warm slowly. The course of the reaction was followed by the change in optical density (measured by a Lumetron colorimeter) and the end-point was chosen as constant optical density. The reaction mixture was poured into a cold aqueous sodium bicarbonate solution. The aqueous layer was removed and the organic layer was extracted once with aqueous sodium bicarbonate and once with water. The chloroform was removed *in vacuo* and the crystalline residue was recrystallized from acetone, affording 95.5 mg. of crystalline material (50.5%). Recrystallization from the same solvent gave 72.5 mg. (38.4%) of deuterium-containing 3β-acetoxy-6β-bromocholestan-7-one, m.p. 177–178°.

Anal. Calcd. for $C_{29}H_{47}O_3Br$: C, 66.52; H, 9.05. Found: C, 66.93; H, 9.24.

This material contained 1.08 relative atom per cent. deuterium corresponding to 0.85 atom excess deuterium per molecule. A second run under identical conditions provided material containing 0.88 atom excess deuterium per molecule.

Zinc–O-Deuteroacetic Acid Debromination of 3β-Acetoxy-6β-bromocholestan-7-one. Run I.—To a solution of 1.454 g. of 3β-acetoxy-6β-bromocholestan-7-one in 75 ml. of anhydrous ether and 7 g. of acetic acid-*d* (prepared by heating acetic anhydride with an equimolar amount of deuterium oxide) was added 1.1 g. of zinc dust. The reaction mixture was stirred magnetically at room temperature for 18 hours. The reaction mixture was diluted with ether to a total volume of 200 ml., the ethereal solution was decanted from the unused zinc, and the zinc was washed with fresh ether. The combined ether extracts were washed twice with 5% aqueous sodium hydroxide and finally with water. The ethereal solution was filtered through a cotton plug and concentrated to dryness. The solid residue was recrystallized from ethanol–water, affording 1.051 g. (85.1%) of deuterated 3β-acetoxycholestan-7-one, m.p. 149.8–151°, designated hereafter as XXIII. This material was a mixture composed of approximately 90% 3β-acetoxy-6β-deuterocholestan-7-one and 10% 3β-acetoxy-6α-deuterocholestan-7-one. The infrared spectrum of (XXIII) displayed absorption bands at 2134 and 2164 cm.$^{-1}$ and a slight shoulder at 2181 cm.$^{-1}$ The intensities of the two common bands were reversed relative to those observed in the spectrum of authentic 3β-acetoxy-6β-deuterocholestan-7-one.

Zinc–Acetic Acid-*d* Debromination of 3β-Acetoxy-6α-bromocholestan-7-one.—A mixture of 569 mg. of 3β-acetoxy-6α-bromocholestan-7-one, 60 ml. of anhydrous ether, 9 g. of acetic acid-*d*, and 900 mg. of zinc dust was treated as described above for the zinc–acetic acid-*d* debromination of 3β-acetoxy-6β-bromocholestan-7-one, affording 408 mg. (84.7%) of a mixture of 6α- and 6β-deutero-3β-acetoxycholestan-7-one (designated as XXIV), m.p. 149.3–150.3°. This material was composed of approximately 90% 3β-acetoxy-6β-deuterocholestan-7-one and 10% 3β-acetoxy-6α-deuterocholestan-7-one. The infrared spectrum of XXIV exhibited absorption bands at 2134 and 2164 cm.$^{-1}$ and a slight shoulder at 2181 cm.$^{-1}$ and was indistinguishable from that of XXIII.

Zinc–Acetic Acid-*d* Debromination of 3β-Acetoxy-6β-bromocholestan-7-one (XIII). Run II.—A mixture of 1.622 g. of 3β-acetoxy-6β-bromocholestan-7-one, 90 ml. of anhydrous ether, 10 ml. of chloroform (containing 0.75% ethanol), 17 g. of acetic acid-*d* and 1.3 g. of zinc dust was treated in the manner described above (run I), affording 1.375 g. (89.3%) of a mixture of 3β-acetoxycholestan-7-one, 6α- and 6β-dentero-3β-acetoxycholestan-7-one (designated as XXV), m.p. 149–150°. This material was a mixture composed of approximately 36% 3β-acetoxycholestan-7-one, 58% 3β-acetoxy-6β-deuterocholestanone-7, and 6% 3β-acetoxy-6α-deuterocholestan-7-one. This run was made before the presence of ethanol in the solvent was known; however, the product was still satisfactory for further studies.

Bromination of Sample XXV of 6α- and 6β-Deutero-3β-acetoxycholestan-7-one.—A solution of 1.228 g. of (XXV) in 25 ml. of chloroform was treated with a chloroform solution (6.2 ml.) containing 67 mg. of bromine per ml. in the manner described above for the bromination of 3β-acetoxy-6β-deuterocholestan-7-one (X), affording 510 mg. of crystalline material. Recrystallization from acetone afforded 380 mg. (26.2%) of a mixture composed of approximately 45% 3β-acetoxy-6β-bromocholestan-7-one and 55% 3β-acetoxy-6α-deutero-6β-bromocholestan-7-one (designated as XXVI), m.p. 173.5–174.5°.

Zinc–Acetic Acid Debromination of Sample XXVI of 3β-Acetoxy-6α-deutero-6β-bromocholestan-7-one and 3β-Acetoxy-6β-bromocholestan-7-one.—To a solution of 319 mg. of XXVI in 20 ml. of anhydrous ether and 7 ml. of acetic acid was added 800 mg. of zinc dust. The reaction mixture was stirred magnetically at room temperature for 18 hours and was worked up in the manner described above for the zinc–acetic acid-*d* debromination of 3β-acetoxy-6β-bromocholestan-7-one (XIII), yielding 219 mg. (81.1%) of deuterium-containing 3β-acetoxycholestan-7-one (designated as XXVII), m.p. 148–149.5°. Deuterium analysis of this material revealed the presence of 1.15 relative atom percentage of deuterium corresponding to 0.553 atom excess deuterium per molecule. The infrared spectrum of XXVII displayed bands at 2137 and 2181 cm.$^{-1}$. This material (XXVII) was a mixture containing approximately 45% 3β-acetoxycholestanone-7, 50% 3β-acetoxy-6α-deuterocholestan-7-one and 5% 3β-acetoxy-6β-deuterocholestan-7-one.

Bromination of Sample XXVII of 3β-Acetoxycholestanone, 6α- and 6β-Bromo-3β-acetoxycholestan-7-one.—A solution of 176 mg. of XXVII in 3 ml. of chloroform was treated with a chloroform solution (3.6 ml.) containing 22 mg. of bromine per ml. in the manner described for the bromination of 3β-acetoxy-6β-deuterocholestan-7-one, affording 74 mg. of crystalline material. Recrystallization from acetone afforded 52.5 mg. of deuterium-containing 3β-acetoxy-6β-bromocholestan-7-one (designated as XXVIII),

m.p. 176.5–177.5°. Deuterium analysis of this material revealed the presence of 1.05 relative atom per cent. deuterium corresponding to 0.493 atom excess deuterium per molecule.

Zinc–Acetic Acid-*d* Debromination of Sample XXVI of 3β-Acetoxy-6α-deutero-6β-bromocholestan-7-one and 3β-Acetoxy-6β-bromocholestan-7-one.—A mixture of 119 mg. of XXVI, 20 ml. of anhydrous ether, 4 g. of acetic acid-*d* and 600 mg. of zinc dust was treated in the manner described above for the zinc–acetic acid-*d* debromination of 3β-acetoxy-6β-deuterocholestan-7-one, affording 80 mg. (79.2%) of deuterium-containing 3β-acetoxycholestan-7-one (designated as XXIX), m.p. 149.5–151°. The infrared spectrum of this material exhibited bands at 2131 and 2220 cm.$^{-1}$, indicating the presence of 3β-acetoxy-6,6-dideuterocholestan-7-one.

Deuterium Bromide.—The procedure described by Biltz[28] for the preparation of an aqueous solution of hydrogen bromide was adapted to the preparation of a methylene chloride solution of deuterium bromide. The gas was generated by the dropwise addition of 7 ml. of bromine to a mixture of 14 g. of white sand and 3 g. of red phosphorus moistened with 5 ml. of deuterium oxide. The red phosphorus was dried under vacuum at 165°. The deuterium bromide so produced passed through two U-tubes in series. The first was filled with glass beads and cooled with an ice–salt mixture, and the second was filled with glass beads mixed with deuterium oxide-moistened red phosphorus. The gas was collected by bubbling through ice-cooled methylene chloride. A small amount of anhydrous phosphorus pentoxide was added to remove deuterium oxide. The acid solution produced in this manner was 0.28 *M*.

Zinc–Deuterium Bromide Debromination of 3β-Acetoxy-6β-bromocholestan-7-one.—To a solution of 139.3 mg. of 3β-acetoxy-6β-bromocholestan-7-one in 5 ml. of methylene chloride were added 5 ml. of 0.28 *M* deuterium bromide in methylene chloride solution (previously cooled to 0°) and 400 mg. of zinc dust. The reaction mixture was stirred magnetically with ice-bath cooling for 15 minutes, was then diluted with ether, extracted twice with cold 2% aqueous sodium hydroxide and then with water. The ether layer was concentrated to dryness *in vacuo* and the solid residue was crystallized from ethanol–water, affording 71.2 mg. (60.2%) of 6α- and 6β-deutero-3β-acetoxycholestan-7-one (designated as XXX), m.p. 149.3–150.8°. The infrared spectrum of this material displayed bands at 2134, 2164 and at 2181 cm.$^{-1}$ This material (XXX) was a mixture composed of approximately 60% 3β-acetoxy-6β-deuterocholestan-7-one and 40% 3β-acetoxy-6α-deuterocholestan-7-one.

Zinc–Hydrogen Bromide Debromination of Sample XXVI of 3β-Acetoxy-6α-deutero-6β-bromocholestan-7-one and 3β-Acetoxy-6β-bromocholestan-7-one.—A solution of 99 mg. of XXVI in 5 ml. of chloroform was treated with 5 ml. of a chloroform solution of hydrogen bromide (0.5 *M*) and 600 mg. of zinc dust in the manner described above for the zinc–deuterium bromide debromination of 3β-acetoxy-6β-bromocholestan-7-one, affording 54 mg. (64%) of deuterium-containing 3β-acetoxycholestan-7-one (designated as XXXI), m.p. 145–147°. The infrared spectrum of this material contained the same bands observed in the spectrum of XXX. However, in the former the band at 2164 cm.$^{-1}$ was more intense and the band at 2181 cm.$^{-1}$ less intense. This material (XXXI) was a mixture composed of approximately 55% 3β-acetoxycholestan-7-one, 27% 3β-acetoxy-6α-deuterocholestan-7-one, and 18% 3β-acetoxy-6β-deuterocholestan-7-one.

Attempted Isomerization of 3β-Acetoxy-6β-deuterocholestan-7-one with Zinc–Deuterium Bromide.—A solution of 63 mg. of 3β-acetoxy-6β-deuterocholestan-7-one in 5 ml. of chloroform was treated with 5 ml. of a chloroform solution of hydrogen bromide (0.5 *M*) and 500 mg. of zinc dust in the manner described above for the zinc–deuterium bromide debromination of 3β-acetoxy-6β-bromocholestan-7-one (XIII), affording 50 mg. of deuterium-containing 3β-acetoxycholestan-7-one, m.p. 148.5–150°, whose infrared spectrum was indistinguishable from that of the starting material, 3β-acetoxy-6β-deuterocholestan-7-one.

Zinc–Deuterium Bromide Debromination of 3β-Acetoxy-6α-bromocholestan-7-one.—A solution of 79.8 mg. of 3β-acetoxy-6α-bromocholestan-7-one in 5 ml. of methylene chloride was treated with 5 ml. of a methylene chloride solution (0.5 *M*) of deuterium bromide and 340 mg. of zinc dust in the manner described above for the zinc–deuterium bromide debromination of 3β-acetoxy-6β-bromocholestan-7-one, affording 64.2 mg. of an amorphous solid, m.p. 118–120° (cloudy melt). A positive Beilstein test revealed the presence of bromine. The infrared spectrum of this material exhibited bands at 2137 and 2181 cm.$^{-1}$. No bands could be observed in the region near 2164 cm.$^{-1}$.

A mixture of 61 mg. of this amorphous material, 10 ml. of anhydrous ether, 5 ml. of acetic acid and 325 mg. of zinc dust was treated as described for the zinc–acetic acid-*d* debromination of 3β-acetoxy-6β-bromocholestan-7-one, affording 41 mg. of deuterium-containing 3β-acetoxycholestan-7-one (designated as XXXII), m.p. 147.5–149°, whose infrared spectrum was indistinguishable from that of the crude starting material. This material (XXXII) was a mixture, the deuterated component of which contained approximately 95% 3β-acetoxy-6α-deuterocholestan-7-one and 5% 3β-acetoxy-6β-deuterocholestan-7-one.

Zinc–Acetic Acid-*d* Debromination of 3β-Acetoxy-5α-bromocholestan-6-one.—A mixture of 170 mg. of 3β-acetoxy-5α-bromocholestan-6-one,[2] 25 ml. of anhydrous ether, 7 g. of acetic acid-*d* and 600 mg. of zinc dust was treated as described above for the zinc–acetic acid-*d* debromination of 3β-acetoxy-6β-bromocholestanone-7, affording 101 mg. (70.1%) of 3β-acetoxy-5α-deuterocholestan-6-one, m.p. 128–129°. The infrared spectrum of this material displayed a single band in the C–D stretching region at 2128 cm.$^{-1}$.

Zinc–Acetic Acid-*d* Debromination of 3β-Acetoxy-7α-bromocholestan-6-one.—A mixture of 158 mg. of 3β-acetoxy-7α-bromocholestan-6-one, 25 ml. of anhydrous ether, 7 g. of acetic acid-*d* and 610 mg. of zinc dust was treated in the manner described above for the zinc–acetic acid-*d* debromination of 3β-acetoxy-6β-bromocholestan-7-one, affording 3β-acetoxy-7α-deuterocholestan-6-one, m.p. 129–130°. The infrared spectrum of this material displayed a single band in the C–D stretching region at 2138 cm.$^{-1}$.

Zinc–Acetic Acid-*d* Debromination of 2α-Bromocholestan-3-one.—A mixture of 610 mg. of 2α-bromocholestan-3-one, 50 ml. of anhydrous ether, 6.5 g. of acetic acid-*d* and 800 mg. of zinc dust was treated in the manner described above for the zinc–acetic acid-*d* debromination of 3β-acetoxy-6β-bromocholestan-7-one, affording 462 mg. (91.1%) of 2α- and 2β-deuterocholestan-3-one, m.p. 129–129.3°. The infrared spectrum displayed a strong band at 2144 cm.$^{-1}$ and very slight absorption at 2164 cm.$^{-1}$. Comparison with the spectrum of authentic 2β-deuterocholestan-3-one indicates that this material is predominantly the 2β-epimer.[5]

Δ^7-Cholesten-3β-ol.—A solution containing 824 mg. of 3β-acetoxycholestan-7-one, 361 mg. of *p*-toluenesulfonyl hydrazide, 35 ml. of absolute ethanol and 0.75 ml. of concentrated hydrochloric acid was heated to reflux for 40 minutes. Upon cooling 793 mg. of the crude *p*-toluenesulfonyl hydrazone derivative of 3β-acetoxycholestan-7-one,

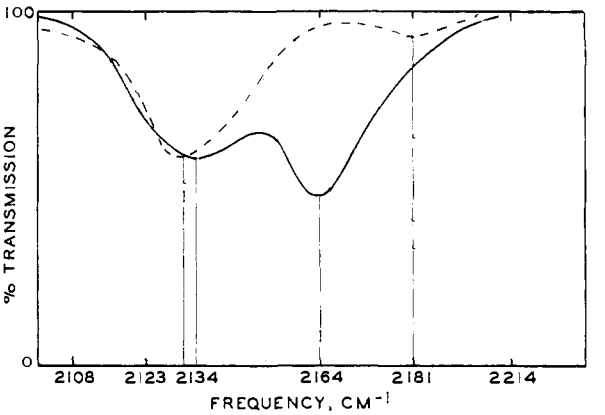


Fig. 4.—C–D stretching absorption in carbon tetrachloride: ——, 6β-deutero-3β-acetoxycholestan-7-one; - - -, 6α-deutero-3β-acetoxycholestan-7-one.

(28) H. Biltz, "Laboratory Methods of Inorganic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1928, p. 71.

m.p. 232°(d.) separated directly from the reaction mixture. To 376 mg. of this crude *p*-toluenesulfonyl hydrazone was added a previously prepared solution containing 1.7 g. of sodium in 50 ml. of ethylene glycol, and the reaction mixture was allowed to reflux for 1.5 hours under nitrogen. The reaction mixture was cooled, diluted with water, and extracted exhaustively with ether. The ether layer was washed with dilute aqueous hydrochloric acid and with water. The ether was evaporated *in vacuo* and the residue was crystallized from ethanol–water, yielding 145.5 mg. of Δ^7-cholesten-3β-ol, m.p. 108–115° (43% from 3β-acetoxycholestan-7-one). Purification was effected by chromatography on a column of alumina, Δ^7-cholesten-3β-ol being eluted with 3–2 benzene–ether, m.p. 120–123°, $[\alpha]^{26}D$ −3° (chloroform) (lit.[29] m.p. 123°, $[\alpha]D$ ±0°).

(29) Fr. Schenck, K. Buchholz and O. Wiese, *Ber.*, **69**, 2696 (1936).

Deuterium analyses were performed by combustion of the organic sample and isotopic analysis of the water formed by the "falling drop" method.[30] The isotope position analyses were calculated from the infrared spectrum of the unknown sample and the spectra of 6α- and 6β-deutero-3β-acetoxycholestan-7-one which were obtained from zinc–deuterium bromide reduction of 6α-bromo-3β-acetoxycholestan-7-one and by the synthesis shown in Fig. 2, respectively, using optical densities at ν_{max}. The spectra of these epimeric 6-deutero-7-ketones are recorded in Fig. 4.

(30) A. S. Keston, D. Rittenberg and R. Schoenheimer, *J. Biol. Chem.*, **122**, 227 (1942).

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Steroid Total Synthesis—Hydrochrysene Approach. I. General Plan and Summary of Major Objectives

BY WILLIAM S. JOHNSON

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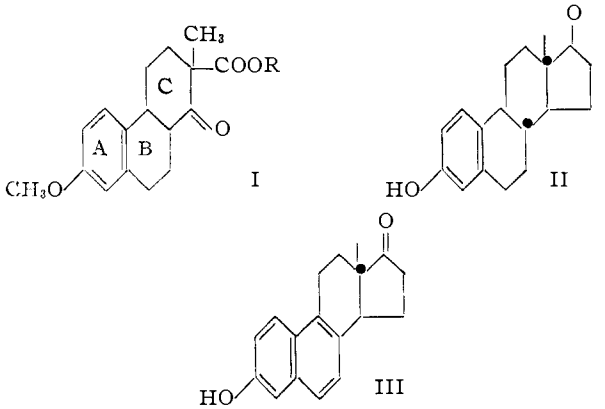
This introductory paper of the series includes a general description of the development of the synthetic plan and a treatment of the major stereochemical problems.

In the early 1930's as the last pieces of the intricate puzzle of the structure of the steroid nucleus were being fitted into place, organic chemists were already initiating studies directed toward the fabrication of this unique honeycomb of carbon atoms with latent physiological potency of wonderful and far-reaching significance. As early as 1936, Robinson and his collaborators[1] had produced a key tricyclic (ring ABC) intermediate I and were clearly already well along toward the completion of the fourth ring D to produce the estrone structure II. But success was not close at hand. The extraordinary difficulties attending the total synthesis of this molecule with four asymmetric centers (*i.e.*, 16 possible isomers) were mainly stereochemical in nature, as emphasized by the fact that a dozen years intervened, during which major contributions were made by various laboratories as described below, before the objective was finally realized.



(1) R. Robinson and E. Schlittler, *J. Chem. Soc.*, 1288 (1935), and R. Robinson and J. Walker, *ibid.*, 747 (1936). For an excellent review of the total synthesis of steroids see J. W. Cornforth, *Prog. Org. Chem.*, **3**, 1 (1955).

Bachmann and his collaborators played a vital role in the early development of the field; indeed Bachmann, Cole and Wilds were the first to accomplish the total synthesis of a natural steroid, equilenin (III), in 1939.[2] This hormone, the simplest of the known steroids, contains one angular methyl group and two centers of asymmetry. All four optical isomers have been prepared.[2] Employing some of the techniques developed in the equilenin synthesis, Bachmann, Kushner and Stevenson[3] turned their hand to the estrone problem and in 1942 published an account of the total synthesis of one of the seven possible unnatural racemates; then the ensuing war years interrupted most of the progress in the field. A relay of efforts to the laboratories of Miescher saw the old keto ester I prepared in quantity, separated into three of its four possible racemic modifications and converted into estrones by the Bachmann sequence for attaching ring D. Thus in 1948, Anner and Miescher[4] announced the total synthesis of estrone and several stereoisomers. Two years later Johnson, Banerjee, Schneider and Gutsche[5] disclosed a fundamentally different synthetic approach which led to the natural hormone as well as to some further stereoisomers. By now seven of the eight possible racemates represented by formula II have been prepared and their configurations proved.[6] A third highly stereoselective approach to estrone was dis-

(2) W. E. Bachmann, W. Cole and A. L. Wilds, THIS JOURNAL, **61**, 974 (1939); **62**, 824 (1940).

(3) W. E. Bachmann, S. Kushner and A. C. Stevenson, *ibid.*, **64**, 974 (1942).

(4) G. Anner and K. Miescher, *Experientia*, **4**, 25 (1948); *Helv. Chim. Acta*, **31**, 2173 (1948); **32**, 1957 (1949).

(5) W. S. Johnson, D. K. Banerjee, W. P. Schneider and C. D. Gutsche, THIS JOURNAL, **72**, 1426 (1950); W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg and L. J. Chinn, *ibid.*, **74**, 2832 (1952).

(6) W. S. Johnson, I. A. David and W. F. Johns, unpublished work.