[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE RICE INSTITUTE]

Heats of Hydrogenation. II. Heats of Hydrogenation and the Acid-catalyzed Isomerization of Some Unsaturated Steroids[1]

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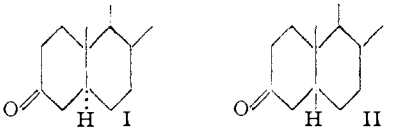
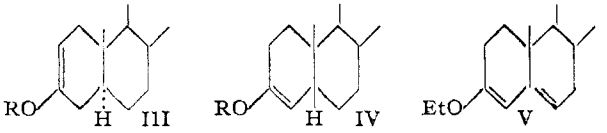
The heats of hydrogenation of cholest-1-ene, cholest-2-ene, cholest-3-ene, cholest-5-ene, cholest-6-ene and of 3α-hydroxy-Δ^{11}-cholenic acid have been determined and correlated with conformational properties of these molecules. The observed stability order—$\Delta^2 \simeq \Delta^5 > \Delta^1 \simeq \Delta^6 > \Delta^3 > \Delta^{11}$—is consistent with various observations made in connection with a study of acid-catalyzed double bond migration in these systems.

In connection with a general program dealing with measurements of heats of catalytic hydrogenation in solution, the heats of hydrogenation of several steroid olefins have been determined. The results provide a quantitative measure of stability relationships among olefins possessing double bonds at various positions in a fused ring system. The experimental procedure employed in this investigation has been described in the first paper of this series[2] and requires no further discussion. As a supplement to the hydrogenation experiments, a study of the isomerization of steroid olefins under conditions of acid catalysis also was undertaken. The results of these two lines of investigation are reported in the present communication.

It has been known for many years that monobromination of cholestan-3-one (I) furnishes mainly 2-bromocholestan-3-one, whereas monobromination of coprostan-3-one (II) yields 4-bromocoprostan-3-one as the only isolable product.[3] Similar directional specificity is encountered in sulfonation of the two ketones[4] and in various other allied reactions. Since the bromination reaction has been shown to involve an enol intermediate,[5] the demonstration that cholestan-3-one furnishes enol derivatives (ethers and esters) of structure III, whereas coprostan-3-one yields analogous derivatives of structure IV,[6] is of special relevance in this connection. Particularly noteworthy is the fact that partial catalytic hydrogenation of cholestenone enol ether (V) yields III (R = C_2H_5) with double bond migration rather than the expected Δ^3-isomer.[6b] It may therefore be concluded that a double bond at the 2,3-position of the cholestane nucleus is energetically favored over a double bond at the 3,4-position and that the converse is true for the corresponding olefins of the coprostane series.





Examination of molecular models of coprost-2-ene and of coprost-3-ene reveals a severe steric compression of the 4α- and 7α-hydrogen atoms in coprost-2-ene, which has no counterpart in the Δ^3-isomer and which may be expected to contribute to the thermodynamic instability of the Δ^2-olefin. Other conformational aspects of the coprostene problem have been discussed by Taylor[7] in terms of properties of the *cis*-octalins. The origins of the apparent energy difference between cholest-2-ene and cholest-3-ene recently have been dealt with by Corey and Sneen[8] and are considered further from a slightly different point of view in a later section of this paper.

Directional specificity of the type noted above also has been observed in various derivatives of *cis*- and *trans*-decalin. Thus, dehydration of *trans*-2-decalol over potassium bisulfate yields almost pure *trans*-2-octalin, whereas similar treatment of *cis*-2-decalol affords a mixture in which *cis*-1-octalin represents the major component.[9] Substitution reactions of *trans*-2-decalone occur mainly at the 3-position, but the situation with respect to *cis*-2-decalone is less well defined. Chlorination of this substance gives, in low yield, a product that has been formulated as a 3-chloro derivative.[10] Great caution must therefore be exercised in extrapolating stability relationships from one series of compounds to another, in spite of the existence of close structural similarities.[11,12]

(1) The work described in this paper was supported by funds made available by the Eli Lilly Co. and by the Research Corporation.

(2) R. B. Turner, W. R. Meador and R. E. Winkler, THIS JOURNAL, 79, 4116 (1957).

(3) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935).

(4) A. Windaus and E. Kuhn, *Ann.*, **532**, 52 (1937); A. Windaus, and K. H. Mielke, *ibid.*, **536**, 116 (1938).

(5) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 231.

(6) (a) H. H. Inhoffen, G. Stoeck, G. Kölling and V. Stoeck, *Ann.*, **568**, 52 (1950); (b) H. H. Inhoffen, W. Becker and G. Kölling, *ibid.*, **568**, 181 (1950); (c) W. G. Dauben, R. A. Micheli and J. F. Eastham, THIS JOURNAL, **74**, 3852 (1952).

(7) D. A. H. Taylor, *Chemistry & Industry*, 250 (1954).

(8) E. J. Corey and R. A. Sneen, THIS JOURNAL, **77**, 2505 (1955).

(9) W. Hückel, R. Danneel, A. Schwartz and A. Gerke, *Ann.*, **474**, 121 (1929).

(10) The observation of J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 817 (1937), that condensation of *cis*-2-decalone with ethyl oxalate occurs at the 3-position can be explained in terms of product equilibrium and is hence not relevant to the present discussion; *cf.* G. Stork and R. K. Hill, THIS JOURNAL, **79**, 495 (1957).

(11) *Cf.* G. Stork and A. W. Burgstahler, THIS JOURNAL, **77**, 5068 (1955).

(12) With reference to the structural analogy drawn between coprostan-3-one and *cis*-2-decalone, it will be noted that whereas the steroid ring system is relatively rigid, owing to constraints imposed by the *trans* fusion between rings B and C, the conformational mobility of *cis*-2-decalone is not thus restricted. The entropy contribution to free energy will thus assume greater importance in the *cis*-decalin than in the coprostane series, while this differentiation between *trans*-decalin derivatives and cholestane derivatives should be less marked. Arguments based solely on steric interactions that have been advanced in connection with the coprostanone problem will not necessarily hold with equal force for *cis*-2-decalone, particularly since relief of steric strains will be accomplished more easily in the more flexible molecule.

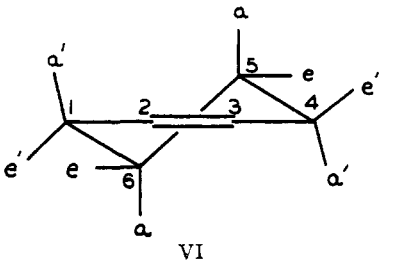
Hydrogenation Data.—The values for the heats of hydrogenation (acetic acid solution, 25°) of six steroid olefins are given in Table I. The precision of the results obtained in this series was limited by the amounts of material that could be employed in view of the relatively low solubility of these substances and of the reduction product, cholestane, in acetic acid. Cholest-4-ene was not included in this investigation, since catalytic hydrogenation of this derivative yields a mixture of stereoisomers.

All of the substances in question possess an olefinic double bond in a six-membered ring, and, with the exception of cholest-5-ene, all are of the *cis*-disubstituted type. The relatively large differences in heat content observed in this series—3 kcal. in the case of compounds 2 and 6—are therefore of considerable interest. In this connection it should be noted that the resonance energy calculated for butadiene from hydrogenation data is 3.5 kcal./mole[13] and that resonance coupling of the benzene ring and vinyl group in styrene results in additional stabilization of only 1.6 kcal./mole.[14] It is evident that steric effects of a rather subtle nature may often overshadow the resonance effect.

The lowest heats of hydrogenation, and hence maximum thermodynamic stabilities, are encountered in the Δ^2- and Δ^5-cholestenes, the values obtained for these substances being indistinguishable within the limits of experimental error. Catalytic hydrogenation of 5:6-unsaturated steroids is known to yield mainly A/B *trans*-fused products, but small amounts (2–4%) of the corresponding A/B *cis* derivatives have been obtained in isolated instances.[15] However, since the energy difference between cholestane (A/B *trans*) and coprostane (A/B *cis*) is small (~ 0.8 kcal./mole),[16] the formation of a few per cent. of coprostane in the reduction of cholest-5-ene should not compromise comparison of the heat of hydrogenation of this substance with that of cholest-2-ene, which yields only cholestane. On the basis of the substitution effect, cholest-5-ene (trisubstituted) should be more stable than cholest-2-ene (disubstituted) by about 1.5 kcal./mole.[17] The 5:6-double bond is, however, exocyclic to ring A, and it is clear from the hydrogenation data that a positional effect of approximately the same magnitude must operate in favor of cholest-2-ene.

The difference in the heats of hydrogenation of cholest-2-ene and cholest-3-ene is 2.1 kcal./mole. The direction of the energy difference establishes the fact that cholest-2-ene is the more stable isomer, and the magnitude of the effect provides an adequate basis for interpretation of the directional specificity observed in the various enol reactions noted previously. The discrepancy between the result obtained for cholest-2-ene (−25.9 kcal./mole) and the heat of hydrogenation of cyclohexene (−27.1 kcal./mole)[2] is presumably attributable in large part to interactions of the axial C.10 methyl group of cholestane with axial hydrogen atoms, which interactions are replaced by hydrogen–hydrogen repulsions in the case of cyclohexane.[18]

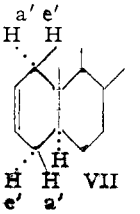
The stability difference between cholest-2-ene and cholest-3-ene has been ascribed by Corey and Sneen[8] to a reduction of the distance separating the C.10 methyl group and the C.6 β-hydrogen atom in the latter compound. An equivalent, but less detailed, treatment of the problem can be given as follows. The preferred conformation adopted by cyclohexene is now generally regarded as the "half-chair" conformation VI, in which carbon atoms 1, 2, 3 and 4 lie in a single plane.[19] The substituent groups attached to carbon atoms 5 and 6 are staggered with respect to each other and are hence considered to have the axial and equatorial properties associated with similarly situated substituents in cyclohexane.



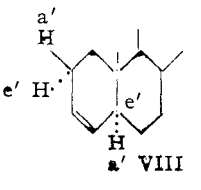
VI

On the other hand, distortion of the molecule necessitated by the planar arrangement of carbon atoms 1–4 forces the substituents on carbon atoms 1 and 4 into partial eclipse with those on carbons 6 and 5, respectively. Atoms or groups attached to carbon atoms adjacent to a double bond are hence neither truly axial nor truly equatorial and are termed quasi-axial (a′) and quasi-equatorial (e′) as the case may be.

With reference to cholest-2-ene (VII), the a′,e′ bonds are all attached to hydrogen, and as a consequence the conformation of ring B is essentially unaffected. On the other hand, in cholest-3-ene (VIII) the 5:6-bond must be quasi-equatorial with respect to ring A if the double bond is planar, and ring B is therefore forced into a deformed "chair" conformation with resultant increase in strain.



VII



VIII

Conversely, restoration of the most favored con-

(13) G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, THIS JOURNAL, 58, 146 (1936).

(14) M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky and W. E. Vaughan, *ibid.*, 59, 831 (1937).

(15) T. Reichstein and A. Lardon, *Helv. Chim. Acta*, 24, 955 (1941); E. B. Hershberg, E. Oliveto, M. Rubin, H. Staeudle and L. Kuhlen, THIS JOURNAL, 73, 1144 (1951).

(16) R. B. Turner, *ibid.*, 74, 2118 (1952).

(17) J. B. Conant and G. B. Kistiakowsky, *Chem. Revs.*, 20, 181 (1937).

(18) It is of interest to note that the energy difference between axial and equatorial methyl groups in the 6-membered ring has been estimated as 1.8 kcal./mole by S. Winstein and N. J. Holness, THIS JOURNAL, 77, 5562 (1955).

(19) C. W. Beckett, N. K. Freeman and K. S. Pitzer, *ibid.*, 70, 4227 (1948); D. H. R. Barton, R. C. Cookson, W. Klyne and C. W. Shoppee, *Chemistry & Industry*, 21 (1954).

TABLE I

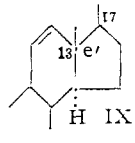
HEATS OF HYDROGENATION OF VARIOUS STEROID OLEFINS (ACETIC ACID, 25°)

No.	Compound	Mmoles	PtO_2, mg.	$-\Delta H$, kcal./mole
1	Cholest-1-ene	1.375	99.7	27.08
		1.354	99.8	27.52
		Average		27.30 ± 0.24[a]
2	Cholest-2-ene	1.078	99.9	25.81
		1.379	100.0	26.01
		0.921	99.8	25.73
		Average		25.85 ± 0.17
3	Cholest-3-ene	1.370	99.0	28.04
		1.290	99.0	27.74
		1.046	99.6	28.08
		Average		27.97 ± 0.14
4	Cholest-5-ene	1.352	99.6	25.77
		1.323	100.0	25.92
		Average		25.85 ± 0.13
5	Cholest-6-ene	1.304	100.0	27.43
		1.337	99.7	27.28
		Average		27.36 ± 0.10
6	3α-Hydroxy-Δ^{11}-cholenic acid	2.065	99.8	29.10
		2.087	100.3	28.85
		2.098	99.7	28.84
		Average		28.93 ± 0.15

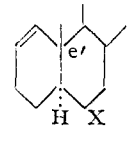
[a] Deviations include uncertainty in the heat of hydrogenation of the catalyst.

formation in ring B must lead to torsional strain in the 3:4-double bond.

Extension of this reasoning to cholest-6-ene, which possesses a double bond adjacent to two *trans* fusions, would suggest that this substance should be thermodynamically less stable than cholest-3-ene, in which only one *trans* fusion is directly involved. Comparison of the heats of hydrogenation of these compounds, however, indicates that cholest-6-ene is more stable than cholest-3-ene by a small, but experimentally significant, amount. A rationalization of this apparent anomaly can be derived from examination of the cholest-6-ene model. In this substance the deformation of ring C, brought about by the presence of a planar olefinic linkage at the 6:7-position, is such that the transoid character of the C/D fusion is somewhat reduced. In the case of 3α-hydroxy-Δ^{11}-cholenic acid (IX), however, introduction of a quasi-equatorial bond at the 13:17-position increases the transoid character of the C/D fusion with resultant increase in strain, and this substance possesses



IX



X

the highest heat of hydrogenation (lowest stability) of any compound in the series.

A small difference was also observed between the heats of hydrogenation of cholest-1-ene and cholest-3-ene, indicating a slightly greater stability for the Δ^1-isomer. Both olefins contain a double bond adjacent to a single *trans* fusion, and the structural factors responsible for the difference in heats of hydrogenation are difficult to assess. It may be noted, however, that in cholest-1-ene the bulky C.10 methyl group possesses an a′-orientation and that in this molecule, but not in cholest-3-ene, conformational effects associated with ring A are directly transmitted to ring C through a quasi-equatorial bond (*cf.* X).

No mention has thus far been made of the part that hyperconjugation may play in determining stability relationships in this series. Since the relative abilities of a′ and e′ hydrogen atoms to participate in hyperconjugation have not been established,[20] any consideration of the hyperconjugative phenomenon is subject to considerable uncertainty. Although it is clear from the data of Table II that more hydrogens are available for possible hyperconjugation in the most stable, than in the least stable, olefins, we do not feel that any useful generalization of this information can be made at the present time.

TABLE II

STABILITY ORDER AND α-HYDROGEN BOND TYPE

Stability order	$\Delta^2 \simeq \Delta^5$	>	$\Delta^1 \simeq \Delta^6$	>	Δ^3	>	Δ^{11}
No. of a′ hydrogens	2	2	1	2	2		1
No. of e′ hydrogens	2	2	1	0	1		0

In 1954, Henbest, Meakins and Wood[21] reported a stability order ($\Delta^2 > \Delta^3 \simeq \Delta^1 > \Delta^6 > \Delta^{11}$) for the cholestenes based upon examination of the infrared spectra of these compounds in the olefinic stretching and C–H out-of-plane bending regions. The principal difference between the order proposed by the British investigators and that derived from the hydrogenation data (Table II) lies in the position assigned to cholest-3-ene. Now the strain introduced in these molecules by the presence of unsaturation will be distributed over torsional strain in the olefinic linkages, angle strain in tetrahedral and trigonal bonds and steric strain associated with non-bonded repulsive interactions in such a way that the total energies of the molecules will be minimized. It is not surprising, therefore, that heat of hydrogenation differences, which as a first approximation reflect total energy differences, should give a stability order at variance with the infrared measurements, which are concerned mainly with strain in the double bonds.

Acid-catalyzed Isomerizations.—In addition to the hydrogenation experiments discussed in preceding paragraphs, the behavior of various cholestenes in the presence of acid has been investigated. This work was originally undertaken in the hope that equilibria could be established, which would furnish quantitative data on free energy relationships in this series. However, owing to the intervention of skeletal rearrangement, this hope was realized only for the cholest-4-ene–cholest-5-ene system, and the information that has been obtained is therefore of qualitative rather than of quantitative interest.

When cholest-5-ene is treated with *p*-toluenesulfonic acid in a refluxing mixture of acetic acid

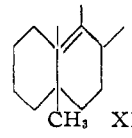
(20) *Cf.* A. Streitwieser, R. H. Jagow and S. Suzuki, THIS JOURNAL, **77**, 6713 (1955); S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955); V. J. Shiner, *ibid.*, **78**, 2653 (1956).

(21) H. B. Henbest, G. D. Meakins and G. W. Wood, *J. Chem. Soc.*, 800 (1954).

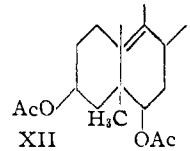
and cyclohexane (85°), it is rapidly converted into an oily mixture containing both cholest-5-ene and cholest-4-ene as indicated by infrared analysis. No other components, for example acetate esters or other double bond isomers, are spectrophotometrically detectable, and the specific rotation of the product (−17.5°) suggests the presence in the mixture of approximately 55% of cholest-4-ene and 45% of cholest-5-ene, corresponding to a free energy difference of only 0.1 kcal./mole. The infrared spectrum of a synthetic mixture of this composition is indistinguishable from that of the isomerization product. Similar treatment of cholest-4-ene affords identical material, and since no further change is effected by prolonged heating with acid under the conditions specified above, the isomerization product is regarded as an equilibrium mixture.

Treatment of the equilibrium mixture, or of either pure olefin, with *p*-toluenesulfonic acid in refluxing acetic acid for 2.5 hr., results in the formation of a colorless oil, which has resisted all attempts at crystallization. Although this product appears to be chromatographically homogeneous, it is not unlikely that the material represents a mixture of two or more substances. Unsaturation was demonstrated by the tetranitromethane test, and examination of the ultraviolet spectrum of the tetranitromethane treated material indicated the presence of a tetrasubstituted double bond.[22] Support for this conclusion is derived from the failure of the product to undergo catalytic hydrogenation under normal conditions. Hydrogenation can, however, be accomplished under forcing conditions,[23] and the oily product obtained in this way proved to be saturated in the tetranitromethane test.

In intact cholestane or coprostane structures only three positions, 8:9, 8:14 and 17:20, can accommodate a tetrasubstituted double bond. The 17:20-position is unlikely in view of the general difficulty encountered in the introduction of a tetrasubstituted double bond in this position[24] and would further appear to be excluded by the observation that both cholest-7-ene and cholest-8:14-ene furnish a different isomerization product. Examination of the infrared spectrum of the reduced material revealed no detectable amounts of cholestane or coprostane. Since forced hydrogenation of 8:9- and of 8:14-cholestene and coprostene derivatives leads to the formation of the corresponding cholestanes and coprostanes, respectively,[23,25] it follows that the tetrasubstituted olefin described above must be formed by skeletal rearrangement. The most reasonable suggestion that can be made regarding the structure of this material is that it represents the product of Wagner–Meerwein rearrangement (XI) involving intermediate formation of a C.5 carbonium ion followed by migration of the C.10-methyl group. The resulting 9:10-olefin can, of course, equilibrate the corresponding 8:9- and 8:14-unsaturated derivatives. An analogy for such a rearrangement is available in the observation that cholestane-3β,5α,6β-triol 3,6-diacetate



XI



XII

undergoes rearrangement on acid-catalyzed dehydration to yield a substance for which structure XII has been established with reasonable certainty.[26]

Cholest-1-ene, cholest-2-ene, cholest-3-ene and cholest-6-ene, on treatment with *p*-toluenesulfonic acid in acetic acid-cyclohexane at 85°, are unaffected apart from the appearance of small amounts of acetate esters formed by addition of acetic acid to the double bonds. These observations are consistent with the fact that secondary carbonium ions, obtained by proton addition to the four olefins noted above, are less stable than the tertiary carbonium ion derived from cholest-4-ene and cholest-5-ene. The appearance of acetate ester in the absence of isomerization is in accord with the suggestion that olefin addition reactions can occur by a mechanism in which conventional carbonium ion intermediates are not involved.[27]

Under more vigorous conditions (*p*-toluenesulfonic acid in refluxing acetic acid), cholest-1-ene, cholest-2-ene, cholest-3-ene and cholest-6-ene are all slowly transformed into material which, after removal of acetate esters, shows infrared absorption characteristics identical with those of product XI. Interruption of the cholest-1-ene and cholest-3-ene isomerizations at an intermediate stage gives, after removal of esters, material consisting very largely of cholest-2-ene, as indicated by infrared analysis. The predominance of cholest-2-ene in these cases is consistent with the results of the hydrogenation experiments, which establish that this olefin is more stable than the Δ^1- and Δ^3-isomers by 1.5 and 2.1 kcal./mole, respectively. It is of interest to note that cholest-3-ene is converted into XI with prior isomerization into cholest-2-ene, rather than directly through cholest-4-ene.

The rearrangement of cholest-6-ene into product XI is regarded as proceeding through cholest-5-ene as an intermediate. The particular point of interest that arises in this connection is the preference of the Δ^6-olefin for isomerization in this direction as opposed to isomerization and rearrangement *via* cholest-7-ene. A possible explanation for this observation may be found in the fact that the C.7 carbonium ion, formed by proton addition at C.6, possesses a 1,3-diaxial methyl–hydrogen interaction that is absent in the C.6 carbonium ion, obtained by attack at C.7. As a corollary to this argument, it will be observed that proton addition (a) in the axial sense at C.6 (see XIII) is sterically

(22) E. Heilbronner, *Helv. Chim. Acta*, **36**, 1121 (1953).

(23) A. Windaus and G. Zühlsdorff, *Ann.*, **536**, 204 (1938).

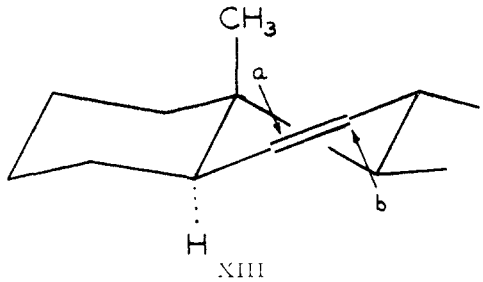
(24) B. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944); O. Dalmer, F. v. Werder, H. Honigmann and K. Heyns, *Ber.*, **68**, 1814 (1935).

(25) J. C. Eck and E. W. Hollingsworth, THIS JOURNAL, **63**, 2986 (1941); R. B. Turner and E. C. Kendall, unpublished results.

(26) V. A. Petrow, O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 677 (1938); V. A. Petrow, *ibid.*, 998 (1939); P. Bladon, H. B. Henbest and G. W. Wood, *ibid.*, 2737 (1952).

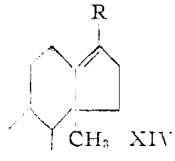
(27) G. S. Hammond and T. D. Nevitt, THIS JOURNAL, **76**, 4121, 4124 (1954); D. H. R. Barton and E. Miller, *ibid.*, **72**, 370, 1066 (1950).

hindered by the C.10 methyl group, whereas approach of a proton as in (b) is unencumbered.[28]



XIII

Treatment of cholest-7-ene with *p*-toluenesulfonic acid in acetic acid–cyclohexane at 85° results in rapid conversion of this compound into a noncrystalline mixture in which cholest-8:14-ene predominates. Prolonged treatment of the mixture, or of pure cholest-8:14-ene, under these conditions furnishes an unsaturated oil with infrared absorption characteristics differing from those of the starting materials and of product XI. As in the case of XI, the material possesses a tetrasubstituted double bond,[22] and on forced hydrogenation it furnishes a saturated, amorphous substance in which the presence of traces of cholestane can be detected by infrared measurements. However, since cholestane is a minor constituent of the reduction product, it seems reasonable to assume that the tetrasubstituted olefin consists mainly of rearrangement products of type XIV.



XIV

Double bond isomerizations in the steroid series, particularly those involving the 7:8-, 8:9-, 8:14 and 14:15-positions are well known and are conventionally brought about by saturated solutions of hydrogen chloride in chloroform.[29] In no previous case, however, has the problem of skeletal rearrangement received attention, and the observations that have been made in connection with this investigation may be taken as a warning that such rearrangements occur under relatively mild conditions. It seems probable that the poor yields encountered in hydrogen chloride–chloroform isomerizations that are not conducted at low temperature may be attributed to this phenomenon.

Experimental[30]

Materials.—**Cholest-1-ene**, m.p. 68–69°, $[\alpha]_D$ +12° (*c* 1.5, chloroform) was prepared from cholest-1-en-3-one by a procedure developed by Henbest.[31] The conjugated ketone was reduced with lithium aluminum hydride, and the resulting unsaturated alcohol was converted into the corresponding 3-chloro derivative by treatment with thionyl chloride. Reductive removal of chlorine with lithium aluminum hydride furnished a crude sample of the desired olefin. Final purification was accomplished by recrystallization of the dibromide, m.p. 134–136°, from which pure cholest-1-ene was obtained by the action of zinc dust in acetic acid.

Cholest-2-ene was prepared by the method of Fieser and Dominguez.[32] The crude olefin was purified through the dibromide, m.p. 124–125°, from which cholest-2-ene, m.p. 74–75°, $[\alpha]_D$ +69.7° (*c* 0.9, chloroform), was regenerated by treatment with zinc and ethanol.

Preparation of **cholest-3-ene** was carried out according to the procedure of Lardelli and Jeger.[33] The product obtained in this way, after purification through the dibromide, m.p. 123–124°, melted at 73.5–74.5°, $[\alpha]_D$ +58.2° (*c* 0.9, chloroform): literature values, 72–73°, $[\alpha]_D$ +65° (chloroform)[33]; 72–72.5°, $[\alpha]_D$ +57° (chloroform).[34]

Cholest-4-ene, m.p. 80–83°, $[\alpha]_D$ +66° (*c* 1.0, chloroform) was synthesized as described by Barton and Rosenfelder.[34]

Cholest-5-ene was obtained by sodium–alcohol reduction of cholesteryl chloride as described by Mauthner and Suida.[35] Crystallization of the crude product from ether–methanol afforded material melting at 92–94°, $[\alpha]_D$ −55.0° (*c* 1.5, chloroform).

The preparation of **cholest-6-ene** was accomplished by a modification of the procedure reported by Cremlyn and Shoppee.[36] A solution of 80.0 g. of 7-ketocholesteryl acetate in 2 l. of benzene containing 80.0 g. of *p*-toluenesulfonic acid was heated under reflux in a nitrogen atmosphere for 7 hr. The solution was then cooled, diluted with ether and washed successively with water, dilute sodium carbonate solution, water and a saturated solution of sodium chloride. After drying over magnesium sulfate and removing the solvents, the residual material was crystallized, first from ethanol and then from acetone. Fifty grams of cholesta-3,5-dien-7-one, m.p. 112–114°, was obtained in this way.

A solution of 20.0 g. of dienone in 200 ml. of ether and 250 ml. of acetic acid was stirred with 2.0 g. of platinum oxide catalyst in an atmosphere of hydrogen for 14 hr., at the end of which time the absorption of hydrogen had ceased. The catalyst was removed by filtration, and the filtrate was diluted with ether and washed with water and dilute sodium hydroxide solution. After drying, the solvent was removed under reduced pressure, and the residual material was chromatographed on alumina. Cholestan-7α-ol (4.4 g.), m.p. 90–94°, was obtained from the petroleum ether–benzene eluates.[37] Two recrystallizations from acetone afforded 3.4 g. of pure material melting at 95–97°. Benzoylation furnished 2.9 g. of the corresponding benzoate as long needles, m.p. 158–160°. A further 940 mg., m.p. 155–158°, was obtained as a second crop.

Pyrolysis of the benzoate (2.47 g.) was carried out under reduced pressure at a bath temperature of 400°. The total crude product, after removal of the benzoic acid, was chromatographed on alumina, whereupon 1.43 g. of pure cholest-6-ene, m.p. 84–85°, $[\alpha]_D$ −84.3° (*c* 1.56, chloroform) was obtained.

Cholest-7-ene has been prepared by Cremlyn and Shoppee[36] by chromatography of the *p*-toluenesulfonyl derivative of cholestan-7β-ol on neutral or alkaline alumina. Four grams of cholestan-7β-ol, m.p. 110–113.5°, obtained in the preceding experiment, was converted into the corresponding tosylate and passed through a column of neutral alumina. The hydrocarbon fraction was reserved for subsequent purification, and the cholestan-7α-ol formed simultaneously was removed from the column and recycled, either by oxidation to cholestan-7-one followed by sodium–alcohol reduction or by epimerization with sodium butylate.[36]

(28) Mechanisms for double bond migration other than the one pictured here can also be formulated, *e.g.*, isomerization through bridged ion intermediates and concerted isomerization–rearrangement processes. The carbonium ion mechanism is employed for illustrative purposes for reasons of simplicity.

(29) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 248.

(30) All melting points are corrected. Infrared spectra were measured in carbon disulfide solution on a Perkin–Elmer model 12C infrared spectrometer.

(31) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).

(32) L. F. Fieser and X. A. Dominguez, THIS JOURNAL, **75**, 1704 (1953).

(33) G. Lardelli and O. Jeger, *Helv. Chim. Acta*, **32**, 1817 (1949).

(34) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

(35) J. Mauthner and W. Suida, *Monatsh.*, **15**, 85 (1894).

(36) R. J. W. Cremlyn and C. W. Shoppee, *J. Chem. Soc.*, 3515 (1954).

(37) Later fractions contained cholestan-7β-ol, which was utilized for the preparation of cholest-7-ene.

The total olefin obtained in this way, after recrystallization from acetone and from ether-methanol, melted at 85.8–87°, $[\alpha]_D$ +6°. The infrared spectrum indicated contamination by small amounts of cholest-6-ene, which could not be removed by repeated crystallization.[38] The product was finally rechromatographed on alkaline alumina and, after several passes, a sample, m.p. 86–87°, $[\alpha]_D$ +11.7°, free of cholest-6-ene was obtained.

Cholest-8:14-ene, m.p. 53.5–55°, $[\alpha]_D$ +20° (*c* 1.0, chloroform) was prepared from cholest-7-ene by isomerization over palladium (hydrogenation conditions) as described by Eck and Hollingsworth.[25]

The 3α-hydroxy-Δ^{11}-cholenic acid employed in this investigation was a purified sample, m.p. 165–166°, of material prepared some years ago at the laboratories of Merck and Co., Rahway, N. J.

Acid Isomerization at 85°.—A solution of the olefin and an equal weight of *p*-toluenesulfonic acid in a mixture of acetic acid and cyclohexane (4:1, 6 ml. of solvent for 30 mg. of olefin) was heated to reflux temperature in an electrically heated oil-bath in a flask fitted with a thermometer extending below the surface of the solution. At the end of the selected heating period, the solution was poured into dilute sodium hydroxide, and the aqueous layer was extracted three times with petroleum ether. The combined organic fractions were then washed with dilute alkali, water, saturated sodium chloride and filtered through anhydrous magnesium sulfate. After evaporation of the solvent, the product was twice dissolved in carbon disulfide and taken to dryness in order to ensure removal of the last traces of hydrocarbon solvent prior to infrared analysis.

(38) Cremlyn and Shoppee obtained pure cholest-7-ene directly from the alumina column.

Acid Isomerization at 120°.—The procedure employed for isomerizations at the higher temperature resembled that described above, except that after the reflux temperature had been reached, about 30% of the solvent was distilled off. The cyclohexane and water passed over as an azeotrope, and the temperature of the solution rose to about 120°. When reactions were carried out in acetic acid alone, without removal of small amounts of water that are present under these conditions, the results obtained were erratic. At the end of the reaction period, the products were isolated as before, and the acetate esters were removed by chromatography on alumina before infrared analysis of the hydrocarbon fractions.

Hydrogenation of Product XI.—A sample of product XI was dissolved in 40 ml. of acetic acid–cyclohexane (4:1) and stirred in a hydrogen atmosphere with pre-reduced platinum oxide catalyst. No hydrogen was absorbed, and the recovered material proved to be unsaturated in the tetranitromethane test. The experiment was then repeated with 200 mg. of XI in 35 ml. of acetic acid–cyclohexane (4:1), to which 4 drops of 12 *N* hydrochloric acid was added. After 42 hr. at 60°, 110% of the calculated amount of hydrogen had been absorbed, and the product gave no reaction with tetranitromethane. The infrared absorption spectra of the reduced material showed no detectable amounts of cholestane or of coprostane.

Hydrogenation of Product XIV.—Hydrogenation was carried out at 60° with added hydrochloric acid as described in the preceding experiment. The reaction product showed a negative tetranitromethane test for unsaturation, and the infrared spectrum gave evidence of the presence of small amounts of cholestane.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE RICE INSTITUTE AND OF YALE UNIVERSITY AND FROM THE HICKRILL CHEMICAL RESEARCH FOUNDATION]

Heats of Hydrogenation. III. Hydrogenation of Cycloöctatetraene and of Some Seven-membered Non-benzenoid Aromatic Compounds[1]

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The heats of hydrogenation of several potentially aromatic substances have been measured in solution, and resonance energies have been estimated by comparison of the heats of hydrogenation of these compounds with heats calculated for reasonable models. The compounds that have been examined together with the ΔH values and calculated resonance energies are as follows: cycloöctatetraene ($-\Delta H$ 97.96 ± 0.05 kcal./mole, R.E. 2.4 kcal./mole), 1,3,5-cycloöctatriene ($-\Delta H$ 72.36 ± 0.26 kcal./mole, R.E. 0.9 kcal./mole), azulene ($-\Delta H$ 98.98 ± 0.13 kcal./mole, R.E. 28 kcal./mole), heptafulvene ($-\Delta H$ 92.63 ± 0.41 kcal./mole, R.E. 13 kcal./mole), heptafulvalene ($-\Delta H$ 130.77 ± 0.31 kcal./mole for six molar equivalents of hydrogen, R.E. 28 kcal./mole), dihydroheptafulvalene ($-\Delta H$ 138.81 ± 0.20 kcal./mole) and tropone ($-\Delta H$ 67.58 ± 0.30 kcal./mole to cycloheptanone).

Since the heats of hydrogenation of benzene, and of various related substances including styrene, hydrindene and furan, were measured by Kistiakowsky and his associates[2] some twenty years ago, no further studies of heats of hydrogenation in the aromatic series have been reported. In the meantime several potentially aromatic compounds of considerable theoretical interest have been prepared in sufficiently pure condition for hydrogenation studies. Of these substances cycloöctatetraene, azulene, methylenecycloheptatriene (heptafulvene), cycloheptatrienylidenecycloheptatriene (heptafulvalene), 7-(7′-cycloheptatrienyl)-cycloheptatriene (dihydroheptafulvalene) and cycloheptatrienylium oxide (tropone) have now been examined in the hydrogenation calorimeter.

Experimental

The technique for measurement of heats of hydrogenation in solution described in Paper I[3] was employed in the present investigation with the following modifications. In the cases of heptafulvene and heptafulvalene, Diethylcarbitol was used as the solvent, since these substances are subject to rapid polymerization in acetic acid. Despite extensive purification of the Diethylcarbitol, reduction of the platinum oxide catalyst gave higher heat values in this solvent (−32.94 ± 0.21 cal./100.0 mg.) than in acetic acid (−30.95 ± 0.13 cal./100.0 mg.) and consumed one cc. more hydrogen (*e.g.*, 16.25 cc./100.0 mg. in 275 cc. of Diethylcarbitol *vs.* 15.12 cc./100.0 mg. in 225 cc. of acetic acid). The results were nevertheless consistent, and no discrepancies traceable to the solvent have been noted. All reductions in

(1) This work was supported by the Eli Lilly Co., Indianapolis, and by the Office of Ordnance Research, Contract DA-19-059-ORD-1562 with Yale University.

(2) (a) G. B. Kistiakowsky, J. R. Kuhoff, H. A. Smith and W. E. Vaughan, THIS JOURNAL, **58**, 146 (1936); (b) M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky and W. E. Vaughan, *ibid.*, **59**, 831 (1937); (c) M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky, E. A. Smith and W. E. Vaughan, *ibid.*, **60**, 440 (1938).

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