tains its original configuration and since a 3α-compound has a more positive rotation than its 3β-isomer, the four epimers[7] can be assigned the configurations listed in Table II. On the basis of these configurations, the product formed in the hydrogenation in the present work is the 3β,17β-isomer.

Acknowledgment.—The authors are indebted to the Parke-Davis Co. for their generous supply of the equilenin used in this study.

Experimental[23]

Hydrogenation of Equilenin. (a) Basic Solution.—A mixture of equilenin (1.0 g., m.p. 258–259° with development of equilenin red color in open capillary, m.p. 271–272° in evac. capillary), 4 ml. of W-5 Raney nickel[24] and 135 ml. of 2.5% potassium hydroxide solution was hydrogenated at 85° and an initial pressure of 2800 p.s.i. (25°). After two hours, the reaction was complete and the cooled mixture diluted with 2% potassium hydroxide and benzene. The two-phase mixture was warmed, with stirring, until all organic material dissolved and then was filtered through Super-cel. The benzene layer was separated and the alkaline layer extracted with benzene. The combined benzene solutions were reëxtracted with 2% potassium hydroxide.

The alkaline solution was acidified, and, after digestion, the solid was filtered, yield 250 mg. (25%), m.p. 160–173°, $[\alpha]^{25}D$ +20° (alc.). The material was chromatographed on neutral alumina and the ether eluate yielded 188 mg. of solid. Crystallization of the material afforded colorless needles, m.p. 180.5–181.5°, $[\alpha]^{21}D$ +28° (alc.), $[\alpha]^{27}D$ +17° (diox.).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.14; H, 8.93.

The reported values for 8-isoestradiol[17] are m.p. 181°, $[\alpha]$ +18° (diox.). The 3-benzoate was prepared according to the procedure of Serini and Logemann[17] and recrystallized from dilute ethanol, m.p. 183–186°, $[\alpha]^{21}D$ +10° (diox.). The reported values[17] are m.p. 190°, $[\alpha]$ +9.5° (diox.).

A diacetate was prepared following the procedure employed by Whitman, Wintersteiner and Schwenk[19] with 17β-estradiol, m.p. 79.6–80.6° (reported[18] for 17β-estradiol diacetate, m.p. 126–127°).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.12; H, 7.92. Found: C, 73.66; H, 9.72.

The neutral fraction in benzene solution was isolated by evaporation of the solvent and then recrystallized from dilute acetone, yield 513 mg. (50%), m.p. 160–168°, $[\alpha]^{26}D$ +5.6° (alc.). The material was chromatographed on neutral alumina and only one fraction was eluted and that with ether. The $\Delta^{5,7,9}$-estratriene-3β,17β-diol was recrystallized from dilute methanol, m.p. 165–167.5°, $[\alpha]^{23}D$ +1° (±2) (alc.) (reported[8] m.p. 168°, $[\alpha]$ −5° (±4) (alc.)).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.24; H, 9.01.

The diacetate was prepared according to the procedure of Heard and Hoffman[8] and recrystallized from dilute ethanol, m.p. 111–113° (lit.[8] 115°).

(b) Acidic Solution.—A mixture of equilenin (1.0 g.) in 70 ml. of absolute ethanol, 0.6 ml. of glacial acetic acid and one teaspoon of W-5 Raney nickel[24] was hydrogenated at 115° and initial pressure of 2700 p.s.i. (25°). After two hours, the uptake of hydrogen had ceased. The reaction was cooled and the catalyst filtered. After evaporation of the solvent, the residue was dissolved in ether and the ethereal solution extracted with 2% potassium hydroxide solution to afford 130 mg. of a crude phenolic material which failed to crystallize.

The neutral fraction was isolated and purified as described above and 740 mg. of $\Delta^{5,7,9}$-estratriene-3β,17β-diol, m.p. 158–160°, was obtained.

Hydrogenation of Equilenin Methyl Ether.—A solution of equilenin methyl ether (757 mg., m.p. 196.0–196.5°) in 75 ml. of methanol, 0.5 ml. of glacial acetic acid and 1 teaspoon of W-5 Raney nickel[24] was hydrogenated at 100° and an initial pressure of 2800 p.s.i. (25°). After one hour, the reaction had stopped and the catalyst was filtered from the cooled mixture. The solvent was removed under reduced pressure and the residue chromatographed on neutral alumina. The only material obtained was eluted with ether–benzene (2:1), yield 650 mg. (84%), m.p. 142–149°. The material was recrystallized from dilute ethanol, yield 377 mg., m.p. 150–154°, $[\alpha]^{25}D$ 0 (±3°) (MeOH), λ_{max} 269 mμ, log ε 2.7.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.77; H, 9.30.

BERKELEY 4, CALIFORNIA

(23) All analyses were performed by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley.

(24) H. Adkins and H. R. Billica, THIS JOURNAL, **70**, 695 (1948).

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

Acid Catalysis in the Isomerization of 5α,6β-Dibromocholestane

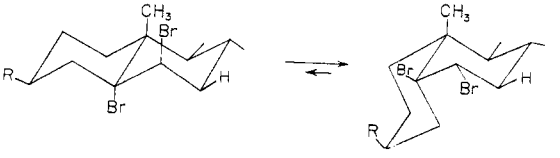
BY HAROLD KWART AND LEWIS B. WEISFELD

RECEIVED JUNE 28, 1955

General acid catalysis has been shown to occur in the isomerization of 5α,6β-dibromocholestane. The significance of this observation in the light of the most recent suggestions for the mechanism of the fundamental mutarotation reaction is discussed. The dependence of the rate on acid concentration is correlated with molecularity in acid. Mechanisms for the acid-catalyzed reaction are considered which correlate both with these rate results and the results of experiments using mixed acid catalysts. Some consideration is given to the question of general acid catalysis in media of very low polarity.

Introduction

Barton and co-workers[1,2] have shown that the dibromide resulting from addition to cholesterol possesses the 5α,6β-configuration (I) and may be readily isomerized to the 5β,6α-configuration (II) Thus when the 3β-substituent (R) is hydrogen, as in the dibromocholestane, the transition of "labile" to "stable" is essentially complete and as the size of this substituent is increased the equilibrium



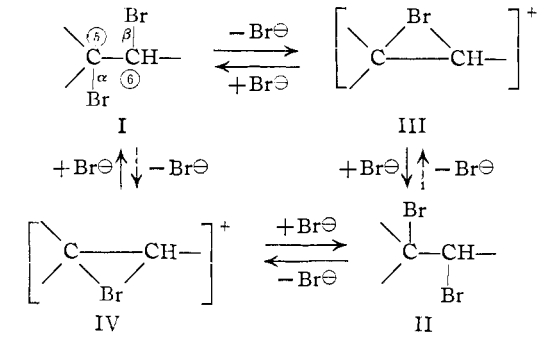
I (labile) II (stable)

constant becomes progressively smaller.[3] Barton and Miller[1] proposed that isomerization proceeded through the β-bromonium ion III and the reverse process through the α-bromonium ion IV

(1) D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950).

(2) D. H. R. Barton, E. Miller and H. T. Young, *J. Chem. Soc.*, 2598 (1951).

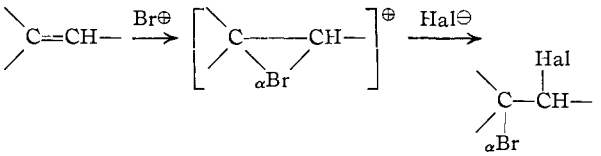
(3) C. A. Grob and S. Winstein, *Helv. Chim. Acta*, **35**, 782 (1952).



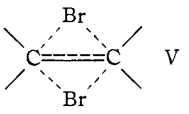
It is clear, however, that the forward and reverse reactions must proceed through the same intermediate and Grob and Winstein[3] concluded that the position of equilibrium was determined solely by the path through the α-bromonium ion in the scheme

$$\text{I} \rightleftharpoons \text{IV} \rightleftharpoons \text{II}$$

The preference for an α-bromonium ion was based upon the existing observations on the course of halogen addition in cholesterol. Thus, Fieser[4] has shown that the "opening mode" of many three-membered ring systems goes contrary to Markownikoff's rule. Barton, Miller and Young[2] along with Ziegler and Shabica[5] have demonstrated very convincingly that the halogenation of cholesterol must involve the opening of a 5,6α-halonium intermediate, proceeding, by far, more rapidly in the anti-Markownikoff fashion to account for the product observed



The observation[3] of a lack of common ion effect or any significant effect of neutral salt or added nucleophilic reagent, the negligible amount of solvolytic side reaction attending mutarotation and the astonishing rate in hexane as compared to much higher dielectric solvents has been interpreted by Grob and Winstein to indicate the occurrence of a very tightly bound intermediate state depicted as bromonium–bromide ion pair V



wherein the bonding of both of the bromine atoms have become equivalent and considerable covalent character exists in the bonds shown by means of dotted lines. In a later article[6] Winstein and his co-workers have discussed an "internal ion pair" presumably corresponding to an intermediate state such as V occurring in reactions in media of low polarity and low ion-solvating power.

Considerable interest recently has been associated with catalysis in non-polar media.[7] It was our object to examine how the mechanistic picture of the mutarotation of the dibromocholestane derivatives advanced by Grob and Winstein could accommodate an acid catalytic effect which we observed in this reaction and which was of the same magnitude experience in the mutarotation of tetramethylglucose by Swain and Brown[7a] using phenols and carboxylic acids as catalysts.

Experimental

Reagent Preparation and Product Recovery.—5-Cholestene was prepared from 3-chlorocholestene by reaction in amyl alcohol with a forty molar excess of metallic sodium in a manner similar to that employed by Wasizu.[8] Recrystallization of the product from acetone (until a negative Beilstein test was obtained) afforded *ca.* 80% yield of white prisms, m.p. 90–92°.

5α,6β-Dibromocholestane was prepared by the method of Windaus.[9] Recrystallization from acetone gave long, fine needles, m.p. 110–111°, $[\alpha]^{44}D$ −50.5 (3.2 C_6H_6). **5β,6α-Dibromocoprostane** was recovered from the individual mutarotation runs permitted to stand for seven days at 44°. This was achieved in near quantitative yield by washing the reaction mixture successively with aqueous sodium hydroxide and water, evaporating the benzene under reduced pressure to about one-tenth the original volume and finally diluting with 95% ethanol. Upon standing, well defined prisms crystallized. Recrystallization from acetone afforded prismatic needles, m.p. 146–147°: $[\alpha]^{44}D$ +55.4 (3.4 C_6H_6); $[\alpha]^{25}D$ +48.4 (6.50 $CHCl_3$).

Source of Other Reagents.—Thiophene-free, anhydrous benzene was employed in all runs. The acid catalysts were purified preliminary to use either by recrystallization, sublimation or distillation as the case required. Fresh benzene solutions of each catalyst were made up immediately prior to a kinetic determination.

Reaction Kinetics.—In every case the concentration of dibromide substrate was about 0.06 *m* in a solution of benzene plus catalyst. The reactions took place in a specially designed four decimeter jacketed polarimeter tube with all-glass sealed windows (no gaskets). The rates of isomerization were followed over a three to five degree rotation using a Bellingham and Stanley polarimeter whose accuracy easily permitted the determination of rotational changes of the order of one hundredth of a degree. Reaction was ordinarily followed to 50–60% completion and the first-order rate constants calculated from the equation

$$2.303 \log \frac{\alpha_0 - \alpha_\infty}{\alpha - \alpha_\infty} = k_t t$$

where α_0 refers to the initial rotation of the solution of labile isomer, α is the rotation at time t in the isomerization, α_∞ is the calculated rotation of the pure isomer at 44°, and k_t is the isomerization rate constant of the forward reaction. In all cases the characteristic linear plot was obtained even when the reaction was carried to near completion. The assumption of irreversibility of reaction was further justified by agreement of the assumed value with the Tau method[10] extrapolation to infinite time value. The absence of significant solvolytic side reaction is also confirmed by this agreement.

The catalytic constants, k_c, were calculated by means of the equation

$$k_t = k_0 + k_c[\text{HA}]$$

where k_0 refers to the uncatalyzed rate constant in pure benzene and [HA], the concentration of general acid catalyst, is expressed in molal units. There is reason to assume that the order of catalysis noted for phenol is the same for all the substituted phenols examined. We have therefore calculated the catalytic constants on the basis of

$$k_t = k_0 + k_c[\text{phenol}]^{1.68}$$

(4) L. F. Fieser, *Experientia*, **6**, 312 (1950).

(5) J. B. Ziegler and A. C. Shabica, THIS JOURNAL, **74**, 4891 (1952).

(6) S. Winstein, E. Clippinger, A. H. Fainberg and G. C. Robinson, *Chem. and Ind.*, 664 (1954).

(7) (a) C. G. Swain and J. F. Brown, Jr., THIS JOURNAL, **74**, 2534 (1952); (b) R. P. Bell and P. Jones, *J. Chem. Soc.*, 88 (1953).

(8) Y. Wasizu, *J. Pharm. Soc. Japan*, **60**, 616 (1940); *C. A.* **35**, 2902 (1941).

(9) A. Windaus, *Ber.*, **39**, 518 (1906).

(10) E. Guggenheim, *Phil. Mag.*, [7] **2**, 538 (1926).

the exact expression found analytically to be observed by (unsubstituted) phenol in each of the *direct* measurements of its catalytic constant. These values, however, must be regarded merely as estimates of the catalytic activity to be used only for quantitative comparison of reactivity amongst various phenols. See Figure 2. All reaction rates were determined at 44.08 ± 0.03°.

Results

The data listed in the accompanying tables demonstrate clearly the existence of general acid catalysis in the mutarotation of 5α,6β-dibromocholestane in benzene solution.

TABLE I

RATE VARIATION OF MUTAROTATION OF 5α,6β-DIBROMOCHOLESTANE WITH ACID CONCENTRATION

Catalyst	Concn., mole/l.	$kt \times 10^4$, sec.	−log [HA]
None	.....	6.16 ± 0.02	...
Chloroacetic	0.01977	7.35	1.704
Chloroacetic	.03874	8.27	1.412
Chloroacetic	.09885	10.7	1.005
Phenol	.1268	13.30	0.896
Phenol	.2232	24.1	.651
Phenol	.4464	65.4	.350

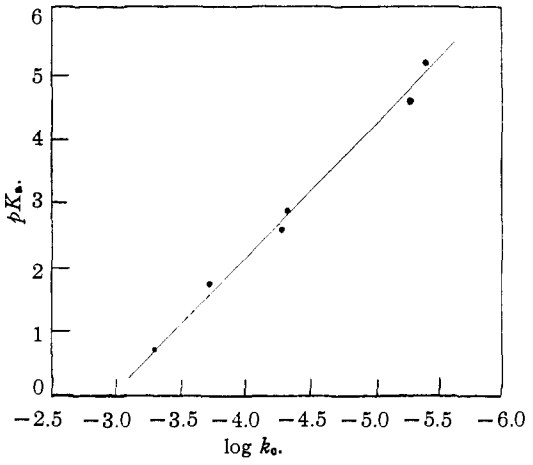


Fig. 1.—Brönsted catalysis in the mutarotation of dibromocholestane by carboxylic acids; comparison of catalytic constants k_o with the relative acid dissociation constants of carboxylic acids in benzene.

typical case of chloroacetic acid. The rate of reaction, it will be noted, approaches the first power of the acid concentration. The catalytic order in phenolic acid has been determined from the data plotted in Fig. 2. The rate of reaction here has a higher (apparent) dependence on the initial phenol concentration (approaching second) than observed for the carboxylic acids plotted on the same Fig. 2.

TABLE II

CATALYSIS[a] OF MUTAROTATION OF 5α,6β-DIBROMOCHOLESTANE

Catalyst	Concn., mole/kg.	$kt \times 10^4$, $sec.^{-1}$	$k_o \times 10^4$, $mole^{-1}\ sec.^{-1}\ kg.$	−log k_o	Relative pK_a in benzene[11]
None	....	6.16 ± 0.02	.....	.....	..
Acetic acid	0.303	7.45 ± .05	4.26 ± 0.12	5.37 ± 0.02	5.18
Benzoic acid	.228	7.40 ± .01	5.43 ± .13	5.26 ± .01	4.58
Chloroacetic acid	.0443	8.27 ± .02	47.6 ± .9	4.32 ± .01	2.90
Salicylic acid	.0287	7.53 ± .03	47.8 ± 1.8	4.31 ± .02	2.55
Dichloroacetic acid	.0553	16.68 ± .03	190 ± 1.0	3.72 ± .00	1.75
Trichloroacetic acid	.0279	20.1 ± 0.2	501 ± 5.0	3.30 ± .00	0.70
Piperidinium acetate	.107	6.44	....	..	..
Acetic acid + piperidine	.626	7.64	3.38 (acetic)	..	..
	.181				
p-Cresol	.356	17.50	64.3	4.19	..
Phenol	.146	13.37	183	3.74	..
p-Chlorophenol	.263	47.4	388	3.41	..
o-Chlorophenol	.226	9.08	35.5	4.45	..
o-Chlorophenol + phenol	.390	54.5	191–235[b]	..	..
	.168				

[a] Brönsted catalysis constant, for carboxylic acids $-d(\log k_o)/d(pK_a) = 0.486$. [b] The lower catalytic constant was calculated on the basis of independent catalysis by both phenol and *o*-chlorophenol; the higher on the assumption that *o*-chlorophenol alone is functioning as the acid (phenol is the proton acceptor), and the equilibrium concentration of phenol-hydronium ion is the catalyzing acid. The actual catalytic constant must be somewhere between these extreme values.

The lack of general base catalysis is demonstrated by the data from runs in piperidinium acetate; no increase in the isomerization rate could be attributed to the introduction of the base acetate anion. The data for carboxylic acid catalysis, for which there are also available the corresponding acidity constants in benzene, afford excellent fit to the Brönsted catalysis law[12] as illustrated by the plot in Fig. 1. The magnitude of the Brönsted catalytic coefficient here is even greater than that for the mutarotation of glucose (0.269 at 18° in water).[13]

The catalytic order in carboxylic acid has been determined from the data plotted in Fig. 2 for the

The Mechanism of Mutarotation.—Of direct concern is how the mechanistic ideas of Grob and Winstein[8] are modified by the observation of general acid catalysis in the mutarotation reaction. The relatively large value of the Brönsted coefficient must indicate that considerable assistance by acid is possible in the rate-determining step(s) of the reaction. Clearly, acid catalysis must be functioning to increase the extent to which bond breaking[14]

(11) V. K. LaMer and H. C. Downes, THIS JOURNAL, **55**, 1840 (1933).

(12) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 222, *et seq.*

(13) J. N. Brönsted and E. A. Guggenheim, THIS JOURNAL, **49**, 2554 (1927).

(14) (a) C. G. Swain and W. P. Langsdorff, Jr., *ibid.*, **73**, 2813 (1951); (b) C. G. Swain, *ibid.*, **72**, 4578 (1950).

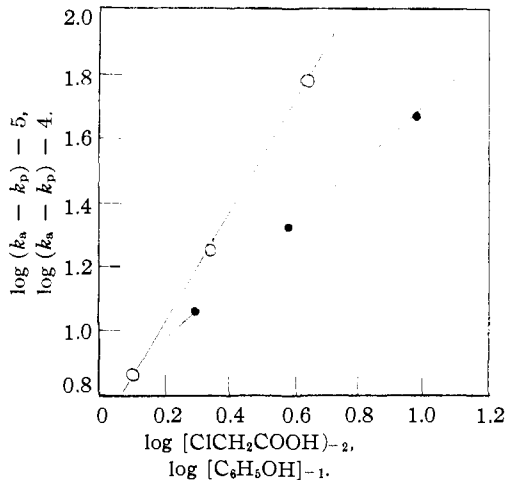
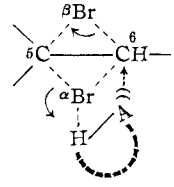


Fig. 2.—Catalytic order in chloroacetic acid (●) and phenol (○): k_a and k_p refer, respectively, to the observed rate constants with added chloroacetic acid and phenol (see Table I).

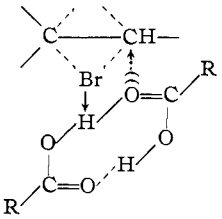
occurs in the transition state by causing a lowering of the electron density in the carbon-bromine bond being broken therein. Furthermore, the magnitude of the catalytic effect exerted indicates that the transition state of the uncatalyzed reaction is also one in which bond breaking is occurring to a *predominant* extent.

The transition state for acid catalyzed mutarotation may be visualized as



It is quite conceivable, also, that the conjugate fragment A of the acid catalyst also exerts an effect in the transition state. The dotted arrow indicates a possible effect tending to lower the charge deficiency at C_6 that accompanies the stretching of the C_6–Br_β bond in the transition state. A concerted response similar to this (and designated as a feature of "polyfunctional catalysis") has been suggested by Swain and Brown[7a] for mutarotation of tetramethylglucose, acid-catalyzed in benzene solution. Coördination between the bulky catalyzing acid $[HA]_2$ and the Br_β in the intermediate is considered improbable. Although an α-bromonium ion is much more readily formed in the bromination of cholestene[2,5] due to the smaller non-bonded interaction with the C_{10} substituent, the driving force for the mutarotation reaction[2] is derived from relief of the Br_β interaction with the angular (β) methyl. Similarly, we would suggest that solvation of Br_β by bulky acid complexes in non-polar media would be rendered sterically more improbable while the halogen–acid coördination complex is easily accommodated in the α-configuration. The reverse reaction ($5\beta,6\alpha \rightarrow 5\alpha,6\beta$), which takes place quite readily where a bulky substituent at C_3 provides an impetus for reversion, must occur by the enantiomorphic route in which the acid catalyst promotes reaction by coördinating the (here, C_6) Br_α.

The Mechanism of the Acid Catalysis.—Apparently, even though the catalysis by carboxylic acid shows an exact first-order dependence on acid concentration, the molecularity in acid must be two. This is required by the established[15] existence of carboxylic acids as dimers in benzene solution. Catalysis of the reaction by carboxylic dimers as demanded by the kinetics confirms the suggestion (above) that $Br_{5\alpha}$ is the more basic of the two halogens in the reagent by virtue of being more accessible to solvation by acids in a bulky complex.



It is further evident that the proton, tightly held in the dimer, is not fully imparted to the halogen On the other hand, both the (differing) kinetic order and the extraordinary catalytic efficiency (out of all proportion to their aqueous acidity constants) indicates a strong difference in the mode of operation of phenolic acids. The observed kinetic order here may be taken to correspond to the molecularity in phenol. The coöperation of approximately two molecules (or an equal number of association aggregates) of phenol in an autoprotolysis step seems to be required for the mechanism of solvation of the α-halogen. In contrast with the carboxylic acid case, the phenolic proton must be considered as more readily (and possibly more fully) imparted to the solvated halogen atom when a second acidic hydrogen is available from a neighboring phenolic hydroxyl group to decrease the developing charge density on the conjugate oxygen atom. Also, the possible assistance of the neighboring hydroxyl oxygen in concertedly reducing the charge deficiency on C_6 is recognized in this picture.

A similar explanation must be considered for the rate acceleration observed in the use of methanol and ethanol as solvents for the reaction.[3] The disproportionately large effect does not correlate with the dielectric change when the alcohol concentration is yet too small to produce an increase in the extent of the solvolytic side reaction.

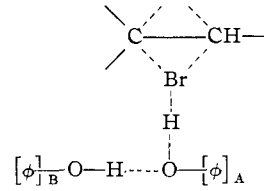
The absence of data on the relative acid strength of phenols in benzene does not allow determination of the existence of linear free energy relationship and Brönsted coefficients comparable with carboxylic acid data. It would, however, occasion no surprise if phenolic catalysis constituted a separate and distinct relationship of this kind.[16] The

(15) E. Baud, *Bull. soc. chim.*, **13**, 435 (1913), has shown that acetic acid in several non-polar solvents is (essentially) entirely in the dimeric form. It would not be possible to account for the magnitude of catalytic activity shown by carboxylic acids on the basis of catalysis by a vanishingly small amount of monomeric acid in equilibrium with its dimer.

(16) The variation of acidity from carboxylic to phenolic is most likely not a permissible variation in the structure of the catalyst[12] if the linear relation is to hold. Nor should structural change in the immediate neighborhood of the reacting phenolic hydroxyl permit even a qualitative relation between rate and the pK_a in an entirely different medium.

requirement of two moles (or molecular aggregates) of phenol in the catalyzed reaction transition state is most dramatically demonstrated in the crossed experiment. The data here show that a mixture of phenol and *o*-chlorophenol is approximately six times more efficient catalytically than either acting alone. We conclude from this result that each catalyst molecule coöperating in an act of catalysis can perform one of the two required functions *most* ably. *o*-Chlorophenol (the poorer catalyst where autoprotolysis is required in solvation of the halogen) is evidently the better solvator of oxygen. The reverse must be the case for phenol. The higher (apparent) activity of the mixture correlates with the transition state picture VI.

An alternate explanation for the crossed catalyst data may be gleaned from a representation of the



VI; $[\phi]_A$ is the phenol and $[\phi]_B$ is the *o*-chlorophenol

VII; the reverse of VI

transition state as VII. Here, conceivably, the more acidic chlorophenol proton solvates the halogen while the relatively more basic oxygen of the cooperating phenol moiety is acting to reduce the growing charge deficiency at C_6.

A program designed to investigate the generality of these observations and the scope of our conclusions is presently in progress in these laboratories.

NEWARK, DELAWARE

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF ILLINOIS INSTITUTE OF TECHNOLOGY]

17- and 17a-Aza-D-homosteroids[1,2]

BY BERNARD M. REGAN[3] AND F. NEWTON HAYES

RECEIVED JULY 5, 1955

Rearrangement of several 17-ketosteroid oximes gave lactams which were shown by two independent methods to be 17a-aza-D-homosteroids, in agreement with a previous report. Rearrangement of a 16-oximino-17-ketosteroid gave a 17-aza-D-homosteroid imide, which was identified by hydrolysis to the corresponding, known dicarboxylic acid. Lithium aluminum hydride reduction of the lactams and imide provided 17a- and 17-aza-D-homosteroid amines, respectively, in excellent yield. Hydrolysis of the lactam function (in part) to an aminoacid hydrochloride and N-acylation of the lactams in ordinary fashion were accomplished contrary to a previous report.

This work was undertaken with the aim of preparing certain altered steroids, which we hoped would function as hormone antagonists or in fewer capacities than the polybiofunctional steroid hormones themselves. We chose to prepare various aza-D-homosteroids since certain oxa-D-homosteroid lactones[4] were shown to possess interesting physiological properties.

Recently, Beckmann rearrangement of 17-ketosteroid oximes was reported to yield 17a-aza-D-homosteroid lactams on the basis that selenium dehydrogenation of "dehydroisoandrololactam" (Vb) gave 1-azachrysene.[5]

We have found that rearrangement of 17-ketosteroid oximes with thionyl chloride in dioxane gave in general slightly higher yields of the desired lactams than Kaufmann's *p*-acetamidobenzenesulfonyl chloride–pyridine method. In the case of estrone oxime, in which the latter method was reported to yield only intractable tars, our method gave the lactam, 17a-aza-D-homoestrone (Ia), in 90% yield. Also, rearrangement with excess thionyl chloride alone was satisfactory, although more vigorous, but thionyl chloride in pyridine was too drastic and a dark, tarry product resulted.

3β-Acetoxy-5-androsten-16,17-dione 16-oxime rearranged only very slowly with a limited amount of thionyl chloride in dioxane and not at all with *p*-toluenesulfonyl chloride in pyridine at room temperature. However, rearrangement was smooth and rapid with excess thionyl chloride with or without benzene. The rearrangement product IX, isolated in 65% yield, was 3β-acetoxy-16,-17-seco-5-androsten-16,17-dioic 16,17-imide. Another theoretically possible[6] product, isomeric with IX, a cyanocarboxylic acid, *e.g.*, XII, was eliminated on the basis of the neutral nature and infrared spectrum of IX.

Conclusive proof of the imide structure was accomplished by alkaline hydrolysis first to an amido-acid, probably Xa, and then after ten days at 110° to the known[7-9] dicarboxylic acid, 3β-hydroxy-16,17-seco-5-androsten-16,17-dioic acid (Xb).

The 17-amido structure Xa was favored over the alternative 16-amido structure for the partially hydrolyzed imide IX because of the ease of attack by hydroxide ion on IX at the primary carboxyl (C_{16}) compared to the tertiary carboxyl (C_{17}), and because of the very slow hydrolysis of the amido-acid which is typical of C_{17} carboxyl derivatives.[7,10]

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(4) R. P. Jacobsen, *et al.*, *J. Biol. Chem.*, **171**, 61, 71, 81 (1947).

(5) St. Kaufmann, THIS JOURNAL, **73**, 1779 (1951).

(6) *E.g.*, rearrangement of isonitrosocamphor with phosphorus pentachloride has given "α-camphornitrilic acid"; H. Rupe and I. Splittgerber, *Ber.*, **40**, 4313 (1907).

(7) S. Kuwada, *J. Pharm. Soc. Japan*, **56**, 75 (1936); S. Kuwada and K. Nakamura, *ibid.*, **58**, 835, 841 (1938).

(8) A. Butenandt, J. Schmidt-Thomé, T. Weiss, D. von Dresler and U. Meinerts, *Ber.*, **72**, 417 (1939).

(9) A. Wettstein, H. Fritzsche, F. Hunzicker and K. Miescher, *Helv. Chim. Acta*, **24**, 332E (1941).

(10) See, *e.g.*, J. Heer and K. Miescher, *ibid.*, **28**, 156 (1945); **29**, 1895 (1946); **30**, 786 (1947); J. Heer, J. R. Billeter and K. Miescher, *ibid.*, **28**, 991 (1945).