The mixed m.p. of this acid with material prepared from the oxidation of XVII (see below) was not depressed. The infrared spectra of the two samples were the same.

Benzylidene Derivative of 3α-Acetoxyetiocholane-11,17-dione (XVII).—A 0.68-g. sample of 3α-acetoxyetiocholane-11,17-dione was converted to its 16-benzylidene derivative by the method already described for the preparation of XV. The product was acetylated at room temperature with pyridine and acetic anhydride to give XVII as prisms from acetone–hexane; m.p. 245–247°, $\lambda\lambda_{max}^{CH_3OH}$ 295 mμ (25,800), 229 mμ (8,300).

Anal. Calcd. for $C_{28}H_{34}O_4$: C, 77.42; H, 7.83. Found: C, 77.20; H, 7.56.

Oxidation of XVII with potassium permanganate gave the acid XVI, m.p. 226–231°, identical with material prepared from the $\Delta^{\alpha\beta}$-ketone VI (*cf.* above).

3α-Acetoxy-11-ketoetiobilianic Acid Anhydride.—Treatment of the acid XVI with acetic anhydride in pyridine at room temperature produced the corresponding anhydride, crystallized from acetone–hexane; m.p. 213–215°, λ_{max} 1800 (5.55), 1765 (5.67), 1710 (5.85) and 1250 cm.$^{-1}$ (8 μ).

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.02; H, 7.45. Found: C, 67.28; H, 7.40.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

The Polarographic Reduction of Prednisone (17α,21-Dihydroxy-1,4-pregnadiene-3,11,20-trione), Prednisolone (11β,17α,21-Trihydroxy-1,4-pregnadiene-3,20-dione) and Their Precursors[1]

BY PETER KABASAKALIAN AND JAMES MCGLOTTEN

RECEIVED MARCH 22, 1956

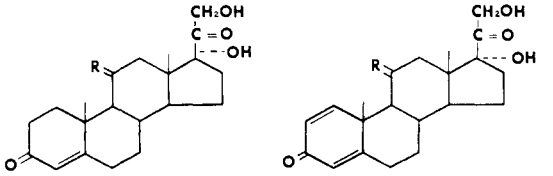
Polarographic data are compiled for prednisone (17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione), prednisolone (11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione), cortisone and hydrocortisone (17α-hydroxycorticosterone) in well-buffered 50% ethanol solutions. The effects of *p*H, temperature, concentration and mercury pressure on the polarographic waves obtained are discussed. A possible electrode reaction mechanism has been proposed on the basis of the results obtained from wave analyses and diffusion coefficient determinations. Preliminary studies of controlled potential electrolysis products support the proposed mechanism.

Introduction

Although it is now well known that the polarographic reduction characteristics of carbonyl compounds depend greatly on many external factors such as *p*H, buffer type, buffer concentration and type of solvent, much of the early work done on the α,β-unsaturated ketosteroids was performed in unbuffered or poorly buffered systems. Adkins and Cox[2] obtained reduction waves for cholestenone in 0.1 *N* ammonium chloride solutions. Later Eisenbrand and Picher[3] observed the behavior of several Δ^4-3-ketosteroids in 90% ethanol 0.1 *N* in lithium chloride. Wolfe, Hershberg and Fieser[4] studied the polarographic reduction of cholestenone, corticosterone, cortisone, desoxycorticosterone, progesterone and testosterone in 35% isopropyl alcohol solutions 0.1 *N* with respect to tetraethylammonium hydroxide.

Sartori and Bianchi[5] reported the half-wave dependence on *p*H for 17-ethinyltestosterone and methyltestosterone, but did not describe any changes in wave form or currents with *p*H. More recently Zuman, Tenygl and Brezina[6] made a fairly exhaustive study on the behavior of certain Δ^4-3-ketosteroids in 30–60% ethanol solutions buffered with Britton and Robinson buffer mixtures.

The present work is concerned with the polarographic behavior of two Δ^4-3-ketosteroids (cortisone and hydrocortisone) and two of the recent $\Delta^{1,4}$-3-ketosteroids (prednisone and prednisolone) in well-buffered 50% ethanol solutions. Some earlier work carried out in 50% methanol is also included.



CORTISONE R O PREDNISONE R O

HYDROCORTISONE R = HO / H PREDNISOLONE R HO / H

Experimental

Apparatus.—The curves for the analysis of the wave were obtained with the Fisher Elecdropode. The remainder of the polarographic work was carried out with the Sargent model XXI recording polarograph. The cells used were small H-type cells (3-ml. sample volume) containing a normal calomel electrode separated from the sample compartment by an agar plug and fritted glass diaphragm. The chloride ion in the calomel cell was furnished by a normal tetramethylammonium chloride solution. The electrode capillary delivered 1.698 mg. of mercury per second at a column height of 41 cm. The drop time was 4.12 seconds and the capillary constant, $m^{2/3}t^{1/6}$, was 1.80 mg.$^{2/3}$ sec.$^{-1/2}$. The constants were determined at an open circuit with the mercury dropping into a 0.1 *N* potassium chloride solution.

All *p*H measurements were made with the Beckman model G *p*H meter using the glass electrode.

The magnetic stirring device and fritted glass diaphragm cell in the diffusion coefficient experiments were similar to those used by Stokes[7] in his diffusion work.

The electrolysis cell in the controlled-potential electrolysis work was similar in design to that used by Pasternak.[8]

(1) Presented at the Seventh Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Pittsburgh, Pa., February 28, 1956.

(2) H. Adkins and F. W. Cox, THIS JOURNAL, **60**, 1151 (1938).

(3) J. Eisenbrand and H. Picher, *Z. physiol. Chem.*, **260**, 83 (1939).

(4) J. K. Wolfe, E. B. Hershberg and L. F. Fieser, *J. Biol. Chem.*, **136**, 653 (1940).

(5) G. Sartori and E. Bianchi, *Gazz. chim. ital.*, **74**, 8 (1944).

(6) P. Zuman, J. Tenygl and M. Brezina, *Collection Czechoslov. Chem. Communs.*, **19**, 46 (1954).

(7) R. H. Stokes, THIS JOURNAL, **72**, 763 (1950).

(8) R. Pasternak, *Helv. Chim. Acta*, **31**, 753 (1948).

The potential was supplied by a filtered full-wave selenium rectifier whose output voltage was adjusted manually. The faradays consumed were measured with a Laur–Knudsen current integrator, type S3, and the currents were measured with a Weston milliammeter.

All ultraviolet spectra were obtained with the Cary recording spectrophotometer, model 11.

Materials.—The solvents and buffer components were determined to be polarographically pure before use. The investigated steroids were prepared and purified in the Schering Laboratories. All references to ethanol throughout this work will refer to denatured alcohol, formula 3A.

Procedure.—Electrolysis solutions for all the qualitative work were prepared by pipetting 5-ml. aliquots of an alcoholic steroidal solution into a 10-ml. volumetric flask and diluting to the proper volume with the appropriate buffer solution. Portions of the electrolysis solution were used to rinse the sample cell and a final portion deaerated with nitrogen for 10 minutes, then electrolyzed. The *p*H of the solution was measured after electrolysis. For the current–concentration work, the sample was weighed directly into the flask using a micro balance and dissolved in 5 ml. of alcohol. Diffusion currents were determined by the method of intersecting lines.

The technique employed in the determination of diffusion coefficients was that used by Stokes[7] in determining the diffusion coefficients of salts. The solvent systems here, however, were the buffered 50% alcohol systems used in the polarographic work. The determinations were made in a constant temperature room with temperature maintained at 24 ± 1.0°. The average diffusion time was 117 hours for a sample whose initial concentration was 5 millimolar.

The controlled-potential electrolyses were performed on solutions identical to the polarographic solutions of *p*H 5.5 except for the steroid concentrations which were increased to approximately 0.02 *M*. Before each experiment a blank current value was obtained by electrolyzing, to constant current, a deaerated blank solution at a cathode voltage corresponding to a point on the diffusion plateau of the compound to be electrolyzed. This electrolysis was then discontinued and the blank solution replaced in the cell by the sample solution. After deaeration of the sample solution the reading of the current integrator was recorded and the sample electrolysis begun at the same cathode potential as for the blank. The course of the reaction was followed by ultraviolet and polarographic measurements made on samples that were withdrawn periodically from the electrolysis vessel. The total withdrawals were limited to 2% or less of the material being reduced. The electrolysis was continued until the current had dropped to the blank current value at which point a final sample was taken, the current integrator reading was recorded and the content of the electrolysis vessel was removed. The faradays consumed were calculated from the integrator readings and after correction for the blank this value, in conjunction with the total steroid converted, was used to determine *n*-values for the reaction.

The reduction products were dehydrated by the method of Oroshnik and Mebane[9] with absolute methanol as the solvent rather than benzene.

Results and Discussion

Effect of *p*H on Half-Wave Potentials.—Half-wave potentials were determined for the four steroids at each of the ten *pH* values listed in Table I. In each case the potential decreases linearly with *p*H. The slopes of the $E_{1/2}$ *vs.* *p*H plots were 0.058, 0.060, 0.061 and 0.060 volt per *p*H unit for prednisone, prednisolone, cortisone and hydrocortisone, respectively. Corresponding zero *p*H intercept values were −0.89, −0.93, −1.04 and −1.09 volts *versus* the normal calomel electrode. It should be noted here that the addition of the double bond at the 1,2-position reduced the half-wave potential about 0.15 volt. The experimental results are compiled in Table II. The concentration of the compounds investigated does not affect half-wave potentials in well-buffered solutions.

(9) W. Oroshnik and A. D. Mebane, THIS JOURNAL, **71**, 2062 (1949).

Effect of *p*H on Diffusion Current.—Since concentrations were kept constant at 1.11×10^{-3} *M* during this series of runs, the diffusion currents were listed directly as such without converting them to current constants (Table II).

The diffusion currents for the first wave of prednisone are constant in the acid range from *p*H 3–5. They decrease gradually from *p*H 5–7, then remain fairly constant from *p*H 7–11. At *p*H 6.3 a second wave appears for prednisone. This wave increases about 10% in height from its point of inception to *p*H 11. However, there are two points in this *p*H range where the second wave is poorly defined and therefore it is not certain whether the increase is continuous or not.

TABLE I

COMPOSITION OF BUFFERS[a]

*p*H 50% EtOH	*p*H aqueous	*p*K_A	Buffer components
2.8	2.3	2.9[b]	0.10 *M* malonic acid + 0.02 *M* NaOH
3.4	2.7		.10 *M* malonic acid + 0.05 *M* NaOH
4.6	3.8		.05 *M* malonic acid + 0.05 *M* NaOH
4.9	4.0	4.8[c]	.08 *M* acetic acid + 0.02 *M* NaOAc
5.5	4.6		.05 *M* acetic acid + 0.05 *M* NaOAc
6.3	5.4		.015 *M* acetic acid + 0.085 *M* NaOAc
7.0	5.8	6.1[d]	.05 *M* malonic acid + 0.09 *M* NaOH
9.9	10.5	10.8[e]	.10 *M* triethylamine + 0.06 *M* HCl
10.2	10.8		.10 *M* triethylamine + 0.04 *M* HCl
10.8	11.4		.10 *M* triethylamine + 0.013 *M* HCl

[a] NaCl added as ionic strength agent. [b] Malonic acid, K_1. [c] Acetic acid. [d] Malonic acid, K_2. [e] Triethylamine.

TABLE II

EFFECT OF *p*H ON HALF-WAVE POTENTIAL AND DIFFUSION CURRENTS

*p*H	Prednisone $-E_{1/2}$ v. *vs.* N.C.E.	Prednisone Wave ht., μa.	Cortisone $-E_{1/2}$ *vs.* N.C.E.	Cortisone Wave ht., μa.	Prednisolone $-E_{1/2}$ *vs.* N.C.E.	Prednisolone Wave ht., μa.	Hydrocortisone $-E_{1/2}$ *vs.* N.C.E.	Hydrocortisone Wave ht., μa.
2.8	1.05	1.85	1.20	2.00	1.10	3.21	1.26	2.53
3.4	1.09	1.91	1.24	1.93	1.13	2.93	1.29	2.27
4.6	1.16	1.86	1.31	1.90	1.21	2.21	1.37	2.18
4.9	1.17	1.91	1.33	1.91	1.23	2.15	1.38	2.20
5.5	1.21	1.80	1.37	1.88	1.26	1.95	1.42	2.15
6.3	1.25[a]	1.72	1.41	1.83	1.30	1.79	1.47	2.06
7.0	1.30	1.60	1.46	1.68	1.35	1.65	1.51	1.52
9.9	1.47	1.61	1.63	1.93	1.53	1.53	1.68	1.74
10.2	1.48	1.55	1.65	2.04	1.55	1.58	1.70	1.73
10.8	1.52	1.62	1.69	2.05	1.59	1.63	1.74	1.67
Slopes	0.058 volt/*p*H		0.061 volt/*p*H		0.060 volt/*p*H		0.060 volt/*p*H	

[a] Second wave of prednisone takes shape at this *p*H and is present as a badly defined wave throughout the succeeding basic *p*H's. $E'_{1/2}$ of a second wave varies from −1.64 to −1.70 v. at *p*H values of 6.3 and 10.8, respectively.

The currents obtained for cortisone are substantially the same throughout the acid region. There is a decrease at *p*H 7 with an equivalent recovery on the basic side.

Prednisolone exhibits an abnormally large current value at *p*H 2.8 which decreases continuously throughout the acid region. The decrease is rapid from *p*H 2.8 to 4.6 (about 20% per *p*H unit), but is considerably slower (about 10% per *p*H unit) from *p*H 4.6 to 6.3. The currents measured above *p*H 7 are nearly constant but low in comparison to those obtained below *p*H 7.

Hydrocortisone yields a high current value at *p*H

2.8 which quickly drops to a lower value at *p*H 3.4 and remains constant until a *p*H of 7 is reached. At this point the current drops almost 30%. The currents then rise slightly (about 10%) and become constant again in the alkaline range.

Effect of Mercury Height on Diffusion Currents.—Analysis of the data presented in Table III indicates that the limiting currents obtained in each case are diffusion controlled.

The currents obtained for the single wave of prednisone at *p*H 5.5, and the two waves at *p*H 8.0 all varied nearly linearly as the square root of the mercury column height. This same dependence on the height of the mercury column was obtained for cortisone, hydrocortisone and prednisolone in buffered solutions of *p*H 5.5 and 8.0.

The equation[10] relating the dependence of diffusion current on the height of mercury for a diffusion controlled electrode process states that the ratio of diffusion current to the square root of mercury column height should not be strictly constant, but should decrease slightly as the mercury height increases. This is the behavior observed in these experiments.

Variation of Diffusion Currents with Concentration.—The variation of diffusion current with concentration for prednisone is substantially linear between 2.8×10^{-4} to 3.4×10^{-3} *M*. Below this concentration range there is a positive deviation from linearity and above this range there is a slight negative deviation.

Prednisolone shows a linear dependence of current on concentration between 1.5×10^{-4} to 2.0×10^{-3} *M*. At concentrations greater than 2.0×10^{-3} *M* the wave is deformed to such an extent that accurate current measurements are no longer possible. Wave deformation occurs at even lower concentrations in 50% methanol solutions.

A linear relationship is obtained between diffusion current and concentration for cortisone and hydrocortisone from 1.5×10^{-4} to 4.5×10^{-3} *M*, with a slight negative deviation in the case of cortisone at 4.5×10^{-3} *M*.

TABLE III

EFFECT OF MERCURY HEIGHT ON DIFFUSION CURRENTS[a]

h, cm.	Prednisone k_a	Prednisone k_b	Prednisone k'_b	Cortisone k_a	Cortisone k_b	Prednisolone k_a	Prednisolone k_b	Hydrocortisone k_a	Hydrocortisone k_b
18.5	0.54	0.68	0.60	0.63	0.90	0.54	0.52	0.63	0.57
26.5	.53	.66	.56	.62	.86	.55	.52	.62	.56
36.5	.52	.64	.55	.61	.80	.54	.51	.60	.55
46.5	.52	.63	.53	.60	.83	.53	.51	.58	.54

[a] h = mercury column height corrected for back pressure; $k_a = i_d/h^{1/2}$ in *p*H 5.5 acetate buffer solution; $k_b = i_d/h^{1/2}$ in *p*H 8.0 phosphate buffer solution; $k'_b = i_d/h^{1/2}$ for prednisone second wave at *p*H 8.0.

Effect of Temperature on Diffusion Current.—Diffusion current values were obtained for each of the four compounds at various temperatures between 8 and 38°. The current–temperature dependency is essentially linear throughout the range examined, with slight deviations from linearity occurring at both ends of the range.

A temperature coefficient of 2.3% per degree (with respect to the 25° value) was determined for these steroids, valid over the temperature interval from 15 to 35°. This temperature coefficient value is of the order of magnitude normally observed for diffusion controlled processes.

Determination of Diffusion Coefficients by Diaphragm Cell Technique.—On the basis of three determinations each, diffusion coefficients (in units of 10^{-6} cm.^{2} sec.$^{-1}$) of 4.03 ± 0.02, 3.83 ± 0.17, 4.83 ± 0.11 and 3.86 ± 0.17 were obtained for prednisone, cortisone, prednisolone and hydrocortisone, respectively.

On inserting these diffusion coefficients into the modified Ilkovic equation[11] n-values of 0.96, 0.99 0.97 and 0.99 are obtained for the electrode processes involved in the reduction of these four compounds at *p*H 5.5.

Wave Form.—The waves of all four compounds investigated are essentially the same. In acid media there was obtained a simple S-shaped current–voltage curve with each of the steroids. The wave is well formed, with slightly rising plateaus.

In basic media (*p*H 7–11) this single S-shaped curve still prevails with all the compounds studied except prednisone, Fig. 1. At these *p*H values prednisone exhibits two waves. The second wave first appears somewhere between *p*H 6 and 7 having a current height somewhat less than the first wave, but whose height increases as the solutions become more basic. When a *p*H of 10.8 is reached, the two waves are equal in height. The height of each wave is equivalent to that observed for the single waves of the other steroids at this *p*H value.

Prednisolone also displays apparent abnormalities in its wave form. In very acid media (*p*H 3.5 and below) the diffusion plateau is extremely steep. This extreme incline of the plateau is not caused by the normal reduction of hydrogen ion which occurs at sufficiently negative potentials to have very little effect on the shape of the wave. A departure from the normal S-shaped curve is also evidenced by this compound at high concentrations. Solutions of prednisolone, 2 millimolar or stronger, give rise to broken waves. The wave will start to rise normally and then at a point about half way up will abruptly flatten for a few hundredths of a volt, then just as abruptly begin to rise again and finish in the customary manner as shown in Fig. 2.

It was noticed with all of the compounds studied that the final rise of the diffusion curve began at a more positive potential than could be accounted for by the hydrogen wave. On examining cortisone and hydrocortisone in solutions containing 0.1 *N* tetrabutylammonium chloride as electrolyte two waves were obtained for each compound. The first wave occurs at the potentials normally observed for the Δ^4-3-keto reduction in neutral solutions. The second wave for each compound occurs at a potential (cortisone −2.04 v. and hydrocortisone −2.11 v. *vs.* N.C.E.) quite close to that observed for the reduction of dihydroxyacetone (−2.18 v.) in the same system. From this it would appear that the Δ^4-3-keto reduction is in turn followed by the reduction of the 17,21-dihydroxy 20-keto side chain. This latter wave

(10) I. M. Kolthoff and J. J. Lingane, "Polarography," Vols. I and II, 2nd Edition, Interscience Publishers, Inc., New York, N. Y., 1952.

(11) J. J. Lingane and B. A. Loveridge, THIS JOURNAL, **72**, 438 (1950).

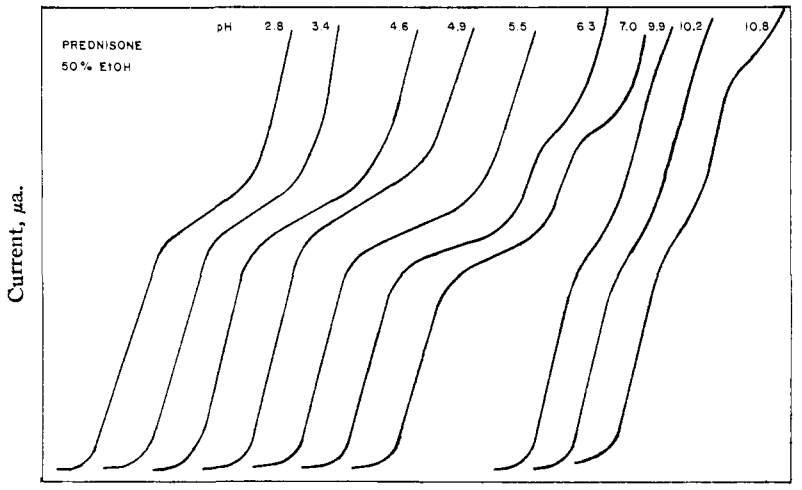


Fig. 1.—Variations in prednisone wave form with *p*H in 50% ethanol solutions.

then merges with the hydrogen wave in the acid systems studied and with the sodium wave in the basic systems.

Analysis of the Wave.—Manually determined polarographic curves for prednisone, prednisolone, cortisone and hydrocortisone were obtained in 50% methanol solutions at *p*H 5.5 and in 50% ethanol solutions at *p*H 5.5 and 10.2.

These curves were analyzed graphically by plotting log $[i/i_d - i]$ *versus* the electrode potentials. The half-wave potentials obtained directly from the curves and those obtained from the graphs were the same (within 4 millivolts) in each case.

With the exception of the curve for prednisolone in methanol and curves for all the compounds in ethanol at *p*H 10.2 the reciprocal slopes obtained were 0.059 (maximum deviation 0.004). The log plots of the curves obtained at *p*H 10.2 had lower reciprocal slope values (0.043 to 0.050). Prednisolone in methanol at *p*H 5.5 gave a curve whose log plot slope was 0.078. The difference in slope between that obtained for prednisolone in methanol and that obtained in ethanol is apparently due to the deformation of the methanolic prednisolone wave.

Reversibility.—The linear plots of half-wave potentials against *p*H which have line slope values of approximately 0.059 volt per *p*H unit are strong evidence that the potential-determining step in the reduction of these compounds is reversible. An additional criterion of reversibility is satisfied when values of $n = 1$, determined by substitution of the experimental diffusion coefficients into the Ilkovic equation, are coupled with reciprocal slope values of 0.059 obtained from the plots of log $[i/i_d - i]$ *vs.* E at *p*H 5.5. Since the final reduction products as suggested in the mechanism section cannot be reversibly oxidized to the starting materials, this reversible step then must be followed by an irreversible step.

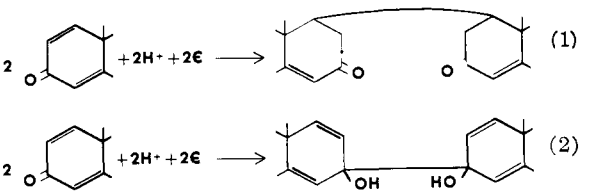
The low reciprocal slope values yielded by the curves obtained in *p*H 10.2 solutions are probably due to a change in electrode reaction and not to any irreversibility of the potential-determining reaction. Generally, curves whose half-waves are independent of concentration and yet are partly or wholly irreversible can be represented by the equation

$$E = E_{1/2} + \frac{0.059}{\alpha} \log \frac{i}{i_d - i}$$

where α is less than one. The curves in question yield "α" values greater than one, even though the diffusion currents obtained indicate that the electrode reaction is still substantially a one-electron process. Also, it has been reported[8] that certain unsaturated and aromatic ketones are reduced by a one-electron bimolecular process in acid solution, but that varying amounts of the homologous alcohols (a two-electron reduction) are formed in basic solutions. A combination of a one-electron process with small amounts of a two-electron process could easily give n-values slightly greater than one which are true pictures of the electrode reaction and not signs of irreversibility.

Mechanism.—One-electron bimolecular reduction processes have been reported for the electrolytic reduction of unsaturated and aromatic ketones[8] and dicarbonyl compounds.[12]

The two types[8] of electrolytic bimolecular reductions observed for unsaturated ketones are (1) 1,4-reduction resulting in a bimolecular ketone and (2) 1,2-reduction resulting in the formation of a pinacol.



The 1,4-addition product for the $\Delta^{1,4}$-3-ketosteroids, illustrated in reaction 1, still contains a carbonyl group conjugated with a double bond.

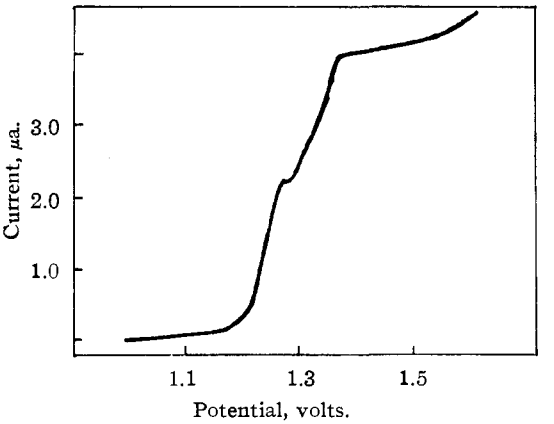


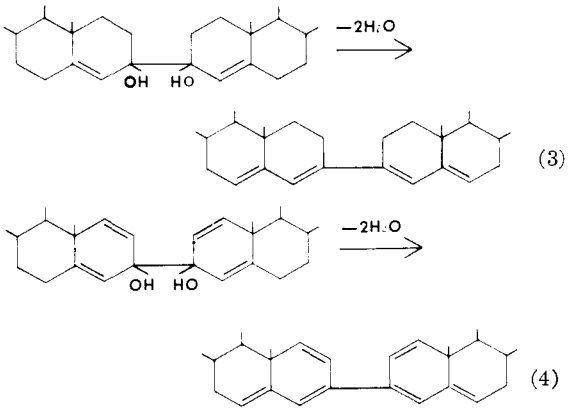
Fig. 2.—Polarogram of 2.3 mM prednisolone in 50% ethanol, *p*H 5.5.

(12) J. C. Pariaud, J. Modiano, R. Sorel and R. Stefani, *Compt. rend.*, **239**, 1217 (1954).

This product should give a second wave corresponding to the reduction of the Δ^4-3-ketosteroid or the Δ^1-3-ketosteroid depending on the coupling points. No such wave is in evidence. The pinacol formation product, reaction 2, contains no conjugation and therefore should be polarographically inert in the range studied. Reaction 2 then probably corresponds to the electrode process in acid solution and probably accounts for the major part of the electrode reaction in the alkaline solutions for at least three of the compounds investigated.

The electrode process involved in the reduction of prednisone in alkaline solutions is apparently somewhat different from that of the other three compounds. The height and *p*H dependency of the first wave indicate that the corresponding electrode reaction is a one-electron, reversible process. The height and *p*H-independent nature of the second wave (varies only 0.06 volt over a *p*H span of 4.5 units) indicate that it is probably a one-electron, irreversible process. The total electrode process at some point on the diffusion plateau of the second wave would then correspond to a one-electron reversible step, followed closely by a one-electron irreversible step. This is essentially the same process proposed by Coulson and Crowell[13] for the reduction of benzaldehyde at the dropping mercury electrode.

Controlled Potential Electrolysis.—Macro amounts of prednisone, cortisone, prednisolone and hydrocortisone in 50% ethanol solutions having a *p*H of 5.5 have been electrolyzed at a stirred mercury pool cathode at controlled potentials. A low threshold current integrator has given *n*-values between 0.9 and 1.0 electron per molecule for the reduction of each of these compounds. The isolated electrolysis products which have not been completely characterized no longer have the Δ^4-3-keto or $\Delta^{1,4}$-3-keto ultraviolet absorption. Upon dehydration, the cortisone and the hydrocortisone reduction products yielded compounds having ultraviolet absorption maxima at 294, 308 and 323 mμ in methanol. These values agree well with the absorption maxima reported[14] for the tetraene structure in 3,3′-bis-3,5-cholestadiene. Upon dehydration, the prednisone and the prednisolone reduction products yielded compounds having a single absorption maximum at 316 mμ rather than the triplet listed above.



These preliminary studies seem to substantiate the hypothesis that the one-electron reduction product of these steroids is a pinacol.

(13) D. M. Coulson and W. R. Crowell, THIS JOURNAL, **74**, 1290 (1952).

(14) R. Dulou, J. Chopin and Y. Raoul, *Bull. soc. chim. France*, 616 (1951).

BLOOMFIELD, NEW JERSEY

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

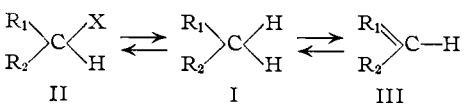
Spectral and Stereochemical Studies with Deuterated Cyclohexanes[1]

BY E. J. COREY, M. GERTRUDE HOWELL, ALMA BOSTON, RICHARD L. YOUNG AND RICHARD A. SNEEN

RECEIVED MARCH 26, 1956

Analysis of infrared absorption due to C–D stretching vibrations is introduced as a tool for determining the orientation of deuterium substituents in cyclohexane systems. The utility of the method is shown by its applicability in three varied examples to distinguish between epimers having axial and equatorial deuterium. The stereochemistry of the reduction of cholesteryl tosylate with lithium aluminum hydride has been studied with deuterium tracer with the finding that the reaction proceeds by way of the cyclocholesteryl cation (substitution at C_3 with retention of configuration) instead of by concerted nucleophilic displacement. The stereochemistry of electrophilic substitution by hydrogen also has been studied briefly and has been found to involve retention of configuration to a high degree in the cases studied.

Stereochemistry is a matter of interest whenever carbon–hydrogen bonds are formed or broken in the system II ⇄ I ⇄ III.



II I III

In each step the acquisition or loss of hydrogen may take place in either of two ways which differ stereochemically because they involve a different spatial relationship between the leaving or entering hydrogen, the central carbon atom and the remaining substituents. The stereochemistry of these transformations is usually studied by the substitution of deuterium or tritium in place of one of the hydrogens of I because of the fact that with singly and stereospecifically labeled I the stereochemistry of the change II ⇄ I ⇄ III can be determined by methods which take advantage of the isotope-induced asymmetry in I. When operable, these methods are capable of distinguishing between the two stereoisomeric forms of labeled I having opposite configurations at the central carbon atom.

(1) Taken in part from the B.S. Theses of M. H., A. B. and R. L. Y.