Results

The acid–base dissociation constants of the N,N′-dialkylethylenediamines are nearly the same from methyl to *n*-butyl with a slight rise in pK_1 and pK_2 with NN′-di-Eten. This same maximum was noted previously for pK_2 of the N-alkylethylenediamine series[2] at N-ethylethylenediamine, although it was not found in pK_1. As is the case in the N-alkylethylenediamine series, NN′-di-*i*-Pren is a stronger base than NN′-di-*n*-Pren. It is likewise noteworthy that although the pK_2 values of the N,N′-dialkylethylenediamines are similar to the pK_2 values of the N-alkylethylenediamines, these are not the same.

TABLE II

DISSOCIATION CONSTANTS AND HEATS OF NEUTRALIZATION OF N,N′-DIALKYLETHYLENEDIAMINES

Amine	pK_1 0°	pK_1 25°	pK_2 0°	pK_2 25°	ΔH, kcal. ΔH_1	ΔH_2
NN′-diMeen[a]	8.30	7.47	10.89	10.29	−12.4	− 8.9
NN′-diEten	8.53	7.70	11.06	10.46	−12.4	− 8.9
NN′-di-*n*-Pren	8.14	7.53	10.97	10.27	− 9.1	−10.4
NN′-di-*n*-Buen	8.18	7.46	10.93	10.19	−10.7	−11.0
NN′-di-*i*-Pren	8.26	7.59	11.12	10.40	−10.0	−10.7

[a] 7.28, 10.06 (No specific temperature was given). Irving, Paper No. 4, "A Discussion on Coördination Chemistry," Butterwick Research Laboratories, I.C.I., Sept. 21–2, 1950.

TABLE III

DISSOCIATION CONSTANTS AND HEATS OF NEUTRALIZATION OF C-SUBSTITUTED ETHYLENEDIAMINES

Amine	pK_1 0°	pK_1 25°	pK_2 0°	pK_2 25°	ΔH, kcal. ΔH_1	ΔH_2
pn[a]	7.81	7.13	10.76	10.00	−10.1	−11.3
dl-bn	7.60	6.91	10.69	10.00	−10.3	−10.3
m-bn	7.55	6.92	10.63	9.97	− 9.4	− 9.8
iso-bn	7.41	6.79	10.74	10.00	− 9.2	−11.0
TetraMeen	7.18	6.56	10.73	10.13	− 9.2	− 8.9
dl-stien (50% dioxane)	4.60	3.95	8.85	8.09	− 9.7	−11.3
m-stien (50% dioxane)	5.55	4.78	8.59	7.85	−11.6	−11.0

[a] 7.00, 9.78 (30°, 0.5 KNO_3). Carlson, McReynolds and Verhoek, THIS JOURNAL, 67, 1334 (1945).

Substitution of methyl groups in the carbons of an ethylenediamine skeleton only slightly decreases the base strength of the amine. However, substitution of phenyl groups, as in stilbenediamine, appears to decrease the base strength but it must be remembered that much of this decrease may be due to a change in solvent. Little difference was noted between *dl*-bn and *m*-bn although the former was slightly more basic, while pK_1 of *dl*-stien is slightly larger than that for *m*-stien and the reverse is true for their pK_2 values.

The heats of neutralization are in the range of −9 to −12 kcal. which is slightly higher than that found for the N-alkylethylenediamines.

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$\Delta^{5,7}$-Steroids. XV.[1] $\Delta^{3,5,7}$-Cholestatriene-3-ol Acetate

BY SEYMOUR BERNSTEIN, MILTON HELLER AND JAMES H. WILLIAMS

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In the previous paper of this series, there was described the preparation of $\Delta^{3,5,7}$-cholestatriene-3-ol acetate by the treatment of $\Delta^{4,7}$-cholestadiene-3-one with acetic anhydride and pyridine. The physical constants [m.p. 101.5–103°; $\lambda_{max}^{abs.\ alc.}$ 302.5–303, 315 and 330.5 mμ, ε17900, 22600, and 16200, respectively; $[\alpha]^{25}D$ −147° (chloroform)] of this preparation were strikingly different than those reported by Dauben and co-workers,[2] who prepared this enol acetate from $\Delta^{4,6}$-cholestadiene-3-one with acetic anhydride and acetyl chloride. In view of the reported conversion of $\Delta^{4,6,22}$-ergostatriene-3-one with acetic anhydride and acetyl chloride to $\Delta^{2,4,6,22}$-ergostatetraene-3-ol acetate (64% yield),[3] it was proposed[1] that the California preparation may have consisted of mixed crystals of $\Delta^{2,4,6}$- and $\Delta^{3,5,7}$-cholestatriene-3-ol acetates.

We now wish to report that, in our hands, treatment of the $\Delta^{4,6}$-3-ketone with acetic anhydride and acetyl chloride gave $\Delta^{3,5,7}$-cholestatriene-3-ol acetate (27% yield), identical in *all* respects with the compound prepared from the $\Delta^{4,7}$-3-ketone. A spectral analysis of the initial mother liquors obtained on the recrystallization of the enol acetate indicated the presence of only starting material (?), and no $\Delta^{3,5,7}$- or $\Delta^{2,4,6}$-enol acetates. This may be accounted for by incomplete reaction, or by unintentional hydrolysis of any enol acetate present. Whether or not a $\Delta^{4,6}$-3-ketone under these conditions gives rise to a mixture of enol acetates remains unsolved.

To substantiate further this method of preparing a $\Delta^{3,5,7}$-enol acetate from a $\Delta^{4,6}$-3-ketone, $\Delta^{4,6}$-androstadiene-17β-ol-3-one benzoate was transformed into $\Delta^{3,5,7}$-androstatriene-3,17β-diol-3-acetate-17-benzoate.

Finally, mention should be made of a pertinent optical rotational analysis. It is known that if C-17 "vicinal action" is absent, a compound with an "ergosterol" side chain will have a specific rotation of about 20° ($\Delta[M]D$ 78°) *more negative* than the corresponding "cholesterol" compound.[4] An examination of the rotations of the four compounds compiled in Table I reveals gross irregularities which unequivocally indicate "vicinal action." These anomalies may be explainable by the suggestion of Barton and Cox[5] of a possible qualitative correlation between anomalies and the ultraviolet absorption spectra of the compounds.

TABLE I

ROTATIONAL ANALYSIS

Compound	$[\alpha]D$ ($CHCl_3$)	$\Delta[\alpha]D$
$\Delta^{4,7}$-Cholestadiene-3-one	+33°[a]	...
$\Delta^{4,7,22}$-Ergostatriene-3-one	−12°[a]	45°
$\Delta^{3,5,7}$-Cholestatriene-3-ol acetate	−147,[a] −145[b]	...
$\Delta^{3,5,7,22}$-Ergostatetraene-3-ol acetate	−144[a]	0

[a] See ref. 1. [b] This work.

(1) Paper XIV, R. Antonucci, S. Bernstein, M. Heller and J. H. Williams, *J. Org. Chem.*, **17**, 1446 (1952).

(2) W. G. Dauben, J. F. Eastham and R. A. Micheli, THIS JOURNAL, **73**, 4496 (1951); m.p. 91–93°, $\lambda_{max}^{alc.}$ 305, 316 and 330 mμ, ϵ_{316} 20,000; $[\alpha]^{25}D$ −69° (chloroform).

(3) I. M. Heilbron, T. Kennedy, F. S. Spring and G. Swain, *J. Chem. Soc.*, 869 (1938).

(4) S. Bernstein, W. J. Kauzmann and E. S. Wallis, *J. Org. Chem.*, **6**, 319 (1941).

(5) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948).

Experimental[6]

$\Delta^{3,5,7}$-Cholestatriene-3-ol Acetate.—A solution of 200 mg. of $\Delta^{4,6}$-cholestadiene-3-one[7] in 10 ml. of acetic anhydride and 20 ml. of acetyl chloride was refluxed for 6 hours, and evaporated *in vacuo*. The residue was treated with methanol which in turn was removed by evaporation *in vacuo*. The methanol treatment was repeated. One recrystallization from methanol afforded 0.18 g., m.p. 91–95°; $\lambda_{max}^{abs.\ alc.}$ 302–303, 316 and 331 mμ, ε13000, 15700 and 11000, respectively (59% *"spectroscopic"* yield based on ϵ_{316} 22000). Three further recrystallizations from methanol yielded 60 mg. (27% yield) of pure enol acetate, m.p. 101–102°; $\lambda_{max}^{abs.\ alc.}$ 302.5, 316 and 331 mμ, ε 17300, 21900 and 15300, respectively; $[\alpha]^{27}D$ −145° (7.2 mg., αD −0.51°). The m.p. was undepressed on admixture with the sample prepared from the $\Delta^{4,7}$-3-one. The infrared spectra were identical in all respects.

The first three mother liquors were combined, and evaporated *in vacuo* and gave an oily residue, $\lambda_{max}^{abs.\ alc.}$ 284–287 mμ (starting material?).

$\Delta^{3,5,7}$-Androstatriene-3,17β-diol-3-acetate-17-benzoate.—To a solution of 0.61 g. of $\Delta^{4,6}$-androstadiene-17β-ol-3-one benzoate[8] in 2 ml. of toluene was added 7 ml. each of acetic anhydride and acetyl chloride. The mixture was refluxed for 4 hours, and was worked-up as above; wt. 0.16 g. (from methanol), m.p. 154–156°; $\lambda_{max.}^{abs.\ alc.}$ 228, 302, 314 and 329 mμ, ε17600, 18200, 22000 and 15500, respectively, $[\alpha]^{27}D$ −71.4° (16 mg., αD −0.57°); 24% yield.

Anal.[9] Calcd. for $C_{28}H_{32}O_4$ (432.54): C, 77.75; H, 7.46. Found: C, 77.53; H, 7.69.

(6) All m.ps. are uncorrected, and were determined with uncalibrated Anschütz thermometers. Optical rotations were performed by solution of the sample in chloroform to make a 2 ml. solution, and were determined in a 1-dm. semi-micro tube.

(7) A. L. Wilds and C. Djerassi, THIS JOURNAL, **68**, 1719 (1946).

(8) C. Meystre and A. Wettstein, *Experientia*, **2**, 408 (1946).

(9) We wish to thank Mr. Samuel S. Modes for the microanalysis.

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Steroidal Cyclic Ketals. IV.[1] The Conversion of 11-Keto- to 11α-Hydroxysteroids. The Preparation of 11-*Epi*-hydrocortisone, and Δ^4-Androstene-11α-ol-3,17-dione

BY SEYMOUR BERNSTEIN, RUDDY LITTELL AND JAMES H. WILLIAMS

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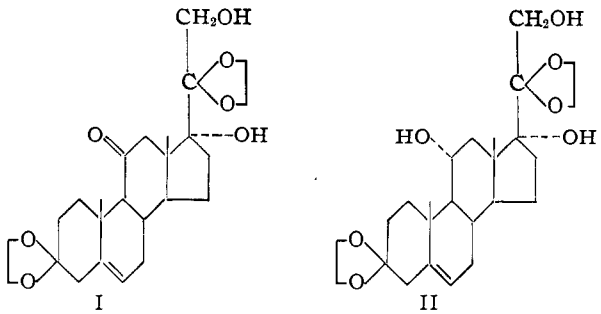
We have recently reported[1] that reduction of the diethylene ketal of cortisone (Δ^5-pregnene-17α,21-diol-3,11,20-trione-3,20-di-ethylene ketal) (I) in tetrahydrofuran with excess lithium aluminum hydride in ether produced not only the expected 11β-hydroxy compound (di-ethylene ketal of hydrocortisone) (58% yield), but also the 11α-hydroxy-compound (di-ethylene ketal of 11-*epi*-hydrocortisone) (II) (8% crude yield). Acid hydrolysis of the latter afforded 11-*epi*-hydrocortisone. This constituted the first time the 11α-epimer has been isolated and characterized in such a reduction. Moreover, the product itself was of interest as it differs solely from the physiologically important hydrocortisone by the configuration of the C-11 hydroxyl group.



I II

(1) Paper III, R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, in press.

The microbiological preparation of 11-*epi*-hydrocortisone has been reported by Murray and Peterson,[2] and by Fried and co-workers.[3] Romo and co-workers[4] have announced the conversion of 11α-hydroxyprogesterone to 11-*epi*-hydrocortisone by incubation of the former with adrenal breis, as well as the chemical synthesis of 11-*epi*-hydrocortisone diacetate from Δ^{16}-allopregnene-3β,11α-diol-20-one diacetate. A closely related synthesis of 11-*epi*-hydrocortisone diacetate has been described by Hershberg and co-workers.[5] It is to be noted that neither the Syntex nor Schering groups have prepared chemically the free steroid, 11-*epi*-hydrocortisone.

In view of the need for a more facile preparation of 11-*epi*-hydrocortisone, and, in general, of 11α-hydroxy-Δ^4-3-ketosteroids, this Laboratory has undertaken a study of the reduction of 11-ketosteroids. While this work was in progress there appeared two publications[5,6] which have an important bearing on this problem. It was shown that reduction of an 11-keto group with sodium and propanol gave in good to excellent yields the corresponding 11α-hydroxy compound. In light of this work, we wish to record that this conversion has been accomplished independently in this Laboratory by use of lithium in liquid ammonia in the presence of alcohol.[7] Under these conditions, the diethylene ketal (I) of cortisone was transformed in 82% yield to the practically pure 11α-hydroxy compound (II). Compound II was identical with the material obtained in the lithium aluminum hydride reduction. Acid hydrolysis gave in 60% yield pure 11-*epi*-hydrocortisone.

This procedure, which involves protection of the reactive keto-groups as ethylene ketals followed by lithium–liquid ammonia–alcohol reduction of the 11-keto group, is apparently general, and has been applied successfully to adrenosterone. The latter was converted accordingly into Δ^4-androstene-11α-ol-3,17-dione.

Experimental[8]

Diethylene Ketal of 11-*epi*-Hydrocortisone (Δ^5-Pregnene-11α,17α,21-triol-3,20-dione-3,20-diethylene Ketal) (II).—

(2) H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769 (July 8, 1952).

(3) J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, THIS JOURNAL, **74**, 3962 (1952).

(4) J. Romo, A. Zaffaroni, J. Hendrichs, G. Rosenkranz, C. Djerassi and F. Sondheimer, *Chemistry and Industry*, 783 (1952).

(5) H. L. Herzog, E. P. Oliveto, M. A. Jevnik and E. B. Hershberg, THIS JOURNAL, **74**, 4470 (1952).

(6) H. Heusser, R. Anliker and O. Jeger, *Helv. Chim. Acta*, **35**, 1537 (1952).

(7) This reduction procedure was suggested by the work of F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 2696 (1952).

(8) All m.ps. are uncorrected and were determined with uncalibrated Anschütz thermometers. All optical rotations are for 2 ml. of solution in the stated solvent and were determined in a 1-dm. semi-micro tube.