TABLE I

N,N,N',N'-TETRAALKYLOXAMIDES, $R_2NCOCONR_2$

R	Formula	B.p. °C.	Mm.	M. p., °C.	$n^{25}D$	d^{25}_4	Yield, %	Nitrogen analyses, % Calcd.	Found
Ethyl[a]	$C_{10}H_{20}N_2O_2$	148–152	10–12	45–47	....	...	75	...	...
n-Propyl[a]	$C_{14}H_{28}N_2O_2$	110–113	0.5	32–33	....	...	53	10.92	10.73
n-Butyl[b]	$C_{18}H_{36}N_2O_2$	132–135	.5	.....	1.4642	0.924	40	8.97	8.97
n-Amyl	$C_{22}H_{44}N_2O_2$	153–158	.5	.....	1.4643	.913	54	7.60	7.54
Isoamyl	$C_{22}H_{44}N_2O_2$	.....	...	51–52	....	...	75	7.60	7.93
n-Hexyl	$C_{26}H_{52}N_2O_2$	176–180	.5	.....	1.4632	.899	70	6.60	6.62
n-Heptyl	$C_{30}H_{60}N_2O_2$	193–197	.5	.....	1.4649	.892	75	5.83	5.85
Morpholino	$C_{10}H_{16}N_2O_4$	.....	...	186–188	....	...	75	12.28	12.05
Benzyl[c]	$C_{30}H_{28}N_2O_2$	.....	...	130–131	....	...	77	6.25	6.17

[a] R. Barré, *Ann. chim.*, 9, 204 (1928), reported R = ethyl, m.p., 31–32°, b.p. 142° (4 mm.); and R = propyl, m.p., 38–39°. [b] Mentioned by A. W. Campbell, U. S. Pat. 2,474,776 (June 28, 1949). [c] Recrystallized from benzene–ethanol.

TABLE II

TETRASUBSTITUTED ETHYLENEDIAMINES, $R_2NCH_2CH_2NR_2$

R	Formula	B.p. °C.	Mm.	$n^{25}D$	d^{25}_4	Yield, %	Nitrogen analyses, % Calcd.	Found	Picrate, m.p., °C.
Ethyl[a]	$C_{10}H_{24}N_2$	178–184	760	1.4330	0.799	87	16.26	15.98	240–243[b]
n-Butyl	$C_{18}H_{40}N_2$	156–158	11–13	1.4438	.808	74	9.85	10.29	185–186[c]
n-Amyl	$C_{22}H_{48}N_2$	192–194	10	1.4472	.823	80	8.23	8.31	143–144[d]
Benzyl[f,g]	$C_{30}H_{32}N_2$	.....	....	....	...	43	6.66	6.66	208–210[e]

[a] H. Gilman and R. M. Pickens, THIS JOURNAL, **47**, 245 (1925), reported b.p. 65° (8 mm.) and b.p. 70–72° (10 mm.) and a hydrochloride salt, m.p. of 187°. [b] H. R. Jones, F. A. Robinson and M. N. Straeharr, *J. Chem. Soc.*, 87 (1946), reported a m.p. of 243°. *Anal.* Calcd. for $C_{22}H_{30}N_8O_{14}$: N, 17.78. Found: N, 17.66. [c] *Anal.* Calcd. for $C_{30}H_{46}N_8O_{14}$: N, 15.09. Found: N, 14.92. [d] *Anal.* Calcd. for $C_{34}H_{54}N_8O_{14}$: N, 14.03. Found: N, 13.76. [e] *Anal.* Calcd. for $C_{42}H_{38}N_8O_{14}$: N, 12.79. Found: N, 12.87. [f] G. Lob, *Rec. trav. chim.*, **55**, 859 (1936), reported a m.p. 95°. [g] Our m.p. 93–94°.

and rapidly in ethyl ether to the corresponding tetraalkylethylenediamines. However, the tetrabenzyloxamide gave trouble on account of its slight solubility in ether. This was partially overcome by using a slurry in a mixture of tetrahydrofuran and ether. The air stability of the tetraalkylethylenediamines was greater than that observed for some of the dialkylethylenediamines.

Experimental

N,N,N',N'-Tetraalkyloxamide General Preparation.—The preparation of the tetraethyloxamide is typical. A solution of 32 g. of oxalyl chloride in 100 ml. of dry benzene was added dropwise to 37 g. of redistilled diethylamine (b.p. 54–55°) (760 mm.) and 50 g. of triethylamine in 350 ml. of benzene contained in a three-necked flask fitted with a stirrer, dropping funnel and reflux condenser protected with a calcium chloride tube. The reaction is highly exothermic and cooling was necessary. After all of the oxalyl chloride was added, the mixture was heated to reflux and filtered hot and the cake washed twice with hot benzene. The filtrate was concentrated *in vacuo* and the residue distilled. The fraction boiling at 148–152° at 10–12 mm., 38 g., solidified on cooling. This procedure was used for all except that the tetrabenzyloxamide crystallized out when the benzene solution was cooled and was purified by crystallization.

Reduction.—For the reduction a solution of 20 g. of tetraethyloxamide in 200 ml. of dry ether was added dropwise to 6 g., a 15% excess, of lithium aluminum hydride in 300 ml. of ether in a three-necked flask fitted with stirrer, dropping funnel and reflux condenser. Upon completion of the reaction (3–6 hr.) the complex was decomposed with water and the slurry filtered. The ether solution was concentrated and the residue distilled, yield 15 g., boiling 177–184°. The same procedure was used for the others except that the tetrabenzyloxamide had to be handled as a slurry and the reduction product was recrystallized.

The picrates were prepared by adding the diamine to an excess of a saturated ethanolic solution of picric acid. The mixture was refluxed for a few minutes and the picrate was filtered off from the hot mixture and washed three times with alcohol. Recrystallization from a large volume of ethanol did not raise the melting point.

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Steroidal Cyclic Ketals. VIII.[1] $\Delta^{4,9(11)}$-Pregnadiene-17α,21-diol-3,20-dione

BY SEYMOUR BERNSTEIN, RUDDY LITTELL AND JAMES H. WILLIAMS

RECEIVED JUNE 5, 1953

In the previous paper of this series,[1] there were described several experiments with C^{11}-α- and β-hydroxy compounds under a variety of conditions. The results showed that ionic elimination reactions with either epimer gave rise to the corresponding $\Delta^{9(11)}$-steroid. Concurrent to this investigation, we devised a method for the synthesis of $\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione (V),[2] the details of which will be presented here.

A synthesis of V was deemed highly desirable for evaluation of its biological activity, both as a mineralo- and glyco-corticoid. Moreover, this compound is of interest for a possible understanding of the enzymatic biosynthesis of C^{11}-hydroxylated steroids. On the basis that diphosphopyridine nucleotide (DPN) is required for C^{11}-β-hydroxylation by beef adrenal homogenates, Hayano and Dorfman[3] have postulated the possible transitory existence of a $\Delta^{9(11)}$- or Δ^{11}-steroid as an intermediate for hydroxylation; thus Reichstein's substance S → $\Delta^{4,9(11)}$- or $\Delta^{4,11}$-pregnadiene-17α,21-diol-3,20-dione → Reichstein's substance M (Kendall's compound F, hydrocortisone). Consequently, perfusion experiments with V would be highly significant.

A direct approach for the synthesis of this com-

(1) Paper VII, S. Bernstein, R. Lenhard and J. H. Williams, *J. Org. Chem.*, in process of publication.

(2) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953), have recently announced the synthesis of $\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (VI) from 11-*epi*-hydrocortisone. This publication appeared after completion of our work.

(3) M. Hayano and R. I. Dorfman, *J. Biol. Chem.*, **201**, 175 (1953).

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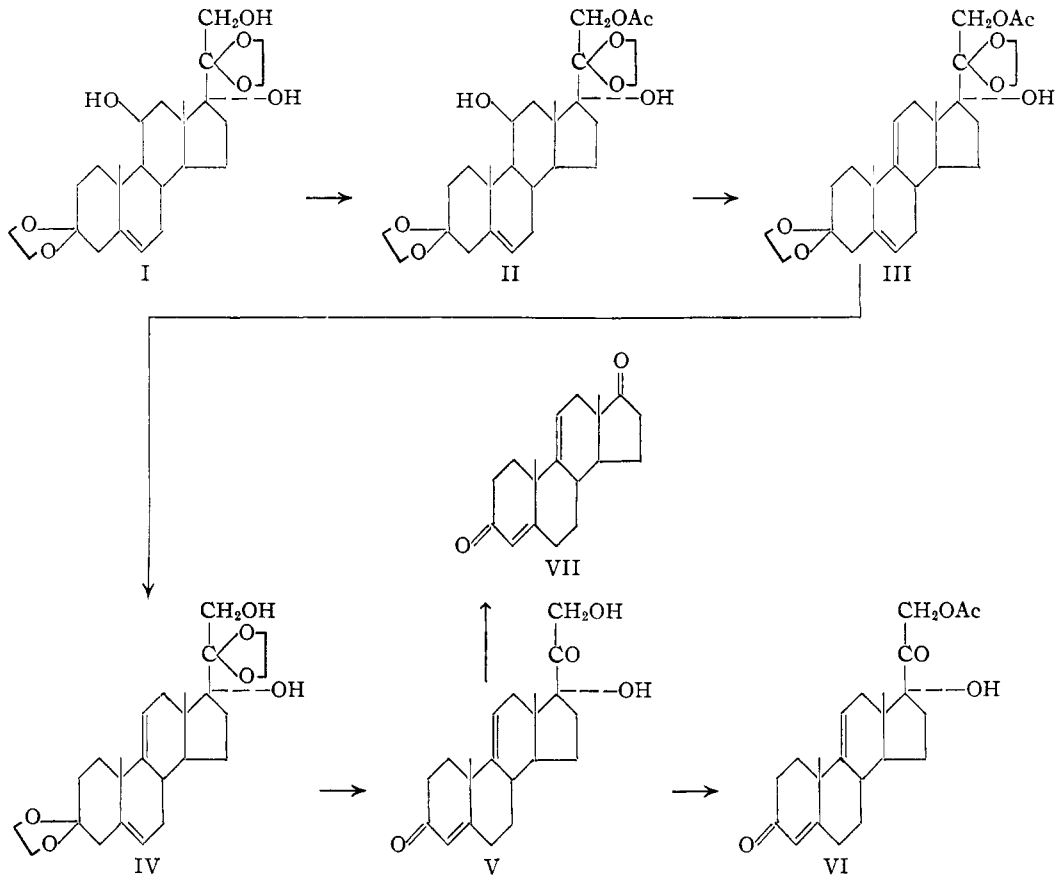

pound would be to perform a selective dehydration at the C^{11}-position of either hydrocortisone 21-monoacetate or 11-*epi*-hydrocortisone 21-monoacetate. An exploratory experiment with the former in this direction (phosphorus oxychloride–pyridine at room temperature) did not appear to be promising. Therefore, it was decided to explore a less direct although more productive route.

For this purpose, we first examined the stability of the C^{17}-α-hydroxyl group in the bis-ethylene ketal of cortisone acetate to phosphorus oxychloride–pyridine at room temperature (16 hours). An excellent return of starting material was obtained. This result together with our previous success with ketals of $C_{19}O_3$-steroids under these conditions for dehydration at C^{11} immediately suggested the bis-ethylene ketal derivative (II) of hydrocortisone 21-acetate as the desired intermediate.

Accordingly, the bis-ethylene ketal (I)[4] of hydrocortisone was acetylated with acetic anhydride and pyridine to give the C^{21}-monoacetate (II). Treatment of II in pyridine with phosphorus oxychloride at room temperature dehydrated selectively the C^{11}-β-hydroxyl group (*polar*–OH *trans* to *polar* C^9–H). Thereby, $\Delta^{5,9(11)}$-pregnadiene-17α,21-diol-3,20-dione-21-acetate-3,20-bis-ethylene ketal (III) was obtained in 70% yield. Alkaline hydrolysis of III gave IV (83% yield). The conversion of IV into the desired $\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione (V) was accomplished in 73% yield by removal of the ketal groups with sulfuric acid–methanol.

(4) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

Also V was prepared, but in lower yield, directly from the acetate-bis-ketal (III) by acid hydrolysis.

The structure of $\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione (V) was based on the following considerations, other than elemental and absorption analysis. The compound gave a pronounced positive Blue Tetrazolium color test, diagnostic for the α-ketol moiety. Acetylation (acetic anhydride–pyridine) resulted in the monoacetate (VI). Oxidation with chromic acid–acetic acid gave $\Delta^{4,9(11)}$-androstadiene-3,17-dione (VIII). The preparation of the latter from either Δ^4-androstene-11β-ol-3,17-dione or Δ^5-androstene-11α-ol-3,17-dione-bis-ethylene ketal has been described.[1]

Others will report on the biological experiments with $\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione (V).

Experimental

Melting Points.—All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers.

Optical Rotations.—The sample was dissolved in the stated solvent to make a 2-ml. solution, and the rotation was determined in a 1-dm. semi-micro tube at wave length 5893 Å. (D).

Absorption Spectra.—The ultraviolet spectra were determined in absolute alcohol with a Beckman spectrophotometer (model DU). The infrared spectra (Nujol mulls) were determined with a Perkin–Elmer spectrophotometer (model 21).

Petroleum Ether.—The fraction used was either b.p. 64–66° or 66–68°, and was purified with concentrated sulfuric acid and potassium permanganate.

Δ^5-Pregnene-11β,17α,21-triol-3,20-dione-21-acetate-3,20-bis-ethylene Ketal (II).—A solution of the bis-ethylene ketal (I) of hydrocortisone (0.8 g.) in pyridine (2 ml.) was treated with acetic anhydride (2 ml.), and was allowed to stand at room temperature overnight. The mixture was poured into

ice-water, and the resulting oil solidified on standing. The crystals were collected, and washed with water; 0.86 g., m.p. 190–197.5°. Recrystallization from acetone afforded pure II; 0.6 g., m.p. 199–201°; infrared spectrum: λ_{max} 3540 and 3440 cm.$^{-1}$ (hydroxyl), 1730 cm.$^{-1}$ (acetate carbonyl), 1695 cm.$^{-1}$ (weak,?), 1260 and/or 1230 cm.$^{-1}$ (C–O stretch acetate), 1102 cm.$^{-1}$ (C–O stretch, ketal[5] and hydroxyl); $[\alpha]^{27}D$ −26° (16.05 mg., chloroform, α_D −0.21°), $[M]_D$ −128.

Anal. Calcd. for $C_{27}H_{40}O_8$ (492.58): C, 65.83; H, 8.19. Found: C, 65.83; H, 8.28.

$\Delta^{5,9(11)}$-Pregnadiene-17α,21-diol-3,20-dione-21-acetate-3,-20-bis-ethylene Ketal (III).—A solution of the bis-ethylene ketal (II) of hydrocortisone acetate (0.1 g.) in pyridine (1 ml.) was treated in the cold with phosphorus oxychloride (0.082 ml.). The mixture was allowed to stand at room temperature for 64 hours[6] when water was added (ice-cooling). The resulting crystals were collected; 84 mg., m.p. 195–197°. One recrystallization from acetone–petroleum ether gave 67 mg., m.p. 197–199° (70% yield). Two further recrystallizations did not alter the m.p. appreciably; 49 mg., m.p. 198–199°; λ_{max} none; infrared spectrum: λ_{max} 3560 cm.$^{-1}$ (hydroxyl), 1740 cm.$^{-1}$ (acetate carbonyl), 1259 and 1245 cm.$^{-1}$ (C–O stretch, acetate), 1096 cm.$^{-1}$ (C–O stretch, ketal and hydroxyl); negative Beilstein test for chlorine; $[\alpha]^{22}D$ −14° (14.8 mg., chloroform, α_D −0.10°), $[M]_D$ −66.

Anal. Calcd. for $C_{27}H_{38}O_7$ (474.57): C, 68.33; H, 8.07. Found: C, 68.22; H, 8.34.

$\Delta^{5,9(11)}$-Pregnadiene-17α,21-diol-3,20-dione-3,20-bis-ethylene Ketal (IV).—A solution of the bis-ketal acetate (III, 0.56 g.) in 2.5% alcoholic potassium hydroxide (15 ml.) was refluxed for one-half hour, treated with water, and cooled. The crystals were collected, m.p. 199–200°, cloudy melt. Recrystallization from acetone–petroleum ether gave 425 mg. (83% yield) of IV, m.p. 198–200°. Admixture m.p. determination with starting material (III) showed non-identity, m.p. 190–192°; infrared spectrum: λ_{max} 3470 cm.$^{-1}$ (hydroxyl), no carbonyl, 1094 cm.$^{-1}$ (C–O stretch, ketal and hyroxyl); $[\alpha]^{23}D$ −10° (21.2 mg., chloroform, α_D −0.11°), $[M]_D$ −43.

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.62; H, 8.23.

$\Delta^{4,9(11)}$-Pregnadiene-17α,21-diol-3,20-dione (V). A.—A solution of III (250 mg.) in alcohol (20 ml.) was refluxed for 1 hour with 8.5 % (v./v.) sulfuric acid (2.5 ml.). Methanol was added; the solution was neutralized with sodium bicarbonate, and filtered. The filtrate was concentrated *in vacuo* until crystals separated. Water was added, and the crude product was collected; 147 mg., m.p. 239–241° dec., with previous softening. Five recrystallizations from acetone–petroleum ether afforded pure V; 21 mg., m.p. 259–260° dec. with previous softening; λ_{max} 237.5–239 mμ (ϵ 16000); infrared spectrum: λ_{max} 3530 and 3480 cm.$^{-1}$ (hydroxyl), 1715 cm.$^{-1}$ (C^{20}-carbonyl), 1665 cm.$^{-1}$ (C^3-carbonyl), 1620 cm.$^{-1}$ (double bond), 1102 cm.$^{-1}$ (C–O stretch, hydroxyl).

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 73.07; H, 8.12.

B.—A solution of IV (375 mg.) in methanol (25 ml.) was refluxed for 1 hour with 8.5% (v./v.) sulfuric acid (3 ml.). Addition of water followed by cooling gave 265 mg., m.p. 245–246°. Pure V was obtained by recrystallization from acetone–petroleum ether; 0.22 g. (73% yield), m.p. 259–261° dec., with previous softening, positive Blue Tetrazolium test for α-ketol moiety; $[\alpha]^{23}D$ +88° (12.3 mg., pyridine, α_D +0.54°), $[M]_D$ +302.

$\Delta^{4,9(11)}$-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate (VI).—The free steroid (V, 38 mg.) in pyridine (2 ml. was acetylated with acetic anhydride (1 ml.) (15 hr., room temperature). Ether was added; the mixture was cooled, and the crystals were collected; 41 mg., m.p. 235–236° with previous softening. Two recrystallizations from acetone–ether gave pure VI; 20 mg., m.p. 239.5–241°, with previous softening; λ_{max} 238.5–240 mμ (ϵ 16600); infrared spectrum: λ_{max} 3450 cm.$^{-1}$ (hydroxyl), 1755 cm.$^{-1}$ (acetate carbonyl), 1730 cm.$^{-1}$ (C^{20}-carbonyl), 1660 cm.$^{-1}$ (C^3-carbonyl), 1620 cm.$^{-1}$ (double bond), 1238 cm.$^{-1}$ (C–O stretch, acetate), 1100 cm.$^{-1}$ (weak C–O stretch, hydroxyl); $[\alpha]^{23}D$ +120° (9.2 mg., chloroform, α_D +0.55°), $[M]_D$ +463.

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.64; H, 8.00.

$\Delta^{4,9(11)}$-Androstadiene-3,17-dione (VII).—The free steroid (V, 125 mg.) in glacial acetic acid (10 ml.) was oxidized with a solution of chromic anhydride (160 mg.) in water (4 drops) and glacial acetic acid (10 ml.) (18 hours, room temperature). The mixture was evaporated *in vacuo* at below 30°. The product was extracted with ether, and the residue obtained on evaporation was submitted to chromatographic analysis (10 g. of aluminum oxide, Merck). The product was eluted from the column with 100% ether; 28 mg. Recrystallization from acetone–petroleum ether (Norit treatment) gave 10 mg. of the dione (VII), m.p. 203–205.5° with previous softening and darkening. Admixture m.p. determination with authentic sample (m.p. 204–206°) gave no depression, m.p. 203–206.5°, λ_{max} 238–239 mμ (ϵ 14800); infrared spectrum: λ_{max} no hydroxyl, 1745 cm.$^{-1}$ (C^{17}-carbonyl), 1670 cm.$^{-1}$ (C^3-carbonyl), 1620 cm.$^{-1}$ (double bond). The infrared spectrum was identical with that of an authentic sample.

Bis-dinitrophenylhydrazone.—M.p. 290° dec., literature[1] m.p. 292.5–293.5° dec.

Acknowledgment.—We are indebted to Messrs. Louis M. Brancone and Samuel S. Modes for the microanalytical data, and to Mr. William Fulmor for the infrared spectra.

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(5) *One* of the principal C–O stretch bands of an ethylene ketal.

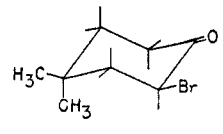
(6) The minimal time required for this dehydration was not investigated.

The Stereochemistry of α-Haloketones. IV. The Stable Orientation of Bromine in 2-Bromocholestane-3-one

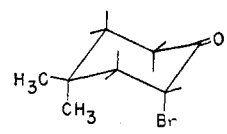
BY ELIAS J. COREY

RECEIVED APRIL 30, 1953

Recently[1] we have described a method for predicting the stable orientation of bromine in α-bromoketosteroids of both the normal and allo series. Application of this method to 2-bromo-3-ketoallosteroids leads to the expectation that the stable epimer should be that in which bromine is α-oriented. This conclusion follows from the fact that the stable molecular configuration of 2-bromo-4,4-dimethylcyclohexanone is IA and not IB.[2]



IA



IB

We have found that 2-bromocholestane-3-one, m.p. 170–170.5°,[3] is not subject to epimerization under the influence of hydrogen bromide in acetic acid, and hence should be formulated as the 2α-bromo epimer. This assignment, which is also indicated by the infrared spectrum of the substance,[4] has now been proved by a chemical method.

After the completion of this work a paper appeared in which the very same reaction sequence that we used was reported to afford results entirely

(1) E. J. Corey, Part III, *Experientia*, in press.

(2) E. J. Corey, THIS JOURNAL, **75**, 2301 (1953).

(3) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935); J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **29**, 654 (1935).

(4) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952).