TABLE I

POTENTIALS OF BARIUM STEARATE MULTILAYER MEMBRANE ELECTRODES

Chain S.C.E. ‖Solution 1 |Membrane |Solution 2 ‖S.C.E.
Temperature, 25°

Solution 1 *M*	Solution 2 *M*	Experimental e.m.f. (corr.), mv.	Calcd. e.m.f., mv.
0.002 $BaCl_2$	0.001 $BaCl_2$	7.65	7.88
0.02 $BaCl_2$	0.01 $BaCl_2$	6.65	6.55
0.01 $BaCl_2$	0.001 $BaCl_2$	25.15	24.21
1.0 $BaCl_2$	0.5 $BaCl_2$	5.28	4.96
0.02 $BaCl_2$	0.01 $BaCl_2$	6.85	7.01
	0.005 NaCl		
0.02 $BaCl_2$	0.01 $BaCl_2$	8.10	8.22
	0.02 NaCl		
1.0 $BaCl_2$	0.5 $BaCl_2$	3.27	..
	2.0 NaCl		

ions or anions could in principle be prepared from insoluble or non-ionized salts which formed multilayers; further work in this direction is in progress.

The specific resistance of the multilayer *transverse* to the axis of orientation was 1.9×10^4 ohm cm. A Multilayer Membrane 50 Å. thick (10 molecule multilayer row) would have a resistance of 0.01 ohm cm.^{2}, a value which approximates that of ion-specific natural membranes.

Multilayer Membrane Electrodes can be used to measure activities of ions in mixed electrolytes. Problems of biochemical interest similarly can be attacked, such as the determination of calcium ion activities, the so-called "unbound" calcium concentration, in blood and other biological fluids.

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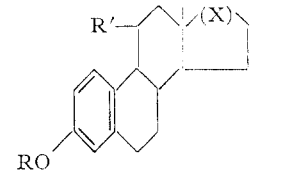
SYNTHESIS OF THE NOVEL 11-OXYGENATED 1,3,5-(10)-ESTRATRIENES

Sir:

Although aromatic A ring steroids are well known, their 11-oxygenated analogs have not been described.[1] We have prepared several members of this novel class of steroids and also have converted them to 11-oxygenated 19-norsteroids hitherto only available through the 11-hydroxylation of the corresponding 11-desoxy-19-norsteroids.[2,7]

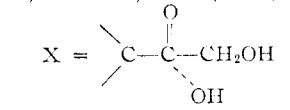
The key intermediate for these chemical transformations is 19-nor-1,3,5(10),17(20)-pregnatetraene-3,11β,21-triol (I), m.p. 200–202°; $[\alpha]_D$ + 110° (acetone); λ_{max}^{EtOH} 281 mμ, a_M 2,000; (*Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.35. Found: C, 76.62; H, 8.66). The surprising stability of the 11β-hydroxyl group under pyrolytic conditions was demonstrated by the conversion of 11β,21-dihydroxy-1,4,17(20)-[*cis*]-pregnatrien-3-one[3] to I in 15% yield at 575° in a mineral oil suspension.[4] Methylation of I yielded the 3-methyl ether, m.p. 143–144°; $[\alpha]_D$ + 122° (chloroform); (*Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.94; H, 8.74). Acetylation gave the oily 11,21-diacetate[5] which when ozonized furnished



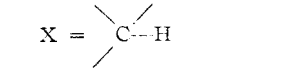
I, R = H; R′ = β-OH; X = >C=CH—CH_2OH

II, R = CH_3; R′ = β-OAc; X = >C=O

IV, R = CH_3; R′ = β-OAc; X = >C(HO)—C(=O)—CH_2OAc

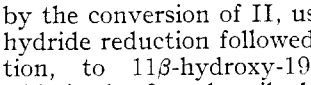


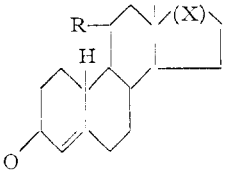
VI, R = OH; R′ = β-OH; X = C(OH)(—C(=O)—CH_2OH)



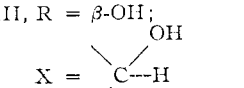
VII, R = OH; R′ = β-OH; X = >C—H

VIII, R = OH; R′ = α-OH; X = C(OH)—H





III, R = β-OH; X = C(OH)—H



V, R = β-OH; X = C(OH)—C(=O)—CH_2OH

the 11β-acetoxy-3-methoxy-1,3,5(10)-estratrien-17-one (II), m.p. 236–238°; $[\alpha]_D$ + 117° (chloroform); (*Anal.* Calcd. for $C_{20}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.46; H, 7.60). The structure of II and therefore also that of I was established by the conversion of II, using a lithium aluminum hydride reduction followed by a Birch type reduction, to 11β-hydroxy-19-nortestosterone (III).[6] This is the first described synthesis of an 11-oxygenated 19-norsteroid wherein the 11-hydroxyl group was present during the chemical modification of Ring A.

A novel reaction was encountered when II was reduced with lithium in ammonia in the presence of alcohol. The expected product III was not detected, but a compound was isolated to which the following structure is assigned: 1-(α-hydroxyethyl)-11β,17β-dihydroxy-4-pregnen-3-one, m.p. 221–222°, λ_{max}^{EtOH} 247 mμ, a_M = 15,000; (*Anal.* Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 72.04; H, 8.90; C-Methyl 2). Oxidation of this compound gave an oily tetraone which showed a maximum in the ultraviolet at 240 mμ, thus ruling out a hydroxyethyl substituent at 2 or 4. We postulate that this unique compound may be formed by an internal Claisen type transfer of the

(1) 11-Ketoequilenin, which has *both* aromatic A and B rings was described by R. E. Marker and E. Rohrman, THIS JOURNAL, **61**, 3314 (1939).

(2) The 11α-hydroxyl group was introduced into a 19-norsteroid by a microbiological procedure, R. L. Pederson, J. A. Campbell, J. C. Babcock, S. H. Eppstein, H. C. Murray, A. Weintraub, R. C. Meeks, P. D. Meister, L. M. Reineke and D. H. Peterson, *ibid.*, **78**, 1512 (1956). The 11β-hydroxyl group was introduced by an adrenal perfusion technique, F. B. Colton and J. W. Ralls, U. S. Patent 2,694,080 (1954).

(3) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, B. J. Magerlein, W. P. Schneider, P. F. Beal and J. Korman, THIS JOURNAL, **77**, 4436 (1955).

(4) E. B. Hershberg, M. Rubin and E. Schwenk, *J. Org. Chem.*, **15**, 292 (1950).

(5) The 11β-hydroxyl group is acylated with acetic anhydride-pyridine at room temperature in the 19-nor series. See also ref. 8, footnote 7.

(6) We are indebted to J. A. Campbell and J. C. Babcock, of the Upjohn Company, for a known sample of 11β-hydroxy-19-nortestosterone, whose preparation was described by J. C. Babcock at the 129th Meeting of the American Chemical Society, Dallas, Texas, April 8–13, 1956. See p. 29M of the Abstracts.

acetate group from oxygen at 11 to the carbanion at carbon 1 which is formed in the initial stage of the Birch reduction.

Treatment of 3-methoxy-11,21-diacetoxy-19-nor-1,3,5(10),17(20)-pregnatetraene with osmium tetroxide and hydrogen peroxide yielded 11β,21-diacetoxy-17α-hydroxy-3-methoxy-19-nor-1,3,5(10)-pregnatrien-20-one (IV), m.p. 127–133° dec., $[\alpha]_D$ + 104° (acetone); (*Anal.* Calcd. for $C_{25}H_{32}O_7.H_2O$: C, 64.91; H, 7.41. Found: C, 65.18; H, 7.38). After the 21-acetate group of IV was selectively saponified with sodium bicarbonate, the 20-ketal, m.p. 220–223°, $[\alpha]_D$ + 61° (acetone); (*Anal.* Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.15; H, 7.50), was prepared by reaction with ethylene glycol and *p*-toluenesulfonic acid in benzene solution. Reduction of the ketal first with lithium aluminum hydride and then with lithium-ammonia and alcohol followed by acidic hydrolysis completed the chemical synthesis of 19-norhydrocortisone V; m.p. 256–259°; $[\alpha]_D$ + 112° (MeOH); λ_{max}^{EtOH} 241 mμ, *a* 4.21.[7]

Acylation of I with two moles of acetic anhydride and pyridine forms the 3,21-diacetate which when treated with osmium tetroxide and hydrogen peroxide gives 3,21-diacetoxy-11β,17α-dihydroxy-19-nor-1,3,5(10)-pregnatrien-20-one, m.p. 167–168°. (*Anal.* Calcd. for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 67.24; H, 6.99). 3,11β,17α,21-Tetrahydroxy-19-nor-1,3,5(10)-pregnatrien-20-one (VI), m.p. 256–258°; (*Anal.* Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.20; H, 7.77), was obtained by mild saponification.

Acylation of I with excess acetic anhydride–pyridine followed by ozonization and lithium aluminum hydride reduction yielded 11β-hydroxyestradiol (VII), m.p. 285–288°; $[\alpha]_D$ + 129° (dioxane); (*Anal.* Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.18; H, 8.50).

Using similar techniques 11α-hydroxyestradiol VIII, m.p. 250–251°, $[\alpha]_D$ −63° (acetone); (*Anal.* Found: C, 75.29; H, 8.23) was prepared.

3,11β,17α,21-Tetrahydroxy-19-nor-1,3,5(10)-pregnatrien-20-one (VI) is as potent as hydrocortisone in the granuloma pouch assay, but lacks the glycogen deposition activity of hydrocortisone.

11β-Hydroxyestradiol possesses 0.6 the estrogenic activity of estradiol in stimulating the uterine weight of castrated female rats, whereas the 11α-hydroxy analog is less active.[8]

Acknowledgment.—The authors are indebted to V. R. Shellman for technical assistance; to Dr. J. L. Johnson, Mrs. G. S. Fonken and J. E. Stafford for infrared and ultraviolet absorption studies; to W. A. Struck and associates for microanalyses; and to L. M. Reineke and associates for papergram studies.

(7) A. Zaffaroni, H. F. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, THIS JOURNAL, **76**, 6210 (1954).

(8) The biological activity of the compounds described in this communication will be published in detail elsewhere by Drs. R. O. Stafford and W. W. Byrnes and associates of the Department of Endocrinology of the Upjohn Company.

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COPPER(II) BROMIDE COMPLEXES

Sir:

We wish to report the results of a study of the complexing of bromide ion with copper(II) ion in alcoholic solvents. Organic solvents effect a substantial increase in association of ions, allowing spectrophotometric observations at much lower concentrations of associating species than possible in water, and avoiding occultation of shorter wavelength ranges.[1]

Recent studies of halide complexing with copper(II) in water[2] allowed determination of the band maximum for only one species, $CuBr^+$.[2b] Otherwise, the end absorptions seemed in agreement with the idea that absorption maxima moved to longer wave lengths with increasing number of complexed halide ions.[2a]

We have found that, as increasing amounts of lithium bromide are added to alcoholic solutions of copper(II) perchlorate, new absorption bands successively appear (Fig. 1 illustrates a typical series). On the basis of measurements with other copper(II) concentrations, we have confirmed that each of the bands varies independently of the

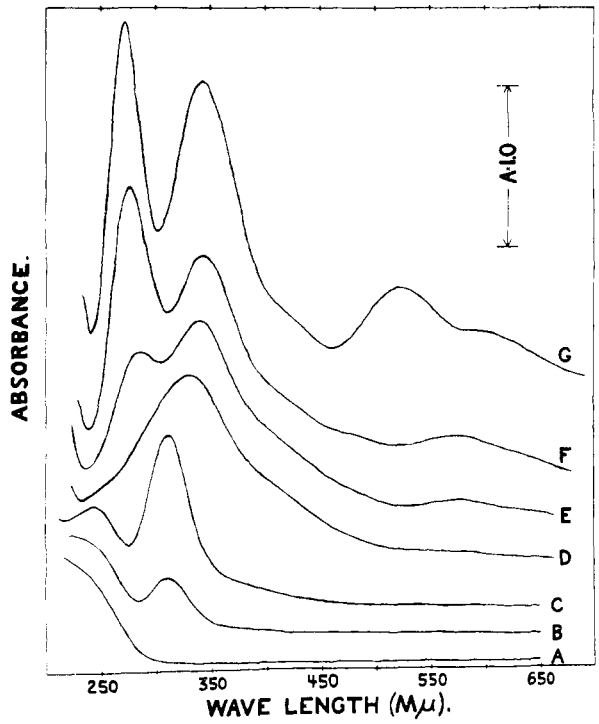

Fig. 1.—$Cu(ClO_4)_2$ concentration in ethanol was 4.00 × 10^{-3} *M*; varying amounts of LiBr were added: A, no LiBr; B, 1.00 × 10^{-3} *M*; C, 4.00 × 10^{-3} *M*; D, 25.0 × 10^{-3} *M*; E, 75.0 × 10^{-3} *M*; F, 720 × 10^{-3} *M*; G, 2800 × 10^{-3} *M* (path length, 0.1 cm.).

(1) Organic solvents were used previously for cobaltous and nickelous complexes by A. v. Kiss, *et al.*, *Z. physik. Chem.*, **A187**, 211 (1940); **A188**, 27 (1940); L. I. Katzin and E. Gebert, THIS JOURNAL, **72**, 5659 (1950); *Nature*, **175**, 425 (1955); L. I. Katzin, *J. Chem. Phys.*, **20**, 1165 (1952); C. K. Jorgensen and J. Bjerrum, *Nature*, **175**, 425 (1955); *Acta Chem. Scand.*, **7**, 951 (1953); C. K. Jorgensen, *ibid.*, **8**, 175 (1954); H. L. Friedman, THIS JOURNAL, **74**, 5 (1952).

(2) (a) H. M. McConnell and N. Davidson, *ibid.*, **72**, 3164, 3168 (1950); (b) P. S. Farrington, *ibid.*, **74**, 966 (1952); (c) R. Kruh, *ibid.*, **76**, 4865 (1954).