Benzylidene-2-aminopyridine was prepared by the method of Kirpal and Reiter[7] using 2 moles[8] of 2-aminopyridine to one mole of benzaldehyde, yield 81%, b.p. 184–188° (18 mm.), $n^{21}D$ 1.6564.

Benzhydryl-2-aminopyridine (IIA).—To a cooled, well-stirred phenylmagnesium bromide solution (190 g. of bromobenzene), there was added dropwise over a period of one-half to one hour a solution of 50 g. (0.27 mole) of benzylidene-2-aminopyridine in 50 ml. of anhydrous ether. The reaction mixture was heated on the steam-bath for three hours and then decomposed by the cautious addition of 650 ml. of 10% ammonium chloride solution. The organic layer was separated and the water layer was extracted several times with ether. The combined ethereal solutions were washed with water, dried over anhydrous sodium sulfate and the ether removed by evaporation on the steam-bath. The product was a light yellow solid, m.p. 94–96°. After two recrystallizations with absolute methanol, the product melted at 103–104°; yield 50 g. (70%).

Anal. Calcd. for $C_{18}H_{16}N_2$: N, 10.76. Found: N, 10.44.

The hydrochloride was prepared by saturating an ethereal solution of the base with anhydrous hydrogen chloride. After recrystallization from absolute ethanol–absolute ether, it melted at 192–193°.[9]

α-Phenethyl-2-aminopyridine (IIB) was prepared by a similar procedure in 75% yield from methylmagnesium iodide and benzylidene-2-aminopyridine. After recrystallization from absolute ethanol, the product melted at 91–92°.

Anal. Calcd. for $C_{13}H_{14}N_2$: N, 14.13. Found: N, 13.89.

α-Phenethylaniline (IID),[10] b.p. 180–182° (19 mm.); $n^{28}D$ 1.5955, and benzhydrylaniline (IIC),[11] b.p. 185–188° (1 mm.) were prepared by the same procedure by the action of methylmagnesium bromide and phenylmagnesium bromide, respectively, on benzalaniline.

N-(β-Dimethylaminoethyl)-N-(2-pyridyl)-α-phenethylamine (IB).—A freshly prepared suspension of sodium amide,[12] from 12 g. (0.5 mole) of sodium metal, in 400 ml. of anhydrous toluene was added slowly over a period of 1.5 hours to a vigorously stirred suspension of 39.6 g. (0.2 mole) of α-phenethyl-2-aminopyridine and 33.2 g. of dimethylaminoethyl chloride hydrochloride in 500 ml. of anhydrous toluene. The deep red reaction mixture was slowly heated to reflux and so maintained with stirring for 18 hours. After cooling, 500 ml. of water was added and the toluene solution separated. The water layer, after two ether extractions, was discarded. The combined toluene and ether solutions were extracted several times with dilute hydrochloric acid (10%), the acid solution made strongly basic with concentrated sodium hydroxide solution and extracted with ether. The ether extracts were washed with water, dried over sodium sulfate and distilled, b.p. 149–153° (1 mm.), $n^{25}D$ 1.5730, yield 34 g. (63%).

Anal. Calcd. for $C_{17}H_{23}N_3$: N, 15.97. Found: N, 15.82.

N-(β-Dimethylaminoethyl)-N-(2-pyridyl)-benzhydrylamine (IA) was prepared in a 28% yield by the sodamide alkylation of benzhydryl-2-aminopyridine according to the above procedure, b.p. 195–198° (1 mm.)[13], $n^{22}D$ 1.6141.

Anal. Calcd. for $C_{22}H_{25}N_3$: N, 12.68. Found: N, 12.77.

The following compounds were prepared by a similar alkylation procedure:

N-(β-Dimethylaminoethyl)-N-phenyl-α-phenethylamine (ID), b.p. 205–208° (17 mm.); $n^{27}D$ 1.5709; yield 47%.

Anal. Calcd. for $C_{18}H_{24}N_2$: N, 10.47. Found: N, 10.43.

N-(β-Dimethylaminoethyl)-N-phenylbenzhydrylamine (IC), b.p. 194–195° (1 mm.); $n^{21}D$ 1.6012; yield 51%.

Anal. Calcd. for $C_{23}H_{26}N_2$: N, 8.48. Found: N, 8.55.

(7) A. Kirpal and E. Reiter, *Ber.*, **60**, 666 (1927).

(8) An equimolar ratio of benzaldehyde and 2-aminopyridine under identical conditions gave the product in 50% yield.

(9) Reference 1 reports a melting point of 192–193°.

(10) M. Busch, *Ber.*, **37**, 2691 (1927).

(11) M. Busch and A. Rinck, *ibid.*, **38**, 1761 (1905).

(12) E. M. Hancock and A. C. Cope, *Org. Syntheses*, **25**, 25 (1945).

(13) The distillation was accompanied by a considerable forerun, b.p. 170–195° (1 mm.).

SCHERING CORPORATION
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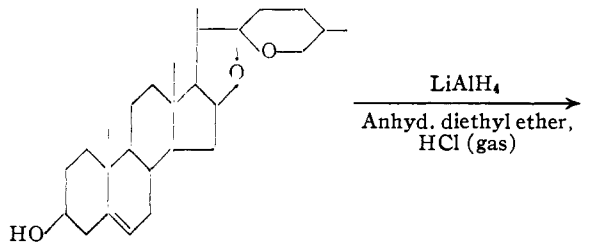
COMMUNICATIONS TO THE EDITOR

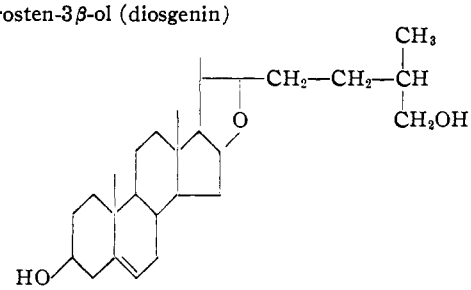
CLEAVAGE OF SAPOGENIN TERMINAL RINGS WITH LITHIUM ALUMINUM HYDRIDE

Sir:

We wish to report a new method for cleaving ring F of steroidal sapogenins.[1] Marker, *et al.*,[2] have reported the preparation of furostane diols (saturated dihydrosapogenins) by reduction of spirostanols and spirostenols, using platinum catalyst in acid solution, but a direct method for the preparation of furostene diols (unsaturated dihydrosapogenins) has not been previously reported. We find that spirostanols and spirostenols are reduced by lithium aluminum hydride ($LiAlH_4$), in the presence of hydrogen chloride gas, to give high yields of the corresponding furostane and furostene diols as illustrated by the reaction shown.



Δ⁵-22-Isospirosten-3β-ol (diosgenin)



Δ⁵-Furostene-3β,26-diol (dihydrodiosgenin) (I)

The sapogenin was dissolved in anhydrous diethyl ether and then the solution was saturated with anhydrous hydrogen chloride gas at 25°. $LiAlH_4$

(1) For nomenclature of steroidal sapogenins see G. Rosenkranz and C. Djerassi, *Nature*, **166**, 104 (1950).

(2) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, THIS JOURNAL, **69**, 2167 (1947).

was added slowly, with stirring, and the reaction mixture refluxed for two hours. This method can undoubtedly be used to advantage to prepare related compounds that are unsaturated in other than the Δ^5 position. Ring F of spirostanols and spirostenols is not cleaved by $LiAlH_4$ in the absence of hydrogen chloride gas.

Some of the compounds that we have prepared by this method are[3]: reduction of Δ^5-22-isospirosten-3β-ol (diosgenin) yielded Δ^5-furostene-3β,26-diol (dihydrodiosgenin) (I), m.p. 158–160°[4], $[\alpha]^{20}D$ −35° $CHCl_3$ (*Anal.* Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.77; H, 10.84). Sandoval, *et al.*[5] reported an optical rotation of $[\alpha]^{20}D$ −33° for $\Delta^{5,20(22)}$-furostadiene-3β,26-diol (ψ-diosgenin). Acetylation of (I) at room temperature yielded Δ^5-furostene-3β,26-diol 3,26-diacetate (dihydrodiosgenin diacetate) (II), m.p. 115–117°, $[\alpha]^{20}D$ −39° $CHCl_3$ (*Anal.* Calcd. for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 74.45; H, 9.73).

Reduction of 22-isoallospirostan-3β-ol (tigogenin) (III) yielded allofurostane-3β,26-diol (dihydrotigogenin) (IV), m.p. 163–166° (lit. m.p. 167–170°[2]), $[\alpha]^{20}D$ −4° $CHCl_3$ (*Anal.* Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.41; H, 10.92). Acetylation of (IV) at room temperature yielded allofurostane-3β,26-diol 3,26-diacetate (dihydrotigogenin diacetate) (V), m.p. 116–117° (lit. m.p. 114–116°[2]), $[\alpha]^{20}D$ −15 $CHCl_3$ (*Anal.* Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.03. Found: C, 74.15; H, 10.04).

Reduction of spirostan-3β-ol (sarsasapogenin) yielded furostane-3β,26-diol (dihydrosarsasapogenin) (VI), m.p. 157–160° (lit. m.p. 165°)[6], $[\alpha]^{20}D$ −2° $CHCl_3$ (*Anal.* Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.45; H, 11.05). Benzoylation of VI at 95° for one hour yielded a crystalline product, furostane-3β,26-diol-3,26-dibenzoate (dihydrosarsasapogenin dibenzoate) (VII), m.p. 95–97°, (*Anal.* Calcd. for $C_{41}H_{54}O_5$: C, 78.55; H, 8.68. Found: C, 78.37; H, 8.51).

It will be noted that sapogenins having the "normal" and "iso" configuration at carbon 22 and the "normal" and "allo" configuration at carbon 5 are cleaved by $LiAlH_4$ in the presence of hydrogen chloride gas but not in its absence. The stability of rings E and F of the steroidal sapogenins to cleavage by $LiAlH_4$ (alkaline) is further confirmed by the work of Djerassi, *et al.*[7] In contrast to the stability of the sapogenins, tomatidine, a steroidal secondary amine,[8] which has yielded Δ^{16}-allopregnen-3β-ol-20-one[9] by what we consider to be typical steroidal sapogenin reactions, is cleaved by $LiAlH_4$ (alkaline) to yield a diol compound, dihydrotomatidine.[8] The structural relationship between tomatidine and steroidal sapogenins will be reported in a future publication.

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(3) We are indebted to M. E. Wall, Eastern Regional Research Laboratory, Wyndmoor, Pennsylvania, for supplying the spirostanols and spirostenols used in this work and for determining optical rotations.

(4) Melting points were taken in capillary tubes in an oil bath and are corrected.

(5) A. Sandoval, J. Romo, G. Rosenkranz, St. Kaufmann and C. Djerassi, THIS JOURNAL, **73**, 3820 (1951).

(6) R. E. Marker and E. Rohrmann, *ibid.*, **61**, 846 (1939).

(7) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1931).

(8) T. D. Fontaine, J. S. Ard and R. M. Ma, THIS JOURNAL, **73**, 878 (1951).

(9) Y. Sato, A. Kats and E. Mosettig, *ibid.*, **73**, 880 (1951).

ELECTRODIALYSIS OF SHEEP ADRENOCORTICOTROPIC (ACTH) PROTEIN PREPARATIONS[1]

Sir:

Adrenocorticotropic hormone (ACTH) protein preparations isolated from sheep and pig pituitary glands by the methods of Li, *et al.* and Sayers, *et al.*,[2] appear to be homogeneous by sedimentation, electrophoresis and solubility studies. Despite this apparent homogeneity, there is now considerable evidence to indicate that the biological activity associated with the protein does not involve the whole protein molecule.[3]

We wish to report the results of electrodialysis experiments on protein preparations[2a] in which the protein is separated into two main fractions. A three-cell electrodialysis apparatus was used.[4] The center cell was separated from the anode by a goldbeater's skin and from the cathode by a vegetable parchment membrane. In a typical experiment, a 0.4% ACTH protein solution (*p*H 3.6) was introduced into the center cell; the anode cell contained 0.5% acetic acid (25 ml.) while the cathode contained distilled water (25 ml.) which

TABLE I

DISTRIBUTION OF NITROGEN AND BIOLOGICAL ACTIVITY IN VARIOUS FRACTIONS OBTAINED BY ELECTRODIALYSIS OF SHEEP ACTH PROTEIN PREPARATIONS

Expt.[a]	Fraction	Nitrogen, mg.	Nitrogen, %	Bioassay[b] ACTH equiv. mg.	Bioassay[b] ACTH equiv. %
	Starting prepn. (L 2011A)	12.6	100	56 (12)[c]	100
I	Center	9.6	76	0 (9)	0
	Combined cathodes	1.9	15	55 (15)	98
	Anode	0.1	0.5	...	...
	Starting prepn. (L 2220A)	5.3	100	85 (15)	100
II	Center	4.1	77	0.6 (6)	<1
	Combined cathodes	1.1	21	53 (20)	62
	Anode	0.0	0	...	...

[a] Electrodialysis was carried out for 5 hours. [b] As measured by the ascorbic acid depletion method of Sayers, *et al.*[5] [c] Number of rats used in parentheses.

(1) Assisted by grants from the National Institutes of Health, United States Public Health Service, the Armour Laboratories, Merck and Company, and Eli Lilly Laboratories.

(2) (a) C. H. Li, H. M. Evans and M. E. Simpson, *J. Biol. Chem.*, **149**, 413 (1943). (b) G. Sayers, A. White and C. N. H. Long, *ibid.*, **149**, 425 (1943).

(3) (a) C. H. Li, *Trans. Macy Conf. on Metabolic Aspects of Convalescence*, **17**, 114 (1948); (b) N. G. Brink, M. A. P. Meisinger and K. Folkers, THIS JOURNAL, **72**, 1040 (1950); (c) J. B. Lesh, J. D. Fisher, I. M. Bunding, J. J. Kocsis, L. S. Walaszek, W. F. White and E. E. Hays, *Science*, **112**, 43 (1950); (d) R. W. Payne, M. S. Rahen and E. B. Astwood, *J. Biol. Chem.*, **187**, 719 (1950). (e) B. Cortis-Jones, A. C. Crooke, A. A. Hewly, P. Morris and C. J. O. R. Morris, *Biochem. J.*, **46**, 173 (1950).

(4) A modification of the apparatus of H. Theorell and Å. Åkesson (*Arkiv. Kemi Mineral. Geol.*, **16A**, No. 8, 1943), designed and kindly made available to us by Professor C. A. Knight.