Thomas and Marlow interpreted their data by assuming an alteration in the coulombic component of the total adsorptive forces, resulting from a progressive delocalization of the positive charge on the cationic head as one ascends the series. While charge delocalization and steric factors are surely involved in the interaction of these compounds with acetylcholinesterase, these factors alone will not explain their inhibitory effects on serum cholinesterase. An alternative explanation involving changes in charge distribution in the aromatic ring is also possible. Before this is considered it will be instructive to review our present day knowledge of the mechanism of cholinesterase action.

The hydrolysis of acetylcholine, as pictured by Wilson, *et al.*,[7] and Ormerod,[8] involves a two-point attachment of the substrate with the two enzymes. The cationic head of the substrate interacts with an anionic site and the acetoxy group with the esteratic site. With acetylcholinesterase, interattraction between the positively polarized carbon of the ester link and the basic group in the esteratic site was envisioned. In case of pseudocholinesterase (serum), interattraction between the negatively polarized carbonyl oxygen and a positively polarized site on the enzyme was suggested.

In the first two members of the series of phenylalkyltrimethylammonium compounds the aromatic ring is essentially positively polarized. In the remaining members, the ring is negatively polarized. This suggestion is supported by the studies of Ingold[9] on the rates of aromatic nitration of these compounds.

In light of this two-point attachment theory of enzyme action for the two different enzymes, it is not unreasonable to assume that the polarized aromatic ring interacts with the esteratic site, the interattraction being greater for the first two members with the esteratic site of acetylcholinesterase and diminishing thereafter. Just the reverse situation could be pictured for interattraction between the ring system and the esteratic site of pseudocholinesterase. Thus, by assuming that a change in charge distribution occurs in the aromatic ring as the series is ascended, one can offer an alternative explanation of the inhibitory effects of these compounds on the two different types of cholinesterases.

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(8) W. E. Ormerod, *Biochem. J.*, **54**, 701 (1953).

(9) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 232.

New Progestational Agents. Nonclassical 17-Alkylpregnene Structures

GEORGE R. ALLEN, JR., AND MARTIN J. WEISS

Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York

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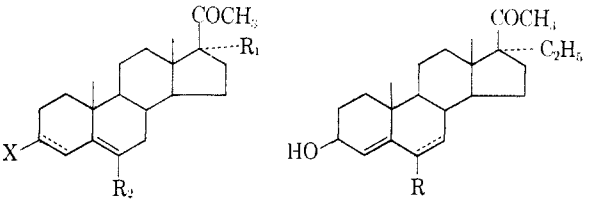
In the past decade the most important advances in the field of new progestational agents have been associated with structural modifications of 17-ethynyltestosterone and 17-acetoxyprogesterone.[1] Recently, however, several nonclassical steroids have been reported to be active progestins.[2] Among these compounds are certain 3-halopregn-5-enes,[2e] 3β-hydroxypregn-4-enes,[2a,b] and pregna-3,5-dienes.[2f] Another recent development in this field has been the observation that introduction of a 17-alkyl group confers oral activity on the progesterone molecule.[3] As a continuation of our interest in the 17-alkylprogesterone series, we now describe the inclusion of the above nonclassical structural features into certain 17-alkylpregnanes.

The 17-alkyl-3β-halopregn-5-enes were readily prepared by known procedures. Thus, treatment of 17-methylpregnenolone,[3b,4,5] 17-ethylpregnenolone,[6] and 17-ethyl-6-methylpregnenolone[3b] with N-(2-chloro-1,1,2-trifluoroethyl)diethylamine[7] gave the corresponding 3β-fluorides (I–III). Moreover, reaction of 17-ethylpregnenolone with thionyl chloride afforded the 3β-chloride IV. For this work the requisite 17-ethylpregnenolone was prepared by preferential reduction of 3-acetoxy-17-ethylpregna-3,5-dien-20-one[3b] with methanolic sodium borohydride.



I, X = F; R_1 = CH_3; R_2 = H
II, X = F; R_1 = C_2H_5; R_2 = H
III, X = F; R_1 = C_2H_5; R_2 = CH_3
IV, X = Cl; R_1 = C_2H_5; R_2 = H
V, X = H; R_1 = C_2H_5; R_2 = H, Δ^5

VI, R = H
VII, R = H, Δ^6
VIII, R = Cl, Δ^6

For the preparation of a 17-alkyl-3β-hydroxypregn-4-ene, reduction of 17-ethylprogesterone[3d,5] with sodium borohydride readily furnished the 17-ethyl-Δ^4-3β-ol (VI), which was also characterized as its acetate. The β-configuration is assigned to this 3-ol, since the reduction of Δ^4-3-ketones with sodium borohydride is known to yield predominantly this isomer.[8] The preferential reduction of the 3-ketone, as well as that of the corresponding 3-enol acetate, further illustrates the steric effect exerted by the 17-ethyl group on the 20-keto function.[3c,5,9]

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(6) R. Degbenghi and R. Gaudry, *Tetrahedron Letters*, **No. 11**, 489 (1962).

(7) D. E. Ayer, *ibid.*, **No. 23**, 1065 (1962); L. H. Knox, E. Velarde, S. Berger, D. Caudriello, and A. D. Cross, *ibid.*, **No. 26**, 1249 (1962).

(8) *Cf.* W. G. Dauben, R. A. Micheli, and J. F. Eastman, *J. Am. Chem. Soc.*, **74**, 3852 (1952); W. W. Zorbach, *ibid.*, **75**, 6344 (1953).

(9) It is noteworthy that in the 17-hydrogen series (progesterone), the corresponding preferential reduction is known to proceed at C-20 [J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955)].

We have also prepared the $\Delta^{4,6}$-3β-ols VII and VIII. These compounds were obtained by reduction of the corresponding 3-ketone with sodium borohydride in methanol.[10]

The desired 17-ethylpregna-3,5-dien-20-one (V) was obtained by dehydration of carbinol VI with 50% acetic acid. The diene V was also prepared, albeit in poor yield, by a sequence involving reduction of 17-ethylprogesterone with lithium aluminum hydride, acid dehydration of the allylic alcohol system in the resulting pregn-4-ene-3,20-diol, and finally oxidation to the 20-one. Noteworthy in this sequence is the reduction of both carbonyl groups in 17-ethylprogesterone by lithium aluminum hydride. This observation is in direct contrast to the preferential reduction of the 3-carbonyl group in this compound by sodium borohydride in methanol and constitutes another expression of the difference in the steric requirements of these metal hydrides.[11]

Biological Evaluation.—These compounds were examined for oral progestational activity (Clauberg procedure) by Dr. Elva G. Shipley at the Endocrine Laboratories, Madison, Wisconsin. All showed significant activity in this assay: the most interesting were 17-ethyl-3β-fluoro-6-methylpregn-5-en-20-one (III) and 6-chloro-3β-hydroxy-17-ethylpregna-4,6-dien-20-one (VIII). The response of the uterine endometrium to several doses of III and VIII and the related 6α-methyl-17-ethylprogesterone (IX)[3d,5] and 6-chloro-6-dehydro-17-ethylprogesterone (X)[3d,e] is given in Table I.

TABLE I

Compound	Total dose, mg.	Oral progestational activity, response
17-Ethyl-3β-fluoro-6-methylpregn-5-en-20-one (III)	5.0	4.0
	1.0	1.2
	0.5	0.8
6α-Methyl-17-ethylprogesterone (IX)	5.0	3.5
	1.25	2.7
	0.625	2.8
	0.312	1.0
6-Chloro-3β-hydroxy-17-ethylpregna-4,6-dien-20-one (VIII)	0.5	4.0
	0.05	0
6-Chloro-6-dehydro-17-ethylprogesterone (X)	1.2	4.0
	0.312	2.9
	0.039	1.2

Experimental

Melting points were determined on a Mel-Temp apparatus in open capillary tubes and are corrected. Rotations were determined at 25° in chloroform solution at 0.5–1.6% concentrations. Ultraviolet spectra were measured in methanol solution on a Cary recording spectrophotometer, and infrared spectra are for pressed potassium bromide disks and were determined on a Perkin-Elmer Model 21 spectrophotometer. All evaporations were carried out under reduced pressure.

17-Ethylpregnenolone.—A solution of 2.334 g. (6.10 mmoles) of 3β-acetoxy-17-ethylpregna-3,5-dien-20-one[3b] in 135 ml. of methanol, 70 ml. of tetrahydrofuran, and 7 ml. of water was treated with 2.70 g. of sodium borohydride and allowed to stand at room temperature for 18 hr. The crude product was isolated with methylene chloride; after removal of the solvent, the residue was dissolved in 120 ml. of methanol and heated at reflux temperature with a solution of 2.0 g. of potassium carbonate in 12 ml. of water for 1 hr. The product was isolated with methylene chloride and recrystallized from acetone–hexane to give, in two crops, 1.63 g. (80%) of crystals, m.p. 184–188°. Additional recrystallizations gave material with m.p. 188–190°; $[\alpha]_D$ −56° [lit.[6] m.p. 200–202° and $[\alpha]_D$ −65° (chloroform)]; no significant absorption in the ultraviolet at 20 γ/ml.; λ_{max} 2.90, 5.94, and 9.36 μ.

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.95; H, 10.52.

Preparation of 3β-Fluoropregn-5-en-20-ones.—A solution of the sterol was treated with 1.1–1.2 molar equiv. of N-(2-chloro-1,1,2-trifluoroethyl)diethylamine in methylene chloride at 0–5° for 16–18 hr. The solution was washed with sodium carbonate solution and water, dried over magnesium sulfate, and evaporated. The residue was then treated as indicated below.

3β-Fluoro-17-methylpregn-5-en-20-one (I) was obtained in 37% yield from 17-methylpregnenolone[3b] after recrystallization from dilute methanol as white crystals, m.p. 129–131°; $[\alpha]_D$ −57.5°; λ_{max} 5.89, 9.70, 9.85, and 10.50 μ.

Anal. Calcd. for $C_{23}H_{33}FO \cdot 0.33H_2O$: C, 78.03; H, 10.02; F, 5.61; H_2O, 1.77. Found: C, 78.35; H, 9.81; F, 5.19; H_2O (Karl Fischer), 1.79.

3β-Fluoro-17-ethylpregn-5-en-20-one (II) was obtained in 78% yield from 17-ethylpregnenolone after recrystallization from methanol as crystals, m.p. 178–180°; $[\alpha]_D$ −64°; λ_{max} 5.90, 9.70, 9.90, and 10.50 μ.

Anal. Calcd. for $C_{23}H_{35}FO$: C, 79.72; H, 10.18; F, 5.49. Found: C, 79.49; H, 10.22; F, 5.76.

3β-Fluoro-17-ethyl-6-methylpregn-5-en-20-one (III) was prepared from 17-ethyl-6-methylpregnenolone.[3b] The solid eluted from silica gel with benzene was recrystallized from dilute methanol to give in 26% yield crystals, m.p. 125–127°; $[\alpha]_D$ −73°; λ_{max} 5.90, 9.70, 9.96, and 10.50 μ.

Anal. Calcd. for $C_{24}H_{37}FO$: C, 79.95; H, 10.34; F, 5.27. Found: C, 79.67; H, 10.07; F, 4.87.

3β-Chloro-17-ethylpregn-5-en-20-one (IV).—A solution of 337 mg. (1.0 mmole) of 17-ethylpregnenolone in 3.5 ml. of thionyl chloride was kept at room temperature for 21.5 hr. The solution was poured onto cracked ice and after the excess reagent had hydrolyzed, the resulting mixture was extracted with methylene chloride. The organic solution was washed successively with saline, dilute sodium carbonate solution, and finally saline, then dried over magnesium sulfate and evaporated. Crystallization of the residue from acetone–hexane gave 114 mg. of needles, m.p. 151–153°. The filtrate was evaporated, and the residue was recrystallized from dilute methanol to give an additional 85 mg. (55%) of white crystals, m.p. 148–150°; $[\alpha]_D$ −46°; λ_{max} 5.90 and 13.19 μ.

Anal. Calcd. for $C_{23}H_{35}ClO$: C, 76.11; H, 9.73; Cl, 9.77. Found: C, 76.07; H, 10.04; Cl, 10.20.

Reduction of 17-Ethylpregn-4-ene(or 4,6-diene)-3,20-diones.—A solution of the dione in methanol (50–350 ml./g.), tetrahydrofuran (25–35 ml./g.), and water (0.5–0.75 ml./g.) was treated with an equal weight of sodium borohydride for 18 hr. The product was isolated with methylene chloride and purified as described below.

17-Ethyl-3β-hydroxypregn-4-en-20-one (VI) was eluted from silica gel by benzene–ether (95:5) and recrystallized from acetone–hexane to give crystals, m.p. 179–181°; $[\alpha]_D$ +43°; ΔM_D (Δ^4-3β-ol − Δ^4-3-one) −170°[12]; no absorption in the ultraviolet; λ_{max} 2.87, 5.92, 6.03, and 9.50 μ.

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.80; H, 10.60.

With pyridine–acetic anhydride this material gave an acetate which on crystallization from acetone–hexane melted at 162–163°; $[\alpha]_D$ −2°; ΔM_D (Δ^4-3β-acetate − Δ^4-3-one) −385°[12]; λ_{max} 5.75, 5.88, 6.00, 8.05, and 9.85 μ.

Anal. Calcd. for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91. Found: C, 77.59; H, 9.93.

3β-Hydroxy-17-ethylpregna-4,6-dien-20-one (VII) after recrystallization from acetone–hexane melted at 202–205°; $[\alpha]_D$ −48°; λ_{max} 232, 239, and 247 mμ (ϵ 23,300, 26,000, 16,800); λ_{max} 2.84, 2.89, 5.94, 6.08, and 6.20 μ.

(10) J. S. Baran [*J. Med. Chem.*, **6**, 329 (1963)] has reported the reduction of $\Delta^{4,6}$-3-ketones to the corresponding $\Delta^{4,6}$-3β-ols with lithium tri-*t*-butoxy aluminum hydride.

(11) A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).

(12) For the progesterone series the recorded (ref. 2b) ΔM_D values are −201° (Δ^4-3β-ol − Δ^4-3-one) and −300° (Δ^4-3β-acetate − Δ^4-3-one).

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.82; H, 10.22.

This material gave an acetate which was obtained from acetone–hexane as crystals, m.p. 184–186°; $[\alpha]D -72°$; λ_{max} 232, 239, and 247 mμ (ε 24,800, 27,200, 17,400); λ_{max} 5.75, 5.88, 6.08, 8.10, and 9.91 μ.

6-Chloro-3β-hydroxy-17-ethylpregna-4,6-dien-20-one (VIII) was recrystallized from acetone–hexane to give crystals, m.p. 192–193°; $[\alpha]D -60°$; λ_{max} 237, 244, and 252 mμ (ε 18,600, 21,700, 14,500); λ_{max} 2.89, 5.93, 6.23, and 9.72 μ.

Anal. Calcd. for $C_{23}H_{33}ClO_2$: C, 73.27; H, 8.82; Cl, 9.41. Found: C, 73.09; H, 8.80; Cl, 9.85.

17-Ethylpregna-3,5-dien-20-one (V).—A solution of crude 17-ethyl-3β-hydroxypregn-4-en-20-one (derived from 500 mg. of 17-ethylprogesterone) in 100 ml. of 50% acetic acid was heated at reflux temperature for 45 min. After 10 min. a solid was deposited from the solution. The chilled mixture was filtered to give 360 mg. of white crystals, m.p. 155–158°. This solid was dissolved in benzene and chromatographed on silica gel. The material eluted by benzene was recrystallized from methanol to give 222 mg. (47%) of white needles, m.p. 160–162°; $[\alpha]D -150°$; λ_{max} 228, 234, and 243 mμ (ε 20,200, 21,600, 13,700); λ_{max} 5.91 and 6.05 μ.

Anal. Calcd. for $C_{23}H_{34}O$: C, 84.60; H, 10.50. Found: C, 84.37; H, 10.61

Acknowledgment.—We thank Mr. W. Fulmor and his associates for the spectral and polarimetric data, Mr. L. Brancone and staff for the microanalyses, Dr. J. L. Fedrick and Mr. R. B. Conrow for a generous supply of 17-ethylprogesterone, and Dr. I. Ringler for assistance in obtaining the biological assays.

New Compounds

Derivatives of 2-Hydroxy-1,3,2-benzodioxastibole[1a]

L. CORTÉS,[1b] J. MANTECÓN,[1b] AND G. CHUCHANI

Department of Chemistry, Instituto Venezolano de Investigaciones Científicas (IVIC), Caracas, Venezuela

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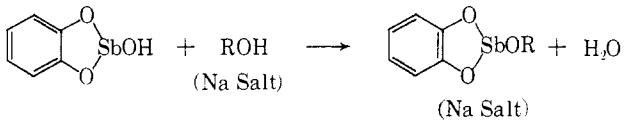
A number of derivatives of 2-hydroxy-1,3,2-benzodioxastibole (I) were synthesized as compounds of potential interest in the chemotherapy of several parasitical diseases. Several phenolic compounds containing $-COOH$ and $-SO_3H$ groups were treated with I[2,3] in basic medium to produce the corresponding condensation products. These were isolated as the sodium salts.

TABLE I

1,3,2-BENZODIOXASTIBOLE DERIVATIVES OBTAINED ACCORDING TO THE REACTION



ROH	%	Formula products[a]	% Sb Found	% Sb Calcd.
5-Chlorosalicylic acid	43	$C_{13}H_7ClNaOSb$	28.8	28.8
5-Bromosalicylic acid	39	$C_{13}H_7BrNaO_5Sb$	26.1	26.0
5-Aminosalicylic acid	39	$C_{13}H_9NNaO_5Sb$	30.2	30.1
5-Sulfosalicylic acid	26	$C_{13}H_7Na_2O_8SSb$	25.0	24.8
3-Phenylsalicylic acid	46	$C_{19}H_{12}NaO_5Sb$	26.3	26.2
3-Methylsalicylic acid	37	$C_{14}H_{10}NaO_5Sb$	30.4	30.2
6-Amino-1-naphthol-8-sulfonic acid	40	$C_{16}H_{11}NNaO_6SSb$	24.9	24.8
5-Amino-4-hydroxybenzenesulfonic acid	45	$C_{12}H_9NNaO_6SSb$	27.8	27.7
7-Amino-1-naphthol-3-sulfonic acid	36	$C_{16}H_{11}NNaO_6SSb$	24.9	24.8
8-Amino-1-naphthol-3,6-disulfonic acid	33	$C_{16}H_{10}NNa_2O_9S_2Sb$	20.5	20.6

[a] None of the compounds melts or decomposes below 300°. On acidification with hydrochloric acid, these compounds are rapidly hydrolyzed.

Experimental

2-Hydroxy-1,3,2-benzodioxastibole (I) was prepared as described by Brown and Austin.[3] The derivatives of I were prepared as described,[3] but with the following modification. After the reaction period the solid by-product (hydrated antimony oxide) was filtered and the filtrate neutralized to precipitate the unchanged I. The solution was then concentrated to incipient crystallization and the product washed with small amounts of cold ethanol.

Alternate Method of Condensation.—2-Hydroxy-1,3,2-benzodioxastibole (I) (0.03 mole) in 0.4 *N* sodium hydroxide solution was added to salicylic acid (0.035 mole) in 2 *N* sodium carbonate solution (18 ml.). The mixture was heated for 2 hr. at 70–75° and neutralized after cooling. The precipitated, unchanged I was removed by filtration and the filtrate concentrated until precipitation started. The solid, 2-(*o*-carboxyphenyloxy)-1,3,2-benzodioxastibole, was unchanged at 300°; yield, 70%.

Anal. Calcd. for $C_{13}H_8NaO_5Sb$: Sb, 31.3. Found: Sb, 31.5.

(1) (a) A portion of this paper was presented before the XI Annual Convention of the Venezuelan Association for the Advancement of Science, Caracas, April, 1961. (b) From theses submitted by L. C. and J. M. in partial fulfillment of the requirements for the degree of Licenciado de Química, Universidad Central de Venezuela, June, 1961.

(2) H. Causse, *Bull. soc. chim. France*, 245 (1892).

(3) H. P. Brown and J. Austin, *J. Am. Chem. Soc.*, **63**, 2054 (1941).

Methyl Analogs of Papaverine[1a]

JAMES G. BEASLEY AND ALFRED BURGER

Department of Chemistry, University of Virginia, Charlottesville, Virginia

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Papaverine and papaveraldine analogs which do not contain ether groups in positions 6 and 7 have not been studied widely. Analogs containing methyl instead of methoxyl groups could contribute to such questions as to the significance of methoxy *vs.* methyl groups,[2] or whether the intramolecular distance between the ether oxygens and the isoquinoline nitrogen[3] has a bearing on the pharmacological activity. Several analogs with methyl groups are described.

(1) Supported by a grant, NB-01445, from the Institute for Neurological Diseases and Blindness, National Institutes of Health, U. S. Public Health Service.

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