[CONTRIBUTION FROM THE SECTION OF EXPERIMENTAL MEDICINE, THE UNIVERSITY OF TEXAS M. D. ANDERSON HOSPITAL & TUMOR INSTITUTE]

Estrogens. II. The Synthesis of 2-Dialkylaminomethylestrogens[1,2]

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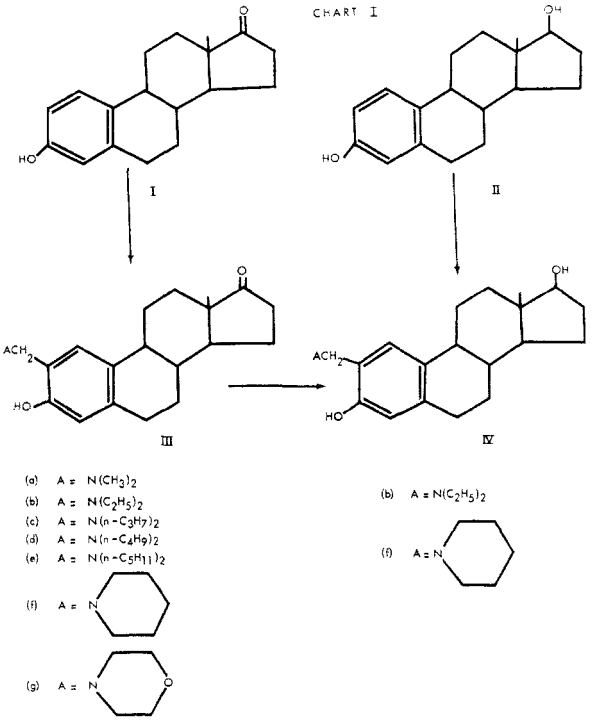
Received May 16, 1960

The synthesis of a series of 2-dialkylaminomethylestrogens and their hydrochlorides are reported. A convenient synthesis of 2-methylestradiol is afforded by reduction and subsequent hydrogenolysis of 2-diethylaminomethylestrone.

In continuation of an investigation of the effects of substituents on the estrogenic activities of estrone and estradiol, a number of 2-dialkylaminomethylestrogens have been synthesized. It is the purpose of this article to describe in detail the experimental procedures for synthesizing the compounds which were reported in an earlier communication[3] and to report some new compounds in this series.

In conformity with the fact that the *ortho* and *para* hydrogens of phenols are sufficiently active to enter into the Mannich reaction,[4] estrone (I) and estradiol (II) were found to react with formaldehyde and secondary amines in a boiling solution of benzene and alcohol to give 2-dialkylaminomethylestrone (III) and 2-dialkylaminomethylestradiol (IV), respectively. This is illustrated on Chart I. The yield of IIIa was only 21–24% when an aqueous solution of dimethylamine was used in the reaction; however, the yield was increased to 69% when *N,N,N′,N′*-tetramethyldiaminomethane was used.[5] This latter yield is more in line with the yields (50–78%) of other members of this series which were synthesized from less volatile secondary amines. Although compounds IIIa, IIIb, IIIc, IIIf, and IIIg were isolated as crystalline products, IIId and IIIe could not be induced to crystallize and were obtained only as their hydrochlorides. As the melting points of IIIa, IIIb, and IIIc decrease progressively from 170° to 160° to 107° as the length of the alkyl chains in the amino group increases from methyl to ethyl to propyl,

CHART I



respectively, IIId and IIIe would be expected to have rather low melting points. This may account for the failure of these two compounds to crystallize.

As two monosubstituted compounds were expected to result from the Mannich reaction on the phenol ring of I, repeated efforts were made to isolate them. The product from the reaction of I with formaldehyde and diethylamine was submitted to chromatography on columns of alumina, acid-washed alumina, and silica gel; however, only one product, IIIb, was isolated.

The unlikely possibility that the product had resulted from reaction at position 16 of I was conclusively eliminated by the following information. First, the infrared spectra of all compounds isolated from the Mannich reaction had a small peak or shoulder of absorption at 7.10–7.12 μ which is characteristic of 17-ketosteroids having an unsubstituted methylene group at C-16.[6] Second, the melting point of IIIa (169.5–171.5°) is considerably different from that reported for 16-

(1) Part I of this series appeared in *J. Org. Chem.* **24**, 1795 (1959).

(2) This investigation was supported by a grant, CY-2873, from the National Cancer Institute, U. S. Public Health Service, and by funds from the Institutional Grant, 23K-12, from the American Cancer Society.

(3) T. L. Patton, *Chem. & Ind. (London)*, 923 (1959).

(4) (a) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939). (b) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 2354 (1939). (c) H. A. Bruson and C. W. MacMullen, *J. Am. Chem. Soc.*, **63**, 270 (1941). (d) J. B. Niederl and F. A. Abbruscato, *J. Am. Chem. Soc.*, **63**, 2024 (1941). (e) F. F. Blicke, *Org. Reactions*, 311 (1942). (f) J. H. Burkhalter, F. H. Tendick, E. M. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Am. Chem. Soc.*, **68**, 1894 (1946).

(5) S. V. Lieberman and E. C. Wagner, *J. Org. Chem.*, **14**, 1001 (1949), showed that methylene bisamines are eligible to function as intermediates and can be successfully used in the Mannich reaction.

(6) R. N. Jones and A. R. H. Cole, *J. Am. Chem. Soc.*, **74**, 5648 (1952).

dimethylaminomethylestrone (125–128°).[7] Third, II, which does not possess a 17-keto group, underwent the Mannich reaction with piperidine to give a product, IVf, which was identical to the product formed by the reduction of IIIf with sodium borohydride.

As substitution must have occurred at either position 2 or 4 on I, an attempt was made to force the reaction to proceed beyond the first formed product to the 2,4-disubstituted product. The submission of I to the Mannich reaction in the presence of a large excess of formaldehyde and diethylamine over a period of ninety-six hours at reflux temperature, however, yielded only one product which was monosubstituted and identical to IIIb. Burkhalter and his collaborators found that 3,4-disubstituted phenols underwent the Mannich reaction at position 6 exclusively[4f]; this position corresponds to position 2 in I. Furthermore, Caldwell and Thompson reported that the Mannich reaction failed to yield a product when 2-isopropyl-4,5-dimethylphenol was employed and, also, that attempts to introduce two dimethylaminomethyl or two morpholinomethyl groups into 3,5-dimethylphenol failed.[4b] Thus, the fact that I yields only one monosubstituted product and fails to undergo disubstitution is not unique.

The crypto-phenolic character of products IIIa, IIIb, IIIc, IIIf, and IIIg is attested by their insolubility in 10% sodium hydroxide, a property characteristic of other aminomethylphenols.[8] In addition, the infrared spectra of these compounds in potassium bromide and of IIIb in carbon tetrachloride solution failed to show any absorption in the 3 μ region which is characteristic of the phenolic OH group. To determine whether this was characteristic of other *o*-dialkylaminomethylphenols, the infrared spectrum of 1-morpholinomethyl-2-naphthol in carbon tetrachloride was determined; the expected absorption band characteristic of the OH group was conspicuously absent. Compounds IIIa, IIIb, IIIc, IIIf, IIIg, and 1-morpholinomethyl-2-naphthol would be expected to possess strongly bonded OH groups which very probably would exhibit absorption bands coincident with the strong CH absorption near 3.5 μ, a phenomenon adequately discussed by Bellamy.[9] The CH stretching absorption of these compounds near 3.5 μ is complicated by the presence of peaks and shoulders on the side of the main absorption band which are not present in the CH absorption of estrone (Table I), and it is quite possible that they may be attributed to the OH groups. Furthermore, compound IIIb could not be etherified with methyl iodide or dimethyl sulfate; this conforms with the observations made by Snyder and Brewster during an investigation of Mannich bases of β-naphthol.[10]

TABLE I

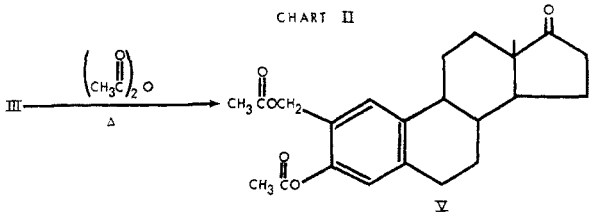
INFRARED ABSORPTION IN THE CH REGION

Compound	Absorption (μ)			
Estrone	3.44	3.50		
IIIa	3.43	3.50	3.54[a]	3.60[b]
IIIb	3.43	3.50	3.54[b]	3.69[b]
IIIc	3.43	3.50	3.54[b]	3.69[a]
IIIf	3.44	3.50	3.57[a]	3.68[a]
IIIg	3.45	3.52		3.65–3.70[a]

[a] Shoulder on the side of main CH absorption peak. [b] Small peak on side of main CH absorption peak.

Although IIIb resisted esterification at room temperature in a solution of acetic anhydride and pyridine, IIIa, IIIb, IIIc, IIId, and IIIf reacted with acetic anhydride at reflux temperature to give 2-acetoxymethylestrone acetate (V) in high yields (Chart II). This shows that these compounds are

CHART II



V

structurally identical and differ only in the composition of the amine group. Although no attempt was made to convert IIIe and IIIg to V, it seems reasonable to assume that the reactions would be successful and that these two compounds would differ from other members of the series III compounds only by the composition of the amine group.

The NMR spectra of IIIa and V support the assignment of position 2 as that at which the Mannich reaction occurred. The spectrum of each compound indicated the presence of two different kinds of aromatic hydrogen atoms which were not spin-coupled to each other. Previous experience has shown that *m*- and *p*-hydrogen atoms are not spin-coupled while *o*-hydrogen atoms are spin-coupled.[11] The correlation of these generalities with the NMR spectra limits the assignment of the position of the dimethylaminomethyl group in IIIa and of the acetoxymethyl group in V to position 2.

Compound IIIb was converted to 2-methylestrone (VI) by refluxing an ethanolic solution of

(7) P. L. Julian, E. W. Meyer, and H. C. Printy, U. S. Patent 2,562,194, (July 31, 1951).

(8) J. R. Feldman and E. C. Wagner, *J. Org. Chem.*, 7, 31 (1942).

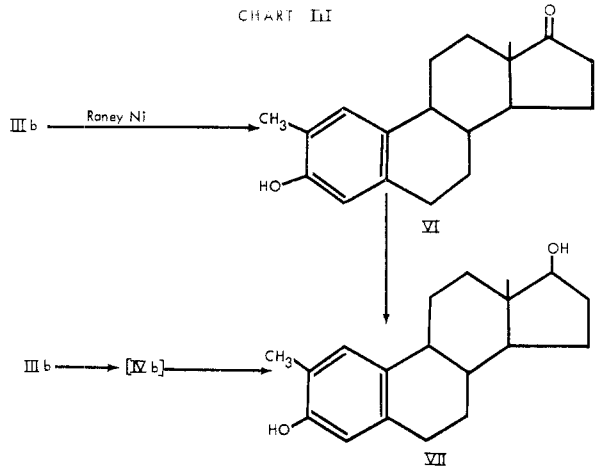
(9) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, N. Y., 1958, p. 104–105.

(10) H. R. Snyder and J. H. Brewster, *J. Am. Chem. Soc.*, 71, 1058 (1949).

(11) The author wishes to express his gratitude to Mr. Nugent F. Chamberlain of the Humble Oil and Refining Company, Baytown, Tex. for determining and interpreting the NMR spectra.

it in the presence of a large excess of Raney nickel; VI was then reduced to 2-methylestradiol (VII) by sodium borohydride (Chart III). The infrared

CHART III



spectrum of VII was indistinguishable from the infrared spectrum of 2-methylestradiol which had been synthesized by another route.[12] This provides conclusive evidence that the structures assigned to III and IV are correct. The synthesis of 2-methylestradiol results in higher yields if IIIb is first reduced to IVb with sodium borohydride and, then, the crude IVb submitted to hydrogenolysis over Raney nickel. Because IVb is so difficult to crystallize, the purification step is omitted.

Biologically, it may be stated that the presence of a dialkylaminomethyl group at C-2 essentially destroys the estrogenic activity of the parent steroid, I. The dosages of compounds IIIa–g required to produce a positive estrogenic response in half of the mice are approximately 30,000 times larger than that of II when bioassayed by the Allen-Doisy vaginal smear technique.[13] The estrogenic activities of compounds IIIa–g did not seem to be affected by the structure of the amino groups. Although these steroids did not produce any observable side effects in the mice, their hydrochlorides were toxic, producing convulsions and death. The intraperitoneal injection of aqueous solutions of IIIa and IIIb produced convulsions in all mice at a dosage of 150 mg./kg. body weight and five out of six mice in each group died shortly thereafter. That the toxicity decreased with increasing length of the alkyl groups on the amino group is indicated by the fact that a dosage of 200 mg. of IIIc was necessary to produce convulsions in all the mice, but only one mouse in the group of six died. Also, neither convulsions nor death occurred after the same dosage of IIId was injected. Compound IIIg was much less toxic than IIIa–d; a dosage of 400 mg./kg. body weight was required to produce convulsions in five out of six mice but no deaths occurred. The investigation of the biological properties of these compounds is continuing.

(12) The author is indebted to Dr. J. Iriarte for an authentic specimen of 2-methylestradiol which was synthesized by the procedure reported by J. Iriarte and H. J. Ringold, *Tetrahedron*, **3**, 28 (1958).

(13) The bioassays have been done in these laboratories with the collaboration of Dr. Leon Dmochowski. A detailed account of the bioassays will appear in a separate publication.

EXPERIMENTAL[14]

2-Dimethylaminomethylestrone (IIIa). (A). *Using aqueous dimethylamine.* Compound I (2.70 g.; 0.01 mole) was dissolved in a solution of benzene (30 ml.), ethanol (50 ml.), and 25% aqueous dimethylamine (20 ml.) by heating to reflux temperature. Then 37% formaldehyde was added in two portions (3 ml. each) 1 hr. apart. After refluxing for 18–26 hr. it was concentrated to one quarter volume. The residue was diluted with water, and the product which precipitated was extracted with ether. The combined ether extracts were washed with several volumes of 10% hydrochloric acid to separate the amines from unchanged estrone. The acid washes were combined, cooled, and made alkaline with ammonium hydroxide. The solid product was collected and recrystallized from ethanol to give 0.685 g. (21% yield) of IIIa, m.p. 169.5–171.5°; $\lambda_{max}^{C_2H_5OH}$ 286 mμ (ε 2960); λ_{max}^{KBr} 3.43 (s), 3.50 (s), 3.54 (shoulder), 3.60 (ms), 5.74 (s), 6.15 (m), 6.30 (m), 6.66 (s), 7.11 (m), 11.10 (m), and 11.30 (m) μ; $[\alpha]_D$ + 154°. It was insoluble in 10% sodium hydroxide.

Anal. Calcd. for $C_{21}H_{29}O_2N$: C, 77.02; H, 8.92; N, 4.27. Found: C, 76.85; H, 8.85; N, 4.21.

The NMR spectrum shows the presence of two aromatic hydrogen atoms which are not spin-coupled.[11]

The *hydrochloride* of IIIa was prepared by bubbling anhydrous hydrogen chloride through a solution of it in absolute ethanol; the salt was precipitated by diluting the solution with anhydrous ether. After recrystallization from ethanol-ether it melted at 264° dec.; $\lambda_{max}^{C_2H_5OH}$ 289 mμ (ε 3020); $\lambda_{max}^{H_2O}$ 286 mμ (ε 2950); λ_{max}^{KBr} 2.87–2.97 (m, shoulder), 3.22 (s, broad), 3.40 (s), 3.88 (s, broad), 3.96 (s), 4.02 (s), 4.20 (shoulder), 5.75 (s), 6.14 (m), 6.25 (w), 6.60 (s), 7.09 (m, shoulder), 11.15 (m), and 11.35 (m) μ.

Anal. Calcd. for $C_{21}H_{30}O_2NCl$: C, 69.30; H, 8.30; N, 3.84; Cl, 9.74. Found: C, 69.24; H, 8.39; N, 3.93; Cl, 9.72.

(B) *Using N,N,N',N'-tetramethyldiaminomethane.*[15] To a solution of I (2.70 g., 0.01 mole) in benzene (30 ml.) and ethanol (50 ml.) was added *N,N,N',N'*-tetramethyldiaminomethane (2 g., 0.02 mole) and paraformaldehyde (0.30 g.; 0.01 mole). After heating at reflux temperature for 18 hr., the product was isolated by the procedure used in method A. It weighed 2.28 g. (69% yield), m.p. 167–171°. Recrystallization from ethanol increased the melting point to 169–171°. The infrared spectrum of this product was indistinguishable from that of IIIa prepared by method A.

2-Diethylaminomethylestrone (IIIb). Compound I (5.4 g., 0.02 mole) was dissolved in benzene (60 ml.), ethanol (100 ml.), and diethylamine (20 ml.); 37% formaldehyde (12 ml.) was added in two equal portions 1 hr. apart. After refluxing for 16 hr. the solvents and excess reagents were removed at reduced pressure. The product was isolated by the

(14) Melting points were taken on a Fisher-Johns block and are uncorrected. The micro nitrogen analyses were done by Miss Marilyn Neumann of this laboratory; all other microanalyses were done by Dr. Carl Tiedcke, Laboratory of Microchemistry, Teaneck, N. J. The infrared spectra were recorded with a Perkin-Elmer model 21 infrared spectrophotometer using a sodium chloride prism (s, m, w = strong, medium, weak intensities). The optical rotations were all done in dioxane at 23 ± 2°.

(15) Prepared according to the method reported by J. K. Lindsay and C. R. Hauser, *J. Org. Chem.* 22, 355 (1957): b.p. 82–84°.

procedure used for the synthesis of IIIa by method A. The crude product weighed 5.53 g. (78% yield). After recrystallization from ethanol the product melted at 157–158°. It was insoluble in 10% sodium hydroxide solution. An analytical sample melted at 159–160°; $[\alpha]_D$ + 149°; $\lambda_{max}^{C_2H_5OH}$ 286 mμ (ε 2850); λ_{max}^{KBr} 3.43 (s), 3.50 (s), 3.54 (s), 3.69 (m), 5.74 (s), 6.15 (m), 6.29 (m), 6.66 (s), 7.11 (shoulder), 11.26 (m), and 11.55 (m) μ. There was also no absorption in the 3.0 μ region (OH) when dissolved in carbon tetrachloride.

Anal. Calcd. for $C_{23}H_{33}O_2N$: C, 77.70; H, 9.35; N, 3.94. Found: C, 77.67; H, 9.29; N, 3.77.

The crude product was submitted to chromatography on columns of alumina and acid-washed alumina and eluted with benzene, benzene:methanol (99:1, 98:2, 95:5, and 9:1), and acetone. Only one product was obtained from the eluates; it was in the benzene:methanol (9:1) eluate from both columns and was identical with IIIb.

When the crude product was absorbed on a column of silica gel from benzene solution and eluted with benzene, benzene:acetone (99:1), benzene:ether (95:5), and benzene:ethanol (99:1, 98:2, 97:3, 95:5, 9:1, and 8:2), a single product, identical with IIIb, was isolated. It was removed by the benzene-ethanol (95:5) solution.

IIIb did not form a benzoate when allowed to stand in a solution of benzoyl chloride and pyridine at room temperature for 24 hr.

IIIb did not form an acetate when allowed to remain in a solution of acetic anhydride and pyridine for 24 hr.

IIIb resisted etherification by methyl iodide and dimethylsulfate.

The infrared spectra of the products isolated from these three attempts to form a derivative of IIIb were identical with the spectrum of IIIb.

The *hydrochloride* of IIIb melted at 233–234°; $\lambda_{max}^{C_2H_5OH}$ 289 mμ (ε 3150); $\lambda_{max}^{H_2O}$ 286 mμ (ε 2940); λ_{max}^{KBr} 2.88 (s), 3.20 (s, broad), 3.41 (s), 3.48 (ms), 3.78 (ms), 4.00 (w), 5.74 (s), 6.14 (m), 6.26 (w), 6.60 (s), 7.12 (m), 11.11 (m), and 11.41 (m) μ.

Anal. Calcd. for $C_{23}H_{34}O_2NCl$: C, 70.47; H, 8.74; N, 3.57; Cl, 9.04. Found: C, 70.34; H, 8.74; N, 3.46; Cl, 9.07.

Attempt to form 2,4-bis(diethylaminomethyl)estrone. To a solution of I (2.7 g.; 0.01 mole) in benzene (30 ml.), ethanol (50 ml.), and diethylamine (31.2 g.; 0.4 mole) was added paraformaldehyde (3.0 g.; 0.1 mole). After refluxing for 96 hr., the product was isolated by the same procedure used for the synthesis of IIIa by method A. It was absorbed on a column of alumina and eluted with benzene and benzene:methanol (99:1, 98:2, 96:4, 9:1, 3:1). The only product isolated was eluted with benzene:methanol (98:2) and weighed 1.06 g.; m.p. 159–160°. The infrared spectrum was indistinguishable from that of IIIb. Therefore, disubstitution did not occur.

2-Di-n-propylaminomethylestrone (IIIc). To a solution of I (2.7 g.; 0.01 mole) in benzene (30 ml.), ethanol (50 ml.), and di-*n*-propylamine (10 ml.) at reflux temperature was added 37% formaldehyde (6 ml.) in two equal portions as previously described, and the synthesis was completed by the procedure used for the synthesis of IIIa by method A. The crude product, m.p. 98–101°, weighed 2.87 g.; after two recrystallizations from ethanol the product weighed 2.01 g. (53% yield) and melted at 106–107°. It was insoluble in 10% sodium hydroxide. An analytical sample melted at 107.0–107.5°; $\lambda_{max}^{C_2H_5OH}$ 286 mμ (ε 2850); λ_{max}^{KBr} 3.43 (s), 3.50 (s), 3.54 (s), 3.69 (shoulder), 5.75 (s), 6.14 (m), 6.30 (m), 6.66 (s), 11.16 (m), 11.27 (ms), and 11.45 (m) μ; $[\alpha]_D$ + 128°.

Anal. Calcd. for $C_{25}H_{37}O_2N$: C, 78.28; H, 9.72; N, 3.65. Found: C, 78.07; H, 9.58; N, 3.58.

The *hydrochloride* melted at 218–220°; $\lambda_{max}^{C_2H_5OH}$ 289 mμ (ε 3300); $\lambda_{max}^{H_2O}$ 286 mμ (ε 3080); λ_{max}^{KBr} 2.92 (s), 3.21 (s), 3.42 (s), 3.49 (ms, shoulder) 3.81 (m, broad), 3.95 (w), 5.74 (s), 6.15 (m), 6.26 (w), 6.61 (s), 7.10 (m), 11.21 (m), and 11.44 (m) μ.

Anal. Calcd. for $C_{25}H_{38}O_2NCl$: C, 71.48; H, 9.11; N, 3.33; Cl, 8.44. Found: C, 71.43; H, 9.18; N, 3.39; Cl, 8.47.

2-Di-n-butylaminomethylestrone (IIId). Compound I (2.70 g.; 0.01 mole) was dissolved in benzene (30 ml.), ethanol (50 ml.), and di-*n*-butylamine (10 ml.). Then 37% formaldehyde (6 ml.) was added in the usual way and the procedure used for the synthesis of IIIa by method A was followed. The product was a viscous oil which resisted crystallization. It was taken up in ether and washed with 10% hydrochloric acid; the *hydrochloride* crystallized out of the aqueous phase. It weighed 3.49 g. (78% yield), m.p. 195–201°. Two recrystallizations from ethanol-ether gave an analytical sample, m.p. 204–206°; $\lambda_{max}^{C_2H_5OH}$ 289 mμ (ε 3140); $\lambda_{max}^{H_2O}$ 286 mμ (ε 2800); λ_{max}^{KBr} 2.92 (m), 3.25 (s), 3.41 (s), 3.49 (shoulder), 3.70 (m), 3.80 (m), 4.24 (w, shoulder), 5.74 (s), 6.15 (m), 6.26 (w), 6.61 (s), 7.10 (shoulder), 11.15 (m), and 11.43 (m) μ.

Anal. Calcd. for $C_{27}H_{42}O_2NCl$: C, 72.37; H, 9.44; N, 3.12; Cl, 7.91. Found: C, 72.39; H, 9.44; N, 3.24; Cl, 7.96.

2-Di-n-amylaminomethylestrone (IIIe). Compound I (2.70 g.; 0.01 mole) was dissolved in benzene (30 ml.), ethanol (50 ml.), and di-*n*-amylamine (10 ml.). Then 37% formaldehyde (6 ml.) was added in the usual way and the procedure used for the synthesis of IIIa by method A was followed. The product was a viscous oil which could not be obtained in a crystalline form. It was adsorbed on a column of acid-washed alumina and eluted with benzene to give only a viscous oil. The *hydrochloride* was prepared by the same procedure used for the synthesis of the hydrochloride of IIIa. After two recrystallizations from ethanol-ether an analytical sample weighing 2.1 g. (47% yield) was obtained, m.p. 189–191°; $\lambda_{max}^{C_2H_5OH}$ 289 mμ (ε 3130); $\lambda_{max}^{H_2O}$ 286 mμ (ε 2850); λ_{max}^{KBr} 3.25 (s), 3.40 (s), 3.49 (s), 3.80 (m, broad), 5.73 (s), 6.15 (m), 6.26 (w), 6.60 (s), 7.10 (m, shoulder), 11.13 (mw), and 11.45 (mw) μ.

Anal. Calcd. for $C_{29}H_{46}O_2NCl$: C, 73.15; H, 9.73; N, 2.94; Cl, 7.44. Found: C, 73.01, H, 9.71; N, 2.94; Cl, 7.42.

2-Piperidinomethylestrone (IIIf). Compound I (2.70 g., 0.01 mole) was dissolved in a solution of benzene (30 ml.), ethanol (50 ml.), and piperidine (10 ml.). It was heated to reflux temperature and then 37% formaldehyde (6 ml.) was added in the usual way. The procedure was identical with that of method A used for the synthesis of IIIa. Recrystallization from ethanol gave 2.39 g. of material, m.p. 186–191°. Further recrystallization from ethanol raised the melting point to 195.5–197° which was the same as that of an analytical sample. It was insoluble in 10% sodium hydroxide. The pure product weighed 2.1 g. (55% yield); $\lambda_{max}^{C_2H_5OH}$ 286 mμ (ε 2860); λ_{max}^{KBr} 3.44 (s), 3.50 (s), 3.57 (shoulder), 3.68 (shoulder), 5.74 (s), 6.15 (m), 6.30 (m), 6.65 (s), 7.12 (m), 11.27 (m), 11.52 (m) μ; $[\alpha]_D$ + 142°.

Anal. Calcd. for $C_{24}H_{33}O_2N$: C, 78.43; H, 9.05; N, 3.80. Found: C, 78.25; H, 9.04; N, 3.94.

2-Morpholinomethylestrone (IIIg). Compound I (5.4 g.; 0.02 mole) was dissolved in benzene (60 ml.), ethanol (100 ml.), and morpholine (20 ml.). Then 37% formaldehyde (12 ml.) was added as usual and the reaction completed by the procedure described in method A for the synthesis of IIIa. The crude product was insoluble in 10% sodium hydroxide and weighed 4.4 g. (60% yield), m.p. 208–211°. Two recrystallizations from ethanol gave an analytical sample, m.p. 213–214°; $\lambda_{max}^{C_2H_5OH}$ 286 mμ (ε 2890); λ_{max}^{KBr} 3.45 (s), 3.52 (s), 3.65–3.70 (shoulder), 5.75 (s), 6.14 (m), 6.31 (m), 6.66 (s), 7.12 (m), 11.31 (m), and 11.57 (ms) μ.

Anal. Calcd. for $C_{23}H_{31}O_3N$: C, 74.76; H, 8.45; N, 3.78. Found: C, 74.63; H, 8.45; N, 3.86.

The *hydrochloride* was prepared in ether-ethanol solution with anhydrous hydrogen chloride. The pure product melted at 225–228°; $\lambda_{max}^{C_2H_5OH}$ 289 mμ (ε 3240); $\lambda_{max}^{H_2O}$ 285 mμ (ε 2760); λ_{max}^{KBr} 3.09 (s, broad), 3.40 (s), 3.49 (s), 3.74 (m), 3.85 (s), 3.92 (shoulder), 4.03 (m), 5.74 (s), 6.15 (m), 6.25 (w), 6.64 (s), 7.10 (m), 11.10 (m), and 11.55 (m) μ.

Anal. Calcd. for $C_{23}H_{32}O_3NCl$: C, 68.04; H, 7.94; N, 3.46; Cl, 8.73. Found: C, 67.92; H, 7.88; N, 3.51; Cl, 8.71.

2-Piperidinomethylestradiol (IVf). *A. From II.* Compound II (2.72 g.; 0.01 mole) was dissolved in benzene (30 ml.),

ethanol (50 ml.) and piperidine (10 ml.). Then 37% formaldehyde (6 ml.) was added in the usual way and the procedure used for the synthesis of IIIa by method A was followed. The oily product was adsorbed on a column of acid-washed alumina which was eluted with benzene and benzene:ethanol (99:1, 98:2, and 95:5). A viscous oil was eluted with the 98:2 solution; it partially solidified after several days. Recrystallization from ethanol gave 1.3 g. (35% yield), m.p. 99–101°; $\lambda_{max}^{C_2H_5OH}$ 286 mμ (ε 2620); λ_{max}^{KBr} 3.05 (m), 3.12 (m, on side of 3.05 band), 3.31 (shoulder), 3.40 (s), 3.50 (s), 3.56 (shoulder), 3.67 (shoulder), 6.12 (m), 6.30 (m), 6.66 (s), and 11.30 (ms) μ.

Anal. Calcd. for $C_{24}H_{35}O_2N$: C, 78.00; H, 9.54; N, 3.79. Found: C, 77.84; H, 9.67; N, 3.84.

B. *From IIIf.* A solution of IIIf (0.20 g.) and sodium borohydride (0.10 g.) in methanol (25 ml.) remained at room temperature for 4 hr. It was then acidified with hydrochloric acid, concentrated to 1/3 volume, and diluted with water. The solution was neutralized with sodium bicarbonate and the precipitate was filtered. The yield of IVf was quantitative, and after recrystallization from methanol it melted at 99–101°. The infrared spectrum was identical with that of IVf obtained by method A.

2-Acetoxymethylestrone acetate (V). A solution of Ib (0.15 g.) in acetic anhydride (5 ml.) was refluxed for 5 hr. and then concentrated to about 2 ml. This solution was poured over ice. After the ice melted and all the acetic anhydride had hydrolyzed, the precipitate was extracted three times with ether. The combined extracts were washed successively with water, sodium bicarbonate solution, and water. After drying over anhydrous sodium sulfate, the ether was evaporated. The residue was recrystallized from ethanol-water to give 0.139 g. (85.5%) yield) of colorless crystals, m.p. 147–148°; $\lambda_{max}^{C_2H_5OH}$ 269 mμ (ε 872) and 278 mμ (ε 872); $\lambda_{min}^{C_2H_5OH}$ 275 mμ (ε 754); λ_{max}^{KBr} 3.43 (s), 3.48 (ms), 5.65 (s), 5.75 (s), 6.16 (m), 6.32 (w), 6.64 (ms), 7.04 (m) with a shoulder at 7.10, 8.05–8.30 (s), 11.19 (m), and 11.42 (m) μ; $[\alpha]_D$ + 122°.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.84; H, 7.34. Found: C, 71.74; H, 7.30.

The NMR spectrum indicates that there are two hydrogen atoms on the aromatic ring which are not spin-coupled; therefore, the acetoxymethyl group must be at position 2.[11]

This product was also synthesized from IIIa, IIIc, IIId (oil), and IIIf by the same procedure. The products were shown to be identical by a comparison of their melting points, ultraviolet spectra, and infrared spectra.

2-Methylestrone (VI). A suspension of Raney nickel catalyst (10 g.) in a solution of IIIb (1 g.) in 95% ethanol (160 ml.) was refluxed for 22 hr. with continuous stirring. The Raney nickel was separated from the hot solution by filtration. Evaporation of the alcohol left a residue which was recrystallized from 95% ethanol to give 0.375 g. of crude 2-methylestrone, m.p. 225–227°, and 0.250 g. of material which melted at 184–190°. Recrystallization of the 2-methylestrone raised the melting point to 233° (lit.,[12] m.p. 221–225°). The melting point was not changed by chromatography of the product on a column of silica gel. The low melting product (184–190°) was submitted to separation on a column of silica gel and yielded an additional 0.045 g. of 2-methylestrone, m.p. 232–233°. The total yield of pure product was 0.305 g. (38% yield), $\lambda_{max}^{C_2H_5OH}$ 283 mμ (ε 2660); λ_{max}^{KBr} 3.03 (s), 3.32 (m, shoulder), 3.43 (s), 3.50 (s), 5.80 (s), 6.16 (ms), 6.25 (m), 6.62 (s), 7.13 (m, shoulder), 11.35 (m), and 11.54 (m) μ.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.02; H, 8.39.

The benzoate was prepared by the Schotten-Baumann technique and recrystallized from ether. It melted at 211–212° (lit.,[12] m.p. 212°).

2-Methylestradiol (VII). A. *By reduction of* VI. Sodium borohydride (0.050 g.) was added to a solution of VI (0.035 g.) in 15 ml. methanol. After remaining at room temperature overnight the product was isolated in the usual way to give 0.030 g., m.p. 179–180°. Recrystallization from ether raised the melting point to 182–183° (lit.,[12] m.p. 185–186°). The infrared spectrum of this product was indistinguishable from that of the product synthesized by method B (below).

B. From IIIb. Sodium borohydride (0.5 g.) was added to a solution of IIIb (1 g.) in methanol (200 ml.) and allowed to remain at room temperature overnight. The product, IVb, was isolated in the usual way by ether extraction to give an oil which did not crystallize. The crude product was dissolved in 95% ethanol (160 ml.) and stirred at reflux temperature with Raney nickel (20 g.) for 24 hr. The catalyst was removed from the hot solution by filtration. Evaporation of the alcohol at reduced pressure left a residue which was recrystallized from ethanol to give 0.520 g. (65% yield), m.p. 180–182°. Recrystallization from ether gave an analytical sample, m.p. 184.5–186° (lit.,[12] m.p. 185–186°); $\lambda_{max}^{C_2H_5OH}$ 283 mμ (ε 2633); λ_{max}^{KBr} 2.80 (ms), 2.93 (s), 3.43 (s), 3.49 (s), 6.15 (m), 6.26 (w), 6.60 (s), 11.10 (mw), 11.35 (ms) μ.

The infrared spectrum of this product was identical with that of an authentic specimen of 2-methylestradiol.[12]

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.66; H, 9.06.

Benzoylation of the product (0.050 g.) by the Schotten-Baumann technique and recrystallization of the product from ether gave *2-methylestradiol 3-monobenzoate* (0.035 g.), m.p. 184–186° (lit.,[12] 187–190°).

Anal. Calcd. for $C_{26}H_{30}O_3$: C, 79.97; H, 7.74. Found: C, 79.88; H, 7.81.

The *diacetate* of 2-methylestradiol was prepared by allowing a solution of 2-methylestradiol (0.050 g.) in 3 ml. of acetic anhydride:pyridine (1:1) to remain at room temperature overnight. The product was isolated in the usual way and recrystallized twice from ethanol to give 0.030 g. of product, m.p. 172–173.5°.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.24; H, 8.12.

2-Morpholinomethyl-1-naphthol. This was synthesized by a known procedure to give a product melting at 115° (lit.,[16] m.p. 115–116°). When it was dissolved in carbon tetrachloride there was no absorption in the 3 μ region (OH).

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